Recent Research and Literature Review

A. HIV/AIDS In the District of Columbia

As noted in a number of publications including the Kaiser Family Foundations HIV Fact sheet\(^1\), Washington DC is one of the geographic areas that have been significantly impacted by the HIV epidemic in the United States. Some compare the infection rates to that of developing countries in sub-Saharan Africa that have traditionally received a great deal of attention throughout the 30 years since the identification of the virus. Current research states that 14,465 individuals (2.7%) are living with HIV in the District of Columbia. Hardest hit among this population are African Americans.

References:


Factors Affecting Acceptance of Routine Human Immunodeficiency Virus Screening by Adolescents in Pediatric Emergency Departments

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ABSTRACT

Purpose: Human immunodeficiency virus (HIV) screening in health care settings including emergency departments (EDs) is recommended for adolescents in the United States. This study aimed to evaluate the acceptance of and the factors affecting the HIV screening in pediatric EDs.

Methods: A prospective, cross-sectional study of rapid opt-out oral HIV screening among adolescents ≥ 13 years of age was conducted in two pediatric EDs during 2009–2011. Descriptive statistics and logistic regression models were used to identify factors associated with the acceptance of HIV screening.

Results: During 24 months, 8,519 adolescents were approached for HIV screening; 6,184 (72.6%) did not opt out, and of those 5,764 (93.2%) were tested for HIV. Most adolescents who accepted testing were black (80.5%), female (57.6%), aged 15–17 years (50.1%), and District of Columbia residents (67.7%), and were accompanied by a guardian (69.1%). Acceptance of HIV screening varied by age, race/ethnicity, and state of residence, with younger (< 15 years) (adjusted odds ratio [aOR], 1.67; 95% confidence interval [CI], 1.33–2.09), non-black adolescents (aOR, .88; 95% CI, .77–.99) and non-District of Columbia residents (aOR, .86; 95% CI, .77–.96) being more likely to opt out of testing. Lower odds of opt-out of HIV testing were seen among adolescents with a guardian present (aOR, .42; 95% CI, 0.34–0.53). The reasons for opt-out varied significantly by age and the presence of a guardian.

Conclusions: The patient's age and the presence of a guardian were significantly associated with adolescents' decision and reasons to opt out of HIV screening in pediatric EDs. Further studies are necessary to evaluate the interventions needed to increase routine ED HIV screening in adolescents.

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Implications and Contribution

Our study reports new data on routine human immunodeficiency virus (HIV) screening among adolescents in two urban pediatric emergency departments. The presence of a guardian was associated with lower chances of refusal of HIV screening among adolescents. Most adolescents and their guardians accept routine HIV screening in emergency departments.

Despite an overall steady number of new diagnoses of human immunodeficiency virus (HIV) infection in the United States (US), the incidence of HIV among adolescents and youth aged 13–24 years continues to grow [1–3]. The Centers for Disease Control...
and Prevention (CDC) report that 26% of new infections occur among youth between 13 and 24 years of age [4]. An increased number of youth with HIV are unaware of the infection, remain at risk for advanced disease, and continue to contribute to an ongoing epidemic among their peers [3–6]. Most important, in the era of universal consideration of antiretroviral therapy and availability of pre-exposure prophylaxis, the timely diagnosis of HIV among adolescents and young adults is more crucial than ever before [3,7–10].

To increase access to HIV diagnostics, in 2006 the CDC issued revised recommendations for HIV testing in health care settings [11]. The CDC recommended routine voluntary opt-out HIV screening for all patients 13–64 years of age, which represented a significant change from the 1993 guidelines recommending targeted screening of high-risk patients 15–54 years of age in health care settings with an HIV prevalence of >1% [11,12]. In 2011, the American Academy of Pediatrics, addressing the role of the pediatric care providers, endorsed routine HIV screening among adolescents by recommending “at least one HIV screening test in all adolescents by 16 to 18 years of age in health care settings when the prevalence of HIV in the patient population is >1%” and “routine HIV screening for all sexually active adolescents” [13]. Most recently, in April 2013, the US Preventive Services Task Force released the national recommendation on routine HIV screening as a preventive service for adolescents and adults aged 15–65 years to be covered under the Affordable Care Act [14]. Emergency departments (EDs) provide access to routine HIV screening for a large number of patients, including vulnerable populations without regular medical care. Currently, data on routine HIV screening in EDs are limited in studies conducted in the setting of adult EDs, with few publications on HIV screening in pediatric EDs [15–25].

Children’s National Medical Center (CNMC) serves as a major pediatric care provider in the Washington, District of Columbia (DC) metropolitan area, which has a high HIV prevalence [26]. CNMC operates two pediatric EDs: the Sheikh Zayed ED (SZED), located in the main campus in downtown DC, and the United Medical Center ED (UMCED), located in a community hospital in southeast DC. Both EDs accommodate >126,000 visits/year by predominantly minority (>80%) pediatric (83%) and adolescent (17%) patients from DC and suburban Virginia and Maryland. In 2009–2010, with the support of the DC Department of Health, routine opt-out oral rapid fluid HIV screening of adolescents ≥13 years of age was implemented at SZED (March 2009) followed by UMCED (October 2010). The objectives of this study were to measure overall acceptance rates for HIV testing, as well as to examine the patient- and guardian-related factors that affect the decision to opt out of HIV screening among adolescents in urban pediatric EDs. Based on the results of a patient/guardian survey conducted before implementing the program, which demonstrated high rates of acceptance of the proposed virtual HIV screening by adolescents (73%) and their guardians (77%) in our EDs [27], we hypothesized that HIV screening would be accepted by most (>70%) adolescents and their guardians. Our survey found that more than one third (34%) of adolescents reported that the presence of the guardian with them in the ED would influence their decision regarding HIV testing; half (53%) of these youth stated that they would consider declining the HIV test owing to a guardian’s presence, because they would not want them to find out about the test results. Based on these results, we also hypothesized that the presence of the guardian in the ED would be associated with higher rates of opting out. To test these hypotheses, we examined the acceptance of HIV screening and the reasons for opting out among patients and their guardians. In particular, we sought to explore whether the presence of a guardian in the ED and demographic factors (age, gender, race/ethnicity, and state of residence) affected the acceptance of HIV screening by adolescents.

**Patients and Methods**

**Patients**

A prospective, cross-sectional study was conducted in the two CNMC EDs for 24 months from the start of the program in March 2009 through February 2011. Both EDs are operated and staffed by CNMC personnel and use identical algorithms for care. Both EDs are located in DC, where written consent is not required for HIV testing of adolescents ≥12 years of age regardless of the presence of a guardian [28,29]. The study population included patients ≥13 years of age (defined here as adolescents) and their guardians, who were approached for universal opt-out oral fluid HIV screening in the EDs. The study provided study information sheets to all adolescent patients approached for the HIV screening in both EDs and did not require the consent of patients or guardians. The study protocol was approved by the CNMC Institutional Review Board as part of a larger de-identified data collection on routine ED HIV screening.

In accordance with the HIV screening algorithm, adolescents and their guardians were approached for HIV testing either during triage or in an ED room. If an adolescent had a documented HIV test in the ED within the previous 6 months, the patient was not approached for repeat HIV screening, unless he or she was identified to be at high risk (such as self-disclosure of risk behavior, sexually transmitted disease [STD], or pregnancy). Per ED HIV screening algorithm, the medical staff was requested to document the reason for not approaching a patient ≥13 years of age for HIV screening on the standardized form. The adolescent was considered to be an opt-out if he or she declined the HIV test and/or if the guardian (when present) declined the screening. Both adolescents and guardians who refused screening were asked to specify the reasons for opting out. For every screening approached and declined, the ED staff filled out the standardized multiple choice answer form documenting the reason why the guardian or adolescent declined the test. The forms were collected weekly and the data were transferred into electronic format by the program staff.

HIV screening tests were administered at both EDs as a point-of-care test. OraQuick ADVANCE Rapid HIV-1/2 Antibody test kits (OraSure Technologies, Inc., Bethlehem, PA) are provided by the DC DOH with financial support from the CDC. The HIV tests were administered by dedicated grant-funded personnel at SZED and by ED personnel at UMCED. In the case of a nonreactive test result, the patient was provided with brief post-test counseling including written information on HIV/STD risk reduction. In the case of a reactive test result, a confirmatory Western blot blood test was obtained and the patient received individual counseling with a case manager. Linkage to specialized adolescent HIV services at CNMC was provided to all patients with a reactive test result, with a follow-up appointment 48–72 hours after the ED visit.

**Data collection and statistical analyses**

HIV screening data from both EDs were collected and maintained in a centralized electronic database in which each ED visit
was recorded. Data collected included the numbers of patients approached for screening; guardian presence; patients or guardians who chose to opt out; and patients who were screened, had a reactive HIV test, confirmed a new diagnosis of HIV infection, and were linked to care. Patient demographics included age, race/ethnicity, gender, and state of residence identified by the patient’s ZIP code. Additional data included the documented reasons for not being approached for screening and for opting out by the adolescent and/or guardian.

The unit of analysis was an ED visit by an adolescent. Univariable analyses were conducted to describe HIV testing behaviors in the EDs. Comparisons were made between 13- to 14-year-olds and those age ≥15 years, to address the discrepancy between the current CDC recommendations to start routine HIV screening at 13 years of age and American Academy of Pediatrics and US Preventive Services Task Force recommendations for routine HIV screening of older adolescents (≥15 years of age).

Adolescents who chose to opt out were compared with those who accepted testing, using bivariable analysis. All significant characteristics from this bivariable analysis were included in a multivariable logistic regression model. In addition, the interaction between age and the presence of a guardian was assessed within this model, because it was hypothesized that older adolescents might be less likely to be accompanied by a guardian to the ED. Any variable with p > .10 was dropped from the model using a manual stepwise elimination method, with the exception of gender, which was included as a potential confounder. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

During the 2-year study period, there were 10,991 ED adolescent visits, representing 8,528 individual adolescents aged 13–24 years. Among the 1,615 patients who had more than one ED visit, 70.7% (n = 1,141) had two visits, 17.8% (n = 287) had three visits, and 11.5% (n = 187) had at least four visits during the study period.

A large proportion (n = 8,519; 77.5%) of adolescent visits (n = 10,991) were approached for HIV testing in the EDs (Figure 1). Of 8,519 visits approached, adolescents accepted the HIV screening during 6,184 visits (72.6%), with higher acceptance at UM Ced (83.8%) compared with SZED (72.3%) (p < .0001). Other differences observed between the two EDs were that adolescents at UM Ced were more likely to be female (p = .0005), ≥15 years of age (p = .014), black (p < .001), and DC residents (p < .0001).

The majority (n = 5,764; 93.2%) of those who accepted the screening were tested for HIV. Six percent of adolescents who accepted the screening (n = 370) were not tested because a guardian declined testing; a small proportion (n = 50; 9%) did not get tested owing to logistical ED barriers. Twelve adolescents (.21%) had a reactive OraQuick test, and eight (.14% of 5,764 tested) were confirmed to be HIV positive. Newly identified HIV-infected adolescents had a mean age of 18.6 years (standard deviation, 1.31 years), 50% were female, and all were black. The mean CD4 cell count was 574 cells/mm³ (range, 386–770 cells/mm³) and the mean viral load was 42,229 copies/mL (range, 937–268,345 copies/mL). All patients were linked to care and none had a diagnosis of acquired immunodeficiency syndrome.

For the 2,472 visits in which adolescents were not approached (22.5%), the reason for not approaching the patient was documented in 50% of records. Most frequently recorded reasons for not offering routine HIV screening were insufficient staff time (n = 633; 25.6%) and a medical decision to not address HIV screening (n = 570; 23.1%). An additional 54 adolescent visits (2.2%) were not approached because the patients were known to be HIV positive (Figure 2).

In 2,335 of the 8,519 ED patient visits approached for testing (27.4%), adolescents chose to opt out of HIV screening (Figure 1). The reason for declining testing was documented in 80% of patient visits. The most frequent reasons adolescents provided for their choice to opt out of HIV testing were a recent negative HIV test (n = 818; 35.0%), denying being sexually active (n = 353; 15.1%), and perception of not being at risk for HIV (n = 308; 13.2%). Nearly one fifth of adolescents who declined screening did not provide a reason for opting out (n = 393; 16.8%) (Figure 3). Significant differences in reasons provided for opting out were observed by age. Adolescents ≥15 years of age were more likely to report having recently tested negative, compared with those 13–14 years of age (42.0% vs. 17.4%; p < .0001), were less likely to deny being sexually active (13.4% vs. 19.4%; p = .0003), and were less likely to not provide any reason for opting out (13.7% vs. 24.7%; p < .0001).

Most adolescents who were approached for screening were accompanied by a guardian (n = 5,686; 67%). Adolescents aged 13–14 years were significantly more likely to be accompanied by a guardian compared with those aged ≥15 years (n = 2,101, 85.4% vs. n = 3,585, 59.5%, respectively; p < .0001). For 1,121 of these adolescents (19.7%), the guardian chose to opt out of HIV testing; of these, for most (n = 750; 66.9%), the decline was concordant, with both the adolescent and the guardian choosing to opt out of screening. The most frequently reported reasons provided by guardians when declining HIV testing were an adolescent’s recent negative test (n = 324; 28.9%), perception of the adolescent not being at risk for HIV (n = 218; 19.5%), and believing the adolescent was not sexually active (n = 189; 16.9%) (Figure 3).

The presence of a guardian accompanying a patient in ED when he or she was offered HIV screening was significantly associated with the adolescent’s reasons for choosing to opt out of testing. Adolescents without a guardian present in the ED were significantly more likely to report a recent negative HIV test as the reason for opting out than were adolescents with a guardian present (47.0% vs. 27.6%; p < .0001). Conversely, adolescents with a guardian present were significantly more likely to report a low self-perceived risk for HIV as the reason for opting out than adolescents without a guardian present (15.6% vs. 9.5%; p < .0001).
Discussion

Consistent with our first hypothesis, our study found high rates of acceptance of routine HIV screening among adolescents and their guardians in two urban pediatric EDs. The high overall acceptance of HIV screening among adolescents in our study is comparable to data from similar age cohorts in the US [18,25,30]. In concordance with these studies and other non-ED studies of HIV screening among adolescents, lower acceptance of HIV screening by adolescents <15 years of age was observed in our study [24,25,30,31]. Similar to adult and pediatric ED data, in community-based and urban hospital-based adolescent HIV screening, a higher acceptance of HIV testing was observed among black populations [21,24,31,32]. In contrast to other adult and adolescent HIV screening data, there was no gender difference in the acceptance of the test, although as in other adolescent studies, more females were approached for screening than males in our EDs [24,25,30,31,33,34].

The higher acceptance of HIV screening among urban versus suburban populations observed in our study has been reported in adults from Michigan and South Carolina [33,35]. Given the heightened attention regarding the HIV epidemic in DC in recent years, including a widely publicized HIV testing campaign and ongoing HIV screening in most adult EDs in the area, where the number of HIV tests has tripled during 2007–2011 [26], it is possible that there is more knowledge and less stigma associated with HIV testing in DC.

Adolescents at the smaller-size, lower-acute UMCED, where the screening was conducted by ED personnel, were more likely to accept screening than adolescents at SZED, where the screening was performed by dedicated grant-funded personnel. These results are contrary to findings from adult studies that have reported higher testing rates and higher patient satisfaction when screening was performed by dedicated HIV counselors compared with ED personnel [36,37]. The patient demographics factors (prevalent black race, older age, and DC residence), however, are most likely determinants of the observed difference. The ongoing successful ED screening of adults at UMC might have also contributed to the greater local community acceptance of HIV screening.

We also observed significant differences in the reasons for opting out by age. Adolescents ≥15 years of age were more likely...
to report a recent negative test and were less likely to deny being sexually active compared with 13- to 14-year-olds in our study. Interestingly, the proportion of adolescents who denied being sexually active was only 6% higher within the younger cohort (19.4% among 13- to 14-year-olds) compared with adolescents ≥15 years of age (13.4%). This is consistent with the earlier onset of sexual activity among DC youth; 13% of DC adolescents <13 years of age (13%) versus 7% nationwide reported being sexually active [38].

In our study, .14% of tested adolescents were positive, compared with data from a pediatric ED in Memphis in which only one new HIV case (.06%) was identified [24]. The higher rates of newly diagnosed HIV infections in our cohort were most likely related to the overall higher prevalence of HIV in DC and the high rate of new HIV infections among minority American youth in recent years [4,26]. Different from national and regional trends of primarily male-to-male HIV transmission, half of our new cases were among young females [4,26]. Finally, different from DC data on new HIV diagnoses among youth, there were no diagnoses of acquired immunodeficiency syndrome or late testers among our newly identified HIV cases [26].

Contrary to our second hypothesis, the presence of a guardian was associated with lower odds of opting out of HIV testing among adolescents. During the pre-implementation workshops and hand-on training of our ED staff, we encountered a certain degree of anxiety among ED providers regarding the guardian’s response to HIV testing. The presence of the guardian was cited as a potential legal, social, and emotional barrier to HIV screening of adolescents. It was also suggested that fear of disclosure of sexual activity might negatively influence adolescents’ decisions to accept testing in the presence of a guardian. It is important to recognize this potential barrier, taking into consideration that in pediatric EDs, as in our study, most adolescents are accompanied by an adult guardian. Equally important is knowledge about the local legal requirements for HIV screening of adolescents. To date, 30 states and DC explicitly allow minors to independently consent to HIV testing as part STD services; of those, 11 states require a minor to be of a certain age (12 or 14 years) to be able to consent [28]. With the exception of one state, no state requires that physicians notify guardians about HIV test results [28]. Nevertheless, the presence of a guardian influenced adolescents’ reasons for opting out of HIV testing in our study.

Figure 2. Reasons for not approaching adolescents for human immunodeficiency virus (HIV) testing in the emergency department (ED) (n = 2,472).

Figure 3. Reasons for declining human immunodeficiency virus (HIV) testing in the emergency department (by guardians and adolescents).
Adolescents without a guardian in ED were more likely to report a recent negative test and less likely to report a low self-perceived risk for HIV as reasons for opting out, compared with adolescents with a guardian. This difference may be explained by adolescents not wanting to disclose sexual activity in presence of the guardian. Only 6% of adolescents who accepted screening were not tested because a guardian declined the HIV test. Although this number represents a small proportion of patients in the study, these adolescents reflect a missed opportunity for HIV diagnosis and prevention.

Our study had several limitations. First, it was conducted in the setting of a city with a high HIV prevalence, in which community knowledge and acceptance of HIV testing may already have been high. Second, the study did not collect data on other factors that might affect the acceptance of HIV screening, such as ED census, primary presenting problem, and more detailed information about previous HIV screening and sexual and risk behavior. Our study provides data on routine HIV screening of a large number of adolescents in two urban pediatric EDs. To our knowledge, this is the first pediatric study evaluating the effect of the presence of a guardian on the acceptance of ED HIV screening by adolescents.

Our data on the high acceptance of HIV screening by adolescents and their guardians in two pediatric EDs provide supportive evidence of the feasibility of routine HIV screening in pediatric ED settings. Patient’s age and the presence of a guardian were significantly associated with adolescents’ decision and reasons for opting out of HIV screening in pediatric EDs. With the greatest number of new infections occurring among young Americans, HIV screening in pediatric facilities provides an excellent opportunity to reach out to these vulnerable populations. In a national survey of the pediatric ED providers, <25% of pediatric ED physicians and staff reported that they had rapid HIV testing available in the ED, and 82.5% reported that they did not believe or were unsure whether their institution had a policy or guideline about rapid HIV testing [39]. It is necessary to increase the level of comfort for pediatric providers in addressing HIV screening in pediatric EDs to efficiently confront the HIV epidemic among American youth [3,40].

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References


National HIV Testing Day, June 27, promotes the importance of testing in detecting, treating, and preventing human immunodeficiency virus (HIV) infection. HIV testing is the essential entry point to a continuum of prevention, healthcare, and social services that improve the quality of life and the length of survival for persons with HIV (1). Persons with HIV who receive appropriate treatment, monitoring, and health care also reduce their chances of transmitting HIV to others. CDC recommends that all persons aged 13–64 years be screened for HIV in health-care settings located in areas where the prevalence of undiagnosed HIV infection is >0.1%, and that persons with increased risk for HIV be retested at least annually (2).

In April 2013, the U.S. Preventive Services Task Force updated its 2005 guidelines on HIV screening, to recommend that clinicians screen all persons aged 15–65 years for HIV infection at least once, regardless of their risk; that younger adolescents and older adults with increased risk also be screened; and that persons with increased risk be screened more frequently (3). These updated recommendations are based on increasing evidence of the benefits of early antiretroviral therapy for HIV-infected persons and its effectiveness in preventing HIV transmission. Additional information is available at http://www.uspreventiveservicestaskforce.org/uspstf13/hiv/hivfinalrs.htm#summary, http://www.cdc.gov/features/hivtesting, and http://www.hivtest.cdc.gov.

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The highly infectious phase of acute human immunodeficiency virus (HIV) infection, defined as the interval between the appearance of HIV RNA in plasma and the detection of HIV-1–specific antibodies, contributes disproportionately to HIV transmission (1). The current HIV diagnostic algorithm consists of a repeatedly reactive immunoassay (IA), followed by a supplemental test, such as the Western blot (WB) or indirect immunofluorescence assay (IFA). Because current laboratory IAs detect HIV infection earlier than supplemental tests, reactive IA results and negative supplemental test results very early in the course of HIV infection have been erroneously interpreted as negative (2). To address this problem, CDC has been evaluating a new HIV diagnostic algorithm (3). This report describes two evaluations of this algorithm. An HIV screening program at a Phoenix, Arizona emergency department (ED) identified 37 undiagnosed HIV infections during July 2011–February 2013. Of these, 12 (32.4%) were acute HIV infections. An ongoing HIV testing study in three

INSIDE
495 Routine HIV Screening During Intake Medical Evaluation at a County Jail — Fulton County, Georgia, 2011–2012
504 Ongoing Dengue Epidemic — Angola, June 2013
509 QuickStats

sites identified 99 cases with reactive IA and negative supplemental test results; 55 (55.6%) had acute HIV infection. CDC and many health departments recognize that confirmatory supplemental tests can give false-negative results early in the course of HIV infection. This problem can be resolved by testing for HIV RNA after a reactive IA result and negative supplemental test result.

Early HIV IAs used either viral lysate antigens (first generation) or synthetic peptides and recombinant antigens (second generation) and detected only immunoglobulin G (IgG)-class antibodies. Most laboratories now use either third-generation IAs that detect both immunoglobulin M-class and IgG-class antibodies or fourth-generation combination antigen/antibody IAs that detect both classes of antibody and also p24 antigen (a major core protein of HIV). The p24 antigen can be detected early, before antibody appears, allowing the fourth-generation IAs to identify some HIV infections in the acute phase. In this report, fourth-generation, IA-reactive specimens with a negative supplemental test but detectable HIV-1 RNA were classified as acute HIV infection.

The current laboratory diagnostic algorithm for HIV cannot detect acute infections and misclassifies approximately 60% of HIV-2 infections as HIV-1, based on HIV-1 WB results (4). The new diagnostic algorithm evaluated in this study replaces the WB with an HIV-1/HIV-2 antibody differentiation assay as the supplemental test and includes an RNA test to resolve reactive IA with negative supplemental test results (Figure 1). In retrospective studies, this algorithm performed better than the WB at identifying HIV-antibody–positive persons, detecting acute HIV-1 infections, and diagnosing unsuspected HIV-2 infections (5,6). In this report, data from two evaluations of this algorithm are analyzed, one from an HIV testing program in Phoenix, Arizona, and the other from an ongoing HIV testing study in three sites.

In 2011, the Arizona Department of Health Services collaborated with Maricopa Integrated Health Systems* to 1) screen all adult ED patients (aged 18–64 years) for HIV who had phlebotomy for other reasons as a part of their medical care and 2) validate the new algorithm. Specimens were screened with a fourth-generation IA (Architect HIV Ag/Ab Combo Assay [Architect], Abbott Diagnostics) from July 2011 through February 2013. From July 2011 through February 2012, 10 specimens with repeatedly reactive Architect results were tested with both a WB and a Food and Drug Administration (FDA)-approved HIV-1/HIV-2 antibody differentiation assay (Multispot HIV-1/HIV-2 Rapid Test [Multispot], Bio-Rad Laboratories), and from March 2012 through February 2013, only with a Multispot (27 specimens). Specimens negative by either WB or Multispot were tested for HIV-1 RNA (m2000 RealTime HIV-1 Quantitative Assay, Abbott Diagnostics).

The Screening Targeted Populations to Interrupt On-going Chains of HIV Transmission with Enhanced Partner Notification (STOP) study is evaluating 1) methods to detect
acute HIV infection and enhance partner services in New York, New York; North Carolina; and San Francisco, California, and 2) the new diagnostic algorithm. Participants aged >12 years who received HIV testing at one of 12 venues from September 2011 through September 2012 were screened with Architect. Repeatedly reactive specimens were tested with Multispot and either an HIV-1 WB (Bio-Rad Laboratories) or an in-house IFA. Specimens with negative Multispot, WB, or IFA results were tested for HIV-1 RNA (either Aptima HIV-1 RNA Qualitative Assay [Gen-Probe] or m2000 RealTime HIV-1 Quantitative Assay).

Routine HIV screening with Architect in the Phoenix ED from July 2011 through February 2013 detected previously undiagnosed HIV infection in 37 patients (Table). The diagnosis of acute HIV infection was established by a negative supplemental test but a detectable HIV-1 RNA in 12 (32.4%) of these 37 patients. The other 25 HIV diagnoses were antibody-positive by Multispot, WB, or both. The median HIV-1 viral load among patients with acute infection was 3,636,176 copies/mL (interquartile range: 614,164 to >10,000,000), compared with 27,125 copies/mL (9,519–78,084) among patients with established infection.

In the STOP study, Architect results were repeatedly reactive in 654 (1.7%) of 37,876 patients screened from September 2011 through September 2012 (Figure 2). Multispot was reactive for HIV-1 in 554 (84.7%) patients and for both HIV-1 and HIV-2 in one (0.2%). In the 99 (15.1%) patients with a negative or HIV-1 indeterminate Multispot result, HIV-1 RNA was present in 55 (55.6%), representing 8.4% of all those with repeatedly reactive Architect results. Traditional supplemental tests (either HIV-1 WB or IFA) were negative in 37 (67.3%) and indeterminate in seven (12.7%) of these 55 Architect-reactive specimens from patients with acute HIV-1 infection (Figure 2).
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Editorial Note

Improved HIV IAs enhance the ability to detect HIV infection earlier, even during the acute phase of infection, when substantial HIV transmission occurs. However, specimens with reactive IA and negative supplemental test results must undergo further testing to differentiate acute HIV infection from false-positive results. This report demonstrates that acute HIV infections detected with third- or fourth-generation IAs often are misclassified as HIV-negative by WB or IFA, potentially leading to adverse clinical outcomes for patients and further HIV transmission within the community (1). Applying the HIV testing algorithm evaluated in this analysis averted missed diagnoses in 32% of the HIV-infected patients in the Phoenix ED and 9% of those in the STOP study.

With FDA’s approval of the Multispot HIV-1/HIV-2 rapid test for use as the second test in this algorithm in March 2013, laboratories can adopt this algorithm, which is a recommended option in the Clinical and Laboratory Standards Institute’s Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline (7). The fast turnaround time for test results from most third- and fourth-generation IAs (<1 hour) and the Multispot rapid test (15 minutes) affords the opportunity...
to deliver same-day definitive test results to the majority of HIV-infected persons who are antibody-positive. Regardless of which supplemental test is used, clinicians and laboratories might want to consider further HIV RNA testing for patients whose supplemental antibody test results are negative after a reactive third- or fourth-generation IA result (8).

The ED at Maricopa Integrated Health Systems adopted routine, opt-out HIV screening consistent with CDC’s 2006 recommendations (9), using a fourth-generation IA. As a result, an additional 37 patients with HIV infection, including 12 with acute infection, were identified. Because most currently available FDA-approved rapid HIV tests are second-generation format (i.e., they detect only IgG-class antibodies), these acute HIV infections likely would have been missed if point-of-care rapid tests had been used for screening. The high percentage of HIV infections that were acute among these ED patients was unexpected;
What is already known on this topic?
The highly infectious phase of acute human immunodeficiency virus (HIV) infection, before the appearance of HIV-1-specific antibodies, contributes disproportionately to HIV transmission. Improved HIV laboratory immunoassays (IAs) can detect HIV infection during this acute phase, when traditional HIV supplemental tests (e.g., Western blot) are still negative. Some discordant HIV test results (reactive IA and negative supplemental test) have been erroneously interpreted as HIV-negative.

What is added by this report?
Using an HIV testing algorithm that included RNA testing for all specimens with reactive IA and negative supplemental antibody test results led to the diagnosis of acute HIV infections in various HIV testing settings. Using an HIV IA to screen patients in an Arizona emergency department identified 37 undiagnosed HIV infections, of which 32.4% were acute and would have been misclassified as HIV-negative by current testing practices that rely on antibody tests such as Western blot. An ongoing multisite study of a convenience sample of persons at high risk identified 99 cases with reactive IA and negative supplemental test results; 44.4% were in patients who were not infected, but 55.6% had acute HIV infection. These acute HIV infections would have been misclassified as HIV-negative without RNA testing, potentially leading to adverse clinical outcomes for patients and further HIV transmission within the community.

What are the implications for public health practice?
For patients with a reactive HIV IA result and negative supplemental antibody test results, additional testing for HIV-1 RNA is necessary to identify patients with acute HIV infection. If RNA testing is not available, a follow-up IA should be conducted in 2–4 weeks.

however, consistent with observations that 50%–90% of persons with acute HIV infection develop symptoms that prompt them to seek medical care (10), this finding suggests that acute HIV infection in persons who seek care for its nonspecific symptoms in EDs and other urgent-care venues might go undiagnosed unless HIV screening is conducted with fourth-generation HIV IAs. Currently, only one RNA assay, the Aptima HIV-1 RNA Qualitative Assay, is FDA-approved for HIV diagnosis, but it is available in far fewer laboratories than quantitative HIV-1 (viral load) RNA assays. To facilitate prompt diagnosis of acute HIV infection when faced with discordant screening and supplemental antibody test results, clinicians can order a viral load test to differentiate acute HIV-1 infection from false-positive IA results.

The findings in this report are subject to at least two limitations. First, results might not be generalizable to all HIV screening programs. Although the goal of the Phoenix ED was to screen for HIV as many patients as possible, HIV tests might have been ordered on some patients because of clinical suspicion, potentially increasing the number of HIV or acute HIV infections identified. Second, participants in the STOP study were a convenience sample of persons at high risk for HIV infection attending sexually transmitted infection clinics or community-based HIV testing programs serving men who have sex with men. Therefore, the percentage of HIV-1 infections that were acute might be higher than that observed in other populations.

Third- and fourth-generation IAs are important advances for HIV testing that improve the ability to detect HIV infections earlier. In the two prospective evaluations described in this report, the new diagnostic testing algorithm performed better than the current algorithm for identifying HIV infections. CDC’s recommendation for a new HIV diagnostic algorithm, which will incorporate the findings of this analysis, is under development. Clinicians can use the findings from this report by remaining vigilant for discordant IA and supplemental test results and either ordering an HIV-1 nucleic acid test or obtaining follow-up HIV testing (in 2–4 weeks) to accurately determine whether HIV infection is present.

Acknowledgments

References
Routine HIV Screening During Intake Medical Evaluation at a County Jail — Fulton County, Georgia, 2011–2012

Fulton County Jail (FCJ) in Atlanta, Georgia, is one of the 50 largest jails in the nation, with an average daily census of 2,269 detainees (1). During January 1, 2011–March 15, 2012, FCJ implemented a demonstration project to integrate routine rapid human immunodeficiency virus (HIV) screening into the medical intake process. This report summarizes the results. Nearly 59% of persons booked (22,920 of 39,073) received an intake medical evaluation, and voluntary oral fluid HIV rapid screening was offered, except to those who disclosed a previous HIV diagnosis (473 [2.1%]) or were not able to provide consent. An HIV test was offered on 18,869 visits, and 12,141 HIV tests were conducted. All persons with a reactive result (120 [1.0%]) underwent confirmatory HIV testing unless they subsequently disclosed a previous HIV diagnosis. This project identified 52 persons with newly diagnosed HIV infection; 48 by rapid testing (0.4% of those tested) during the study period. All received medical care in the facility and referral for community services on release. Without this HIV screening project, these persons likely would have been diagnosed later in the course of their infection, resulting in delayed access to care and treatment, and possible transmission of HIV to their partners. Linkage to community services is critical, and coordination with the public health system and community-based organizations are essential to ensure access to HIV care and retention in treatment for persons with HIV released from jail.

Jail nursing staff provided opt-out, rapid HIV testing by oral mucosal swab as a standard component of medical services 24 hours a day, 7 days a week, except for a 6-week period (June 30–August 15, 2011) after a change in the contractor providing medical services for FCJ, when only limited, conventional HIV testing was available. A total of 39,073 bookings into FCJ occurred during the HIV screening project period, representing 31,314 persons, because some persons (17.0%) were booked more than once during this period. A newly diagnosed case of HIV was defined by Western blot laboratory confirmation of infection in a person with no record of a previous HIV diagnosis in either the Fulton County or Georgia Department of Public Health HIV surveillance registry or a FCJ medical chart. The cost per new diagnosis in this program was approximately $7,000 (2). Before implementing the demonstration project, syphilis was the only sexually transmitted infection routinely screened for during the intake medical evaluation, and HIV testing was only available on an opt-in basis. Detainees who requested an HIV test had an additional tube of blood drawn and sent to an outside laboratory for enzyme immunoassay (EIA) with reflex Western blot confirmatory testing, with results available within 14 days. During a 3-month period in 2010, when testing required phlebotomy and conventional testing, the acceptance of HIV screening was 43.2% (2,253 of 5,218 jail entrants). During this demonstration project, acceptance of HIV testing increased by 49%, to 64.3% (12,141 of 18,869), when routine rapid HIV testing of oral fluid, rather than conventional testing, was offered (p<0.001).

FCJ recorded HIV test data to determine the number and characteristics of persons newly diagnosed with HIV from January 1, 2011, through March 15, 2012. Two of 52 newly diagnosed persons received venipuncture alone in early August 2011, when rapid testing was unavailable, and two of the positive oral mucosal swabs occurred on December 29, 2010 (Table). All 52 new diagnoses were among non-Hispanic black men (n = 47) and women (n = 5). Among men with a newly diagnosed HIV infection, 38% (n = 18) reported ever having sex with men. Approximately 69% (36 of 52) of newly diagnosed persons reported a previous HIV test (range: 4 months–4 years earlier); 42% (22 of 52) reported a negative HIV test result in the past 2 calendar years, and one person had a negative HIV test result at FCJ admission 4 months earlier. Obtaining a CD4 count often was delayed until a formal medical evaluation was conducted up to 2 weeks after intake, so only 42% (22 of 52) of the cases had a CD4 cell count recorded in the medical record, with a mean of 372 cells/mm⁰. Of persons newly diagnosed with HIV, approximately 17% (nine) were detained for ≤48 hours, and nearly 58% (30) were detained ≤14 days.

Reported
TABLE. Demographic and clinical characteristics of persons newly diagnosed with HIV upon entry to Fulton County Jail — Atlanta, Georgia, 2011–2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n = 47)</th>
<th>Female (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Mean age (yrs) (SD)</td>
<td>33.7 (10.7)</td>
<td>33.3 (12.2)</td>
</tr>
<tr>
<td>Black race</td>
<td>47 (100.0)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Sexual behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>29 (61.7)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Men having sex with men</td>
<td>14 (29.8)</td>
<td>NA —</td>
</tr>
<tr>
<td>Male and female partners</td>
<td>4 (8.5)</td>
<td>ND —</td>
</tr>
<tr>
<td>Documented narcotics use</td>
<td>40 (85.1)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Previous HIV test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never tested</td>
<td>14 (29.8)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Ever tested for HIV</td>
<td>33 (70.2)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Calendar years since most recent HIV test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (24.2)</td>
<td>— —</td>
</tr>
<tr>
<td>2</td>
<td>13 (39.4)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>3</td>
<td>9 (27.3)</td>
<td>— —</td>
</tr>
<tr>
<td>4</td>
<td>3 (9.1)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Any CD4 count in jail</td>
<td>21 (44.7)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Mean first CD4 (cells/mm³) (SD)</td>
<td>372 (250)</td>
<td>374</td>
</tr>
<tr>
<td>Range</td>
<td>31–950</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>4 —</td>
<td>0 —</td>
</tr>
<tr>
<td>200–349</td>
<td>7 —</td>
<td>0 —</td>
</tr>
<tr>
<td>350–499</td>
<td>5 —</td>
<td>1 —</td>
</tr>
<tr>
<td>≥500</td>
<td>5 —</td>
<td>0 —</td>
</tr>
</tbody>
</table>

Abbreviations: HIV = human immunodeficiency virus; SD = standard deviation; NA = not applicable; ND = not determined.

Editorial Note

Diagnosis of HIV infection is the first step in accessing care and treatment services and preventing future cases of HIV infection. Providing HIV screening during the medical intake process in detention facilities can identify cases of HIV infection among persons who have not been diagnosed through other clinical or nonclinical community-based HIV testing (3). Incorporating routine HIV screening into the FCJ medical intake process resulted in 52 persons being newly diagnosed with HIV infection during the 15-month period. Consistent with findings from a previous jail study (3), available first CD4 counts were high (mean: 372 cells/mm³), indicating diagnosis relatively early in the course of disease. Without this HIV screening project, these persons would likely have been diagnosed later in the course of their infection, resulting in delayed access to care and treatment, and possible transmission of HIV to their partners.

HIV testing is a critical component of the National HIV/AIDS Strategy (4), and an estimated 49% of new infections each year are acquired from persons who are unaware of their infection (5). To prevent new cases of HIV infection in the United States, persons at-risk for HIV infection should be screened for HIV at least annually (6). However, approximately 58% of detainees at FCJ with newly diagnosed HIV infection had not been tested in the past 2 calendar years; only 15% (eight of 52) reported being tested in the past calendar year, and 31% (16 of 52) stated that they had never been tested for HIV. One person seroconverted during the period when the project was being implemented in FCJ, which warrants a strategy of routinely testing persons returning to jail after an interval of >3 months. The cost per new diagnosis in this project is lower than the cost incurred in many screening programs set in other venues (2).

Black men who have sex with men (MSM) are disproportionately infected with HIV, and an estimated 59% of black MSM are unaware of their infection (7). Nearly 40% of the black men newly diagnosed with HIV in this project reported sex with men. Making HIV screening a routine, rather than an exceptional, part of the medical evaluation process in jails in high HIV-prevalence, inner-city communities might help to decrease the stigma of HIV testing in jails and ultimately could decrease the number of persons in all risk categories who are unaware of their infection. There is no evidence of a disproportionate rate of incarceration among MSM compared with other men; however, minority populations, particularly blacks and Hispanics, are disproportionately incarcerated.
compared with whites (I). Hence, the integration of opt-out HIV screening into the intake process might decrease the number of black MSM who are unaware of their infection.

A study of routine, jail-based HIV testing conducted during 2000–2007 in Rhode Island revealed that 0.17% of tests resulted in new diagnoses (8). Although the number of newly diagnosed cases at Rhode Island’s jail declined during this observation period to 10 cases per year, the Rhode Island correctional HIV testing program was responsible for identifying 15% of all new HIV diagnoses in Rhode Island during the period. Rhode Island has one jail for the entire state; Georgia has more than 150 jails. However, the new HIV cases found at FCJ, where 41 of the 52 new cases of HIV were identified during 2011, represented approximately 5.4% (41 of 759) of all new HIV cases linked to Fulton County addresses and approximately 1.1% (41 of 3,621) of cases diagnosed in the state of Georgia that year (Jane M. Kelly; National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC; personal communication; 2013). Four additional large jails in the Atlanta metropolitan statistical area have average daily censuses of approximately 2,000–3,500 detainees (I), and none routinely screen for HIV during the medical intake evaluation. Routine, opt-out HIV testing in each of the other jails, if each had a similar rate of cases, might have identified an additional 164 persons in the Atlanta metropolitan statistical area in 2011.

The findings in this report are subject to at least three limitations. First, cases might have been misclassified as new if they previously had been diagnosed in another state and the patients failed to disclose their previous diagnosis to FCJ staff; only the state and local registry was checked. Second, the mean CD4 count at diagnosis might have been higher or lower than the value reported because the majority of newly diagnosed persons left jail before a CD4 count was obtained. Finally, the percentage of newly diagnosed persons who subsequently were linked to care after release is unknown; however, a previous demonstration project suggests that with adequate case management, a substantial percentage of these persons access care in the community (3).

The FCJ HIV screening project demonstrated that when a large jail in a high-prevalence community incorporated routine, opt-out HIV screening into the intake medical evaluation process, screening resulted in the diagnosis of persons previously unaware of their HIV infection. However, because of the very short detention period for most inmates, detainees with newly diagnosed HIV infection might be released before completion of pretreatment evaluation and initiation of HIV therapy. Linkage to community services is critical, and an opportunity exists for the public health system and community-based organizations to collaborate with jails to ensure access to HIV care and retention in treatment for persons with HIV released from jail (9,10). Research is needed to determine whether screening this population reduces transmission and prolongs survival, and whether interventions to increase linkage to community services are cost-effective.

Acknowledgments
Craig B. Borkowf, Kathy K. Byrd, Jane M. Kelly, Jonathan Mermin, Farah Parvez, Cynthia Prather, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC.

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guidelines/correctional-settings.
Homemade Chemical Bomb Incidents — 15 States, 2003–2011

Homemade chemical bombs (HCBs) are made from commonly found chemicals. The volume of news reports of HCB explosions suggests they are not uncommon. To determine the number of events involving HCBs in the United States and describe the factors associated with them, the Agency for Toxic Substances and Disease Registry (ATSDR) analyzed data from its surveillance system that tracks spills and leaks of hazardous substances. This report describes the results of that analysis, which indicated that, during 2003–2011, a total of 134 events involving HCBs were reported from 15 states. Among those events, 21 (16%) resulted in adverse health effects (i.e., respiratory symptoms, burns, and skin irritation) for 53 persons. The majority (35 [66%]) of these persons were youths. HCBs are hazardous and especially dangerous if detonated in public areas. Increasing awareness of HCBs and their dangers (particularly during summer months) among first-responders, parents, school staff members and others who work with youths might help reduce injuries associated with HCBs.

HCBs are explosives made from readily available chemicals, and instructions for making them are accessible on the Internet. Typically, HCB ingredients are combined in a container, such as a soft drink bottle, which is then sealed and shaken. HCBs explode when the pressure from gases produced by the chemical reaction ruptures the container. The resulting explosion can be unpredictable in both timing and magnitude. Potential hazards include exposure to the blast, shrapnel, and hazardous substances. This report uses data from the ATSDR Hazardous Substances Emergency Events Surveillance (HSEES) system and the National Toxic Substance Incidents Program (NTSIP), which replaced HSEES in 2010 (1), and updates a previous report (2). ATSDR has maintained a state-based surveillance program since 1990. The purpose of these surveillance systems is to track the public health consequences (e.g., morbidity and mortality) from acute toxic substance releases.

Incident records from states that participated in the surveillance program for at least 3 years during 2003–2011 were searched for the keywords “bottle,” “bomb,” or “homemade” in database fields that contain a synopsis of the event and health department comments. The resulting records were then reviewed, and those containing the keywords but not involving an HCB were excluded. Exclusions included events involving pesticide “bug bombs” or chemical bottles inadvertently broken during shipping. Events involving commercial or other, improvised explosives (e.g., pipe bombs) also were excluded.

During 2003–2011, a total of 134 events involving an HCB (0.2% of all HSEES/NTSIP events for the same period) were detected (Table). The number of participating states varied during the reporting period from 15 in 2003 to six in 2011. Notably, New York, Wisconsin, and Minnesota reported 77% of the events. Following are three illustrative case reports on HCB incidents with injuries.

Case Reports

Incident A. A high school janitor found students mixing calcium hypochlorite and other chemicals in a bottle. The janitor seized the bottle, which exploded, releasing chlorine gas. The janitor became ill and vomited, and 12 students and three school workers were treated for respiratory problems. Approximately 1,640 persons were evacuated for 5 hours while a hazardous materials team cleaned and ventilated the school.

Incident B. Two adults were preparing an HCB from hydrochloric acid and aluminum when it prematurely exploded. First responders found one adult unconscious, and both adults sustained physical trauma, respiratory symptoms, and chemical burns. They were treated at a local hospital.

Incident C. An adult picked up an HCB he found outside his home. Without warning, the HCB exploded in his hand. The man sustained trauma and chemical burns to his hand and chest.

Epidemiologic Findings

Twenty-one (16%) of the 134 events identified for the period 2003–2011 resulted in 53 persons with adverse health effects. Thirteen events had one injured person, three events had two, two events had four, two events had five, and one event (incident A) had 16 injured persons. The proportion of HCB events resulting in adverse health effects was 45% greater than that of all other HSEES/NTSIP events during the same period (16% versus 11%). The majority of injured persons were male (29 [55%]); eight (15%) were female, and sex was unknown for 16 (30%). Thirty-five injured persons (66%) were youths; 17 (32%) were adults, and age was unknown for one. Twenty-one injured persons (40%) were students at school; 20 (38%) were members of the public; seven (13%) were employees at the site of the incident, and five (9%) were police officers.

Several injured persons reported more than one adverse health effect; the total number of reported adverse health effects was 62. Respiratory symptoms were most common (26 [42%]), followed by burns (14 [23%]), skin irritation (13 [21%]), and physical trauma (six [10%]). A total of 29 injured persons (55%) were treated on the scene. Fifteen (28%) were treated at the hospital and released; five (9%) were treated at the hospital and admitted; three (6%) had untreated injuries; and treatment data were missing for one. Among all 53 injured
A total of 48 events (36%) occurred within a quarter mile of a school. Summer was the season with the greatest number of events 49 (37%), followed by fall (34 [25%]), spring (28 [21%]), and winter (23 [17%]).

A total of 48 events (36%) occurred within a quarter mile of a school. Summer was the season with the greatest number of events 49 (37%), followed by fall (34 [25%]), spring (28 [21%]), and winter (23 [17%]).

<table>
<thead>
<tr>
<th>State</th>
<th>Period of state participation</th>
<th>No. of years of state participation</th>
<th>Annualized incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>—</td>
<td>134</td>
<td>106</td>
</tr>
<tr>
<td>Colorado</td>
<td>2003–2009</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Florida</td>
<td>2005–2009</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Iowa</td>
<td>2003–2009</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Louisiana</td>
<td>2003–2011</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Michigan</td>
<td>2005–2009</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Minnesota</td>
<td>2003–2009</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Missouri</td>
<td>2003–2005</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>North Carolina</td>
<td>2003–2011</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>New Jersey</td>
<td>2003–2005, 2007</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Oregon</td>
<td>2003–2011</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Texas</td>
<td>2003–2009</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Utah</td>
<td>2003–2011</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Washington</td>
<td>2003–2009</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>2003–2011</td>
<td>23</td>
<td>9</td>
</tr>
</tbody>
</table>

* Average.

What is already known on this topic?
Homemade chemical bombs (HCBs) are made from readily available chemicals. Instructions for making HCBs are accessible on the Internet. Potential hazards from HCB explosions include exposure to the blast, shrapnel, and hazardous substances. Reports of HCB explosions are not uncommon in the United States news media; however, few data on them exist in the scientific literature.

What is added by this report?
Surveillance data from 15 states during 2003–2011 identified 134 events involving HCBs. Twenty-one (16%) events resulted in 53 injured persons with adverse health effects. The majority of these injured persons were youths with health effects associated with exposure to HCB contents, including respiratory symptoms, burns, and skin irritation.

What are the implications for public health practice?
HCBs are hazardous and especially dangerous if detonated in public areas such as schools. It is important for parents, school staff members, and law enforcement to be aware of the potential hazards of HCBs and how to respond if an HCB is found.

Editorial Note
For the period January 1996–March 2003, ATSDR reported 29 events involving HCBs (2). Standardized by state-surveillance year, the rate of HCB events in that report was 0.21 (29 events per 137 state-years). In the present report, that rate was 1.26 (134 events per 106 state-years), suggesting an increase in HCB events. This increase might be the result of greater availability of materials and Internet instructions for making HCBs, the ease with which they are made, and copycatting inspired by other incidents. However, improved HSEES/NTSIP event ascertainment also might have contributed to this increase. Participating states rely heavily on media news reports for HCB event ascertainment; for 50% of HCB events the primary reporting source was the media, versus only 5% for other hazardous substance events. In addition, HCB incidents are more likely to appear in news reports if they involve injured persons or property damage. Thus, the number of HCB incidents in HSEES/NTSIP likely is less than the actual number of events, and HCB incidents with injured persons or property damage might be overrepresented.

Although unlikely to have the injury patterns associated with high-order explosive detonations, HCB explosions have the potential to result in serious injury. In addition to blast-induced trauma, injured persons can be exposed to the chemicals released from the HCB. The most common injuries reported were respiratory symptoms, burns, and skin irritation, and these are consistent with exposure to the acids or bases frequently used in these devices. Acid and base solutions are corrosive to skin and other tissues, and both form fumes.

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that can irritate respiratory tissues when inhaled. Symptoms associated with inhalation of fumes of acids or bases include irritation of the nose, throat, and larynx; cough; and pulmonary edema (3).

The findings in this report are subject to at least three limitations. First, searching the HSEES/NTSIP databases might not capture all events involving HCBs. Second, variability in the number of HCB incidents by state might be explained by differences in state surveillance sources or by copycatting inspired by other incidents. Finally, the number of participating states is limited, and their data might not be representative of the entire United States.

These data indicate that the majority of HCB-injured persons were youths or young adults. Consequently, it is important for parents, school staff members, and law enforcement to be aware of the potential hazards of HCBs and how to respond if an HCB is found. If a suspected or actual HCB is discovered, the surrounding area should be isolated until the situation is assessed by authorities (4). Only trained bomb squad personnel should approach, handle, or attempt to neutralize these devices (2). Persons whose clothing is contaminated with the contents of a bomb, whether as a result of the container bursting or from leakage, should remove contaminated clothing immediately (2,5). If the contents of a bomb come in contact with skin, the affected area should be rinsed with large amounts of water for 3–5 minutes (5). If severe adverse health effects (e.g., trauma, chemical burns, or respiratory irritation) occur, medical attention should be sought immediately.

References
In 1988, the Global Polio Eradication Initiative (GPEI) was established through a partnership between the World Health Organization (WHO), Rotary International, CDC, and the United Nations Children’s Fund (UNICEF). By 2012, the annual incidence of polio had decreased by >99%, compared with 1988, and the number of countries in which wild poliovirus (WPV) circulation has never been interrupted was reduced to three: Afghanistan, Nigeria, and Pakistan (1). However, because of the persistence of endemic WPV transmission and recurring outbreaks in polio-free countries after the original polio eradication target date of 2000 (2–4), the World Health Assembly in 2012 declared the completion of polio eradication a programmatic emergency (5). A key component of GPEI is the Stop Transmission of Polio (STOP) program, which was developed and initiated by CDC with WHO in 1999 to mobilize additional human resources and technical assistance for countries affected by WPV transmission. During 1999–2013, 1,563 volunteers were identified, trained, and deployed for 2,221 assignments in 69 countries. The number of volunteers increased from 90–120 per year during 1999–2011 to 287 in 2012 and 378 in 2013, and the number of volunteer person-months in the field per year increased from 273 in 1999 to 1,456 in 2012. The STOP program has aided GPEI by strengthening the capacity of country-level immunization programs and by allowing a large cohort of volunteers to gain valuable field experience that prepares them well for subsequent work as staff members of WHO, UNICEF, and other public health agencies.

Development and Implementation of the STOP Program

A key factor contributing to the success of the global smallpox eradication program in the 1970s was the deployment of international public health field staff to assist national programs with smallpox outbreak investigation, surveillance, and planning of vaccination activities in endemic countries (6). In 1999, STOP was developed to support GPEI in a similar fashion. STOP teams typically comprise a diverse mix of health professionals, including nurses, physicians, epidemiologists, veterinarians, and information systems and communication specialists. The first STOP volunteers were recruited from CDC staff; however, recruitment was rapidly expanded to include public health professionals from around the world to meet the demand for assistance. STOP volunteers receive daily subsistence allowances, but no other financial remuneration. (Recently, only a small proportion of volunteers are otherwise supported by their employers.) WHO and UNICEF are responsible for assigning volunteers to specific countries to provide technical assistance and training for immunization programs at national, state/province, or district levels and volunteers are supervised by WHO and UNICEF country teams during the assignment.

The initial objectives of STOP field assignments were to conduct and support acute flaccid paralysis (AFP) surveillance and to plan, monitor, and evaluate large-scale supplementary polio immunization campaigns. Field assignment objectives were expanded in 2002 to support accelerated progress toward measles mortality reduction and development of data management systems for disease surveillance. The objectives were further expanded in 2003 to support strengthening routine childhood immunization activities, a key GPEI strategic component; in 2006 to support polio program communications and social mobilization at UNICEF country offices; and in 2011 to support the management needs of immunization and eradication teams at country level.

The STOP program recruits and deploys three types of volunteers: field staff and data managers who work with WHO country teams, and communications officers who work with UNICEF teams. Since 2009, an “enhanced” STOP program component has placed senior, experienced volunteers at the district level in the highest priority areas. All volunteers undergo 10 days of intense technical, security, and cross-cultural training at CDC in Atlanta before being deployed on field assignments of 3–5 months duration. Additional training beyond the 10 days is provided for communication and data management volunteers; volunteers assigned to Nigeria, Pakistan, and Democratic Republic of Congo receive special management training.

Scope of Volunteer Assignments

From January 1999 through June 2013, a total of 1,563 volunteers were identified, trained, and deployed for 2,221 STOP assignments to 69 countries. Among those volunteers, 456 (23%) were from the United States (256 were CDC employees). The assignments included 1,802 field assignments, 217 communications assignments, and 202 data management assignments; 558 (25%) assignments were to polio endemic countries (Afghanistan, Nigeria, Pakistan, and previously, Democratic Republic of Congo receive special management training.)

* Additional information on the STOP program and countries to which volunteers have been assigned (including map) is available at http://www.cdc.gov/polio/stop.
India). Among the assignments, 1,592 (72%) have been to English-speaking countries, 520 (23%) to French-speaking countries, and 109 (5%) to Portuguese-speaking countries. With the declaration of polio eradication as a programmatic emergency by the World Health Assembly in 2012, the number of STOP volunteers deployed increased from 90–120 per year during 1999–2011 to 287 in 2012 and 371 in 2013 (Figure); the number of volunteer person-months in the field per year increased from 273 in 1999 to 1,456 in 2012. Part of this growth in the number of person-months has resulted from an increasing number of volunteers serving on multiple assignments: 56% of the volunteers in 2013 had served in previous assignments. The STOP team deployed in February 2013 had 168 volunteers; the team deploying in July 2013 will be the largest to date, with an estimated 203 volunteers.

### Field Assignment Activities

In February 2013, a survey of 458 volunteers from STOP teams deployed at any time since February 2011 was conducted to assess activities conducted in field assignments. Among 312 (68%) volunteers who returned questionnaires, an average of 51% of their time deployed was reported to be spent on capacity-filling polio eradication activities, (e.g., active surveillance for AFP cases, AFP case verification, and updating supplemental immunization activity microplans), and an average of 49% of their time was spent on capacity-building activities (e.g., training health-care workers). The distribution of time spent on specific activities varied by country. For example, among 82 volunteers with field assignments in polio-endemic countries, an average of 68% of their time was reported to be spent conducting polio-related activities, 22% on routine childhood immunization strengthening activities, and 10% on other health programs. By comparison, among 230 volunteers with field assignments in nonendemic countries, an average of 54% of their time was spent on polio-related activities, 31% on routine immunization strengthening activities, and 15% on other health initiative activities.

### What is already known on this topic?

Since the Global Polio Eradication Initiative (GPEI) was established in 1988, the annual incidence of polio has decreased >99%, and the number of countries in which wild poliovirus (WPV) circulation had never been interrupted has been reduced to three: Afghanistan, Nigeria, and Pakistan. The Stop Transmission of Polio (STOP) program was developed and initiated by CDC with the World Health Organization in 1999 to mobilize skilled personnel and technical resources to assist countries affected by WPV transmission.

### What is added by this report?

The STOP program has become a large human resources deployment mechanism that has worked successfully for GPEI over an extended period. During 1999–2013, 1,563 volunteers were identified, trained, and deployed for 2,221 assignments as part of 42 STOP teams in 69 countries. The number and length of assignments has increased since the World Health Assembly declared the completion of polio eradication a programmatic emergency in 2012. The number of volunteers increased from 90–120 per year during 1999–2011 to 378 in 2013.

### What are the implications for public health practice?

GPEI partnership will continue the STOP program throughout the period of eradication, certification, and progressive withdrawal of oral poliovirus vaccines, as outlined in the Polio Eradication and Endgame Strategic Plan 2013–2018. The STOP model has been replicated within Nigeria and Pakistan as a public health capacity-building mechanism; national field epidemiology programs have been recruiting, training, and deploying qualified national staff members to supervise and implement GPEI activities at country level. These staff members enhance national polio eradication programs overall, and particularly in areas that are not accessible to staff of international organizations because of security concerns.

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**Reported by**

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Editorial Note

The STOP program has made an important contribution to the mission of GPEI by providing countries with critical technical support to strengthen polio eradication activities. In response to requests from countries and WHO regional offices, STOP was expanded to provide a broader range of technical support for immunization programs, and the number of volunteers was increased over time. The flexibility of the STOP program enables volunteers to fill human resource gaps or build local capacity as needed by the country in which they are working. The effectiveness of STOP field assignments might be further enhanced through management training of some STOP supervisors and consistent development of clear work plans by field supervisors, in collaboration with STOP volunteers.

The STOP program concept has served as a model for training programs elsewhere. In Pakistan (since 2011) and in Nigeria (since 2012), for example, national STOP teams of local health professionals have been specifically trained to enhance the implementation of polio eradication activities. National STOP staff members aid national GPEI programs overall, and particularly in areas that are not accessible to staff of international organizations because of security concerns.

The STOP program is a coordinated effort of multiple GPEI partners. During 2000–2012, the Canadian Public Health Association, funded by the government of Canada, collaborated with CDC to identify, recruit, and deploy French-speaking participants for the STOP program. Rotary International and the Bill and Melinda Gates Foundation have contributed to funding for STOP volunteer field assignments. WHO and UNICEF organize field assignments through their regional and country offices. In addition, partners assist during the Atlanta-based training, providing technical and logistical support. The GPEI partnership will continue the STOP program throughout the period of eradication, certification, and progressive withdrawal of oral poliovirus vaccines, as outlined in the Polio Eradication and Endgame Strategic Plan, 2013–2018 (7).

Acknowledgments

Benjamin Nkowane, MD, World Health Organization. Tim Petersen, Bill and Melinda Gates Foundation. Rotary International. Geospatial Research, Analysis, and Services Program (GRASP); Kim Porter, PhD, Global Immunization Div, Center for Global Health, CDC.

References

On June 17, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).

On April 1, 2013, the Public Health Directorate of Angola announced that six cases of dengue had been reported to the Ministry of Health of Angola (MHA). As of May 31, a total of 517 suspected dengue cases had been reported and tested for dengue with a rapid diagnostic test (RDT). A total of 313 (60.5%) specimens tested positive for dengue, including one from a patient who died. All suspected cases were reported from Luanda Province, except for two from Malanje Province. Confirmatory diagnostic testing of 49 specimens (43 RDT-positive and six RDT-negative) at the CDC Dengue Branch confirmed dengue virus (DENV) infection in 100% of the RDT-positive specimens and 50% of the RDT-negative specimens. Only DENV-1 was detected by molecular diagnostic testing. Phylogenetic analysis indicated this virus has been circulating in the region since at least 1968, strongly suggesting that dengue is endemic in Angola. Health-care professionals throughout Angola should be aware of the ongoing epidemic, the recommended practices for clinical management of dengue patients, and the need to report cases to MHA. Persons in Angola should seek medical care for acute febrile illness to reduce the risk for developing complications. Laboratory-confirmed dengue also has been reported from seven countries on four continents among persons who had recently traveled to Luanda, including 79 persons from Portugal. Angola is the third of four African countries to report a dengue outbreak in 2013. Persons returning from Africa with acute febrile illness should seek medical care, including testing for DENV infection, and suspected cases should be reported to public health authorities.

**Background**

Luanda, the capital city of Angola, has a population estimated at 5–20 million. No census has been conducted in Angola for several decades, primarily because of civil war during 1975–2002. A large proportion of the residents of Luanda live in densely populated urban slums and tenement housing. Access to health care is limited. Luanda is visited by many international business travelers, primarily because of commerce in oil.

Weak centralized surveillance for illnesses of public health importance has made it difficult for MHA to focus resources on populations in need. Although malaria is the greatest cause of morbidity and mortality in Angola (1), incidence is comparatively low in Luanda (2); however, an increase in malaria cases was detected in Luanda in 2012. Dengue was reported in travelers recently returned from Angola in 1986 and during 1999–2002 (3). Surveys conducted by the National Malaria Control Program during 2010–2012 showed that *Aedes aegypti* is the only DENV vector in Angola, and is present in all 18 provinces except Mexico.

**Epidemiologic and Laboratory Investigation**

Because routine surveillance for acute febrile illnesses, including dengue, is not well established in Angola, the number of reported fatal and nonfatal cases likely underestimates the actual number. Anecdotal reports from clinicians and residents of Luanda suggest that the number of nonmalaria acute febrile illnesses increased beginning in late January 2013, at which time dengue was included in the differential diagnosis. Testing of these cases with an RDT (Dengue Duo, Standard Diagnostics) that detects DENV nonstructural protein 1 (NS1) and anti-DENV immunoglobulin M (IgM), at the National Public Health Institute identified the first reported RDT-positive case with illness onset on March 1 (Figure 1).

The numbers of RDT-positive and RDT-negative cases began to increase noticeably in early April. A total of 517 suspected dengue cases had been reported to the National Public Health Institute with illness onset dates through May 31, of which 313 (60.5%) had specimens with RDT-positive results. RDT-positive patients were aged 0.8–77 years (median: 25 years), and 184 (59.9%) were male. Two suspected dengue cases were reported from outside Luanda Province, both from Malanje Province, including one with a specimen that was RDT-positive. Although detailed clinical information is unavailable for reported cases, one RDT-positive case has been reported with clinically significant hemorrhagic manifestations (e.g., hematemesis). In addition, one fatal RDT-positive case has been reported; however, anecdotal reports from clinicians and the public suggest that additional fatal cases occurred but were not reported to MHA.

Serum specimens from 49 suspected dengue cases with RDT results from the National Public Health Institute were sent to the CDC Dengue Branch for confirmatory diagnostic testing. Of these 49 specimens, 43 were RDT-positive (41 NS1-positive, 14 IgM-positive, and 12 positive for both NS1 and IgM) and six were RDT-negative. All specimens were tested by real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) (DENV 1–4 Real-Time RT-PCR Assay, CDC) and immunoassay for anti-DENV IgM (DENV Detect IgM Capture ELISA, InBios International). Specimens testing NS1-positive only by RDT and not confirmed by rRT-PCR were submitted to an NS1 test (Panbio Dengue Early ELISA, Alere). Current or recent DENV infection was confirmed in all of the RDT-positive specimens and in three
of the RDT-negative specimens. Only DENV-1 was detected by rRT-PCR. Direct nucleic acid sequencing from five serum specimens and subsequent phylogenetic analysis showed that the DENV-1 currently circulating in Luanda belongs to the American-African lineage (Figure 2). The closest identified ancestor of the virus was isolated from a specimen collected in Nigeria in 1968.

**Entomologic Investigation**

Household surveys of container-breeding mosquitoes were conducted throughout Luanda. A total of 862 households were surveyed, of which 385 (44.7%) had at least one container with mosquito larvae present. Of 3,103 containers examined, 724 (23.3%) were colonized by mosquitoes. Most (63.1%) colonized containers were found indoors, and most were uncovered water-storage containers. The predominant mosquito species identified was *Aedes aegypti*.

**Public Health Response**

Public health messages to alert the population of Luanda to the epidemic have been issued since April. Because public awareness of dengue in Angola is low, messaging has focused on the signs and symptoms of dengue, including how to identify warning signs of severe disease. The public also has been made aware of the need to clean up refuse and empty or cover water containers that can serve as mosquito breeding sites. Proposed biologic and chemical vector-control measures to be conducted by the National Malaria Control Program include fumigation to kill adult mosquitoes using organophosphates (fenitrothion or malathion), indoor residual spraying of households, and treating larval habitats with *Bacillus thuringiensis* israelensis. MHA worked with teams from the World Health Organization and CDC, each composed of one epidemiologist and one entomologist, to guide the public health response to the epidemic. Activities included conducting a rapid assessment of mosquito populations in Luanda, improving clinical awareness of dengue and patient management by conducting training for health-care professionals, and encouraging clinicians to use RDTs to diagnose suspected cases and send the results to the MHA. As a result, increases in case reporting were observed starting in mid-May.

![](image.png)

*FIGURE 1. Number of reported dengue cases, by rapid diagnostic test (RDT) status and date of illness onset — Angola, March 1–May 31, 2013*

*Two RDT-positive cases had no date of illness onset or specimen collection available.*
Reported by


Editorial Note

Recent data suggest that approximately 390 million DENV infections occurred worldwide in 2010, of which 96 million resulted in symptomatic illness (4). Most persons with symptomatic DENV infection will experience an acute febrile illness characterized by fever; headache; joint, muscle, and eye pain; and minor hemorrhagic manifestations (e.g., petechiae and epistaxis) that will resolve within 1 week with bed rest, oral rehydration, and avoidance of aspirin and nonsteroidal anti-inflammatory medications (5). Approximately 5% of persons with symptomatic infections can experience severe manifestations around the time of defervescence because of an increase in vascular permeability leading to plasma leakage and the potential for clinically significant pleural effusions and ascites, hypovolemic shock, severe hemorrhage (e.g., hematemesis and melena), and death. The primary factors that affect the case-fatality rate for severe dengue, which can range from <0.1% to 5%, are the timing and quality of clinical care that patients receive. Life-saving care depends on close monitoring of hemodynamic status and judicious use of intravenous fluids, especially in the 24–48 hours after fever has resolved (5).

Reporting of suspected and RDT-positive dengue cases should continue to be strengthened in Angola. However, because of deficiencies in the national reporting system, direct communication between hospitals and MHA might be the most effective means to monitor dengue activity. Of particular concern from a surveillance viewpoint is the low number of reported fatal cases, given the size of the population of Luanda and lack of experience with clinical management of severe dengue. The apparent lack of fatal case reporting might be explained by deaths that occurred outside the hospital, lack of accurate case diagnosis, lack of postmortem tissue to diagnose suspected dengue-related deaths, and lack of familiarity with how to report cases to MHA.

At least 91 laboratory-confirmed dengue cases have been reported recently in seven countries (Canada, France, Germany, Israel, Portugal, South Africa, and the United States) among persons who had recently traveled to Luanda (6,7). On May 24, CDC posted a travel notice on the Travelers’ Health website,* informing travelers and U.S. citizens living in Angola of the current dengue epidemic and reminding them to employ mosquito avoidance strategies and seek medical care for dengue-like illness. Four countries (Seychelles, Kenya, Angola, and Tanzania) thus far have reported dengue outbreaks in 2013. If travelers to Africa develop signs or symptoms of dengue during

What is already known on this topic?
Dengue is believed to be endemic in much of Africa, where an estimated 64 million dengue virus (DENV) infections occurred in 2010. Dengue has been documented previously in travelers returning from Angola, but information on the epidemiology of dengue in Angola has not been available.

What is added by this report?
This report documents an ongoing dengue epidemic in Angola that at present appears to be primarily affecting Luanda. Only DENV-1 has thus far been detected, and phylogenetic analysis indicated that the most closely related virus was isolated in Nigeria in 1968, demonstrating that this virus has been circulating in the region for at least 45 years and strongly suggesting that dengue is endemic in Angola.

What are the implications for public health practice?
Physicians and public health professionals should be aware that dengue is endemic in Angola and throughout much of Africa and that timely initiation of care of dengue patients can be life-saving. Clinicians in Africa and those examining patients with acute febrile illness and recent travel to Africa should suspect dengue and report cases to public health authorities. Or ≤14 days after their visit, they should seek medical treatment and inform their doctor of their recent travel. Clinicians in the United States are reminded that dengue is a nationally reportable condition, and cases should be reported to local public health authorities. Clinicians can obtain dengue diagnostic testing from several national testing laboratories or state public health laboratories. Residents of and travelers to areas with endemic dengue can reduce their risk for DENV infection by using mosquito repellent, wearing long-sleeved shirts and pants, and sleeping in locations with air conditioning or screens on doors and windows. Up-to-date, destination-specific dengue activity reports can be found on CDC’s DengueMap. Additional information on dengue and dengue prevention activities can be found at the CDC dengue site.

The molecular phylogeny of the DENV-1 currently circulating in Luanda indicates that the virus likely has been circulating in the region since at least 1968. This finding, in combination with reports of dengue in travelers to Angola since the 1980s, strongly suggests that dengue is endemic in Angola, as it is in much of the rest of Africa (3,4). In support of these observations, a recent study predicted that approximately 16% of all DENV infections worldwide occur in sub-Saharan Africa (4). This suggests that dengue in Africa is on par with that of the Americas, where the widespread nature of the illness is recognized. Public health and health-care professionals should be aware that dengue is endemic in Africa and should test suspected cases with available diagnostic tests, including RDTs, and ensure that test results are confirmed at reference laboratories experienced in dengue diagnostic testing. Diagnostic and confirmatory testing should be performed to confirm cases and initiate appropriate clinical treatment, enable early detection of outbreaks or epidemics, and identify the DENV-types circulating in the region.

References
In the report, “Notes from the Field: Outbreak of Poliomyelitis — Somalia and Kenya, May 2013,” the last sentence should have read as follows: "CDC also recommends that all refugees aged <18 years who have arrived from Kenya since the beginning of April 2013 receive 1 inactivated poliovirus vaccine dose regardless of vaccination history.”
From 2001–2002 to 2009–2010, the ambulatory-care visit rate for ADHD for females aged ≤18 years increased by 63%, from 3.1 to 5.0 visits per 100 population. Over the same period, the change in the visit rate for males did not follow a consistent pattern; in 2009–2010, the visit rate for males was 11.0 per 100. Throughout the period, males were more likely than females to have an ambulatory-care visit for ADHD.


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Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

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Summary

These recommendations for human immunodeficiency virus (HIV) testing are intended for all health-care providers in the public and private sectors, including those working in hospital emergency departments, urgent care clinics, inpatient services, substance abuse treatment clinics, public health clinics, community clinics, correctional health-care facilities, and primary care settings. The recommendations address HIV testing in health-care settings only. They do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans). The objectives of these recommendations are to increase HIV screening of patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons
with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States. These revised recommendations update previous recommendations for HIV testing in health-care settings and for screening of pregnant women (CDC. Recommendations for HIV testing services for inpatients and outpatients in acute-care hospital settings. MMWR 1993;42[No. RR-2]:1--10; CDC. Revised guidelines for HIV counseling, testing, and referral. MMWR 2001;50[No. RR-19]:1--62; and CDC. Revised recommendations for HIV screening of pregnant women. MMWR 2001;50[No. RR-19]:63--85).

Major revisions from previously published guidelines are as follows:

For patients in all health-care settings

- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.

For pregnant women

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.
- HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Repeat screening in the third trimester is recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.

**Introduction**

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) remain leading causes of illness and death in the United States. As of December 2004, an estimated 944,306 persons had received a diagnosis of AIDS, and of these, 529,113 (56%) had died (1). The annual number of AIDS cases and deaths declined substantially after 1994 but stabilized during 1999--2004 (1). However, since 1994, the annual number of cases among blacks, members of other racial/ethnic minority populations, and persons exposed through heterosexual contact has increased. The number of children reported with AIDS attributed to perinatal HIV transmission peaked at 945 in 1992 and declined 95% to 48 in 2004 (1), primarily because of the identification of HIV-infected pregnant women and the effectiveness of antiretroviral prophylaxis in reducing mother-to-child transmission of HIV (2).
By 2002, an estimated 38%--44% of all adults in the United States had been tested for HIV; 16--22 million persons aged 18--64 years are tested annually for HIV (3). However, at the end of 2003, of the approximately 1.0--1.2 million persons estimated to be living with HIV in the United States, an estimated one quarter (252,000--312,000 persons) were unaware of their infection and therefore unable to benefit from clinical care to reduce morbidity and mortality (4). A number of these persons are likely to have transmitted HIV unknowingly (5).

Treatment has improved survival rates dramatically, especially since the introduction of highly active antiretroviral therapy (HAART) in 1995 (6). However, progress in effecting earlier diagnosis has been insufficient. During 1990--1992, the proportion of persons who first tested positive for HIV <1 year before receiving a diagnosis of AIDS was 51% (7); during 1993--2004, this proportion declined only modestly, to 39% in 2004 (1). Persons tested late in the course of their infection were more likely to be black or Hispanic and to have been exposed through heterosexual contact; 87% received their first positive HIV test result at an acute or referral medical care setting, and 65% were tested for HIV antibody because of illness (8).

These recommendations update previous recommendations for HIV testing in health-care settings (9,10) and for screening of pregnant women (11). The objectives of these recommendations are to increase HIV screening of patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States.

Single copies of this report are available free of charge from CDC's National Prevention Information Network, telephone 800-458-5231 (Mondays--Fridays, 9:00 a.m.--8:00 p.m. ET).

Background

Definitions

**Diagnostic testing.** Performing an HIV test for persons with clinical signs or symptoms consistent with HIV infection.

**Screening.** Performing an HIV test for all persons in a defined population (12).

**Targeted testing.** Performing an HIV test for subpopulations of persons at higher risk, typically defined on the basis of behavior, clinical, or demographic characteristics (9).

**Informed consent.** A process of communication between patient and provider through which an informed patient can choose whether to undergo HIV testing or decline to do so. Elements of informed consent typically include providing oral or written information regarding HIV, the risks and benefits of testing, the implications of HIV test results, how test results will be communicated, and the opportunity to ask questions.

**Opt-out screening.** Performing HIV screening after notifying the patient that 1) the test will
be performed and 2) the patient may elect to decline or defer testing. Assent is inferred unless
the patient declines testing.

**HIV-prevention counseling.** An interactive process of assessing risk, recognizing specific
behaviors that increase the risk for acquiring or transmitting HIV, and developing a plan to
take specific steps to reduce risks (\textsuperscript{13}).

**Evolution of HIV Testing Recommendations in Health-Care Settings and for Pregnant
Women**

In 1985, when HIV testing first became available, the main goal of such testing was to protect
the blood supply. Alternative test sites were established to deter persons from using blood
bank testing to learn their HIV status. At that time, professional opinion was divided
regarding the value of HIV testing and whether HIV testing should be encouraged because no
consensus existed regarding whether a positive test predicted transmission to sex partners or
from mother to infant (\textsuperscript{14}). No effective treatment existed, and counseling was designed in
part to ensure that persons tested were aware that the meaning of positive test results was
uncertain.

During the next 2 years, the implications of positive HIV serology became evident, and in
1987, the United States Public Health Service (USPHS) issued guidelines making HIV
counseling and testing a priority as a prevention strategy for persons most likely to be infected
or who practiced high-risk behaviors and recommended routine testing of all persons seeking
treatment for STDs, regardless of health-care setting (\textsuperscript{15}). "Routine" was defined as a policy
to provide these services to all clients after informing them that testing would be conducted
(\textsuperscript{15}).

In 1993, CDC recommendations for voluntary HIV counseling and testing were extended to
include hospitalized patients and persons obtaining health care as outpatients in acute-care
hospital settings, including emergency departments (EDs) (\textsuperscript{10}). Hospitals with HIV
seroprevalence rates of $>1\%$ or AIDS diagnosis rates of $>1$ per 1,000 discharges were
encouraged to adopt a policy of offering voluntary HIV counseling and testing routinely to all
patients aged 15--54 years. Health-care providers in acute-care settings were encouraged to
structure counseling and testing procedures to facilitate confidential, voluntary participation
and to include basic information regarding the medical implications of the test, the option to
receive more information, and documentation of informed consent (\textsuperscript{10}). In 1994, guidelines
for counseling and testing persons with high-risk behaviors specified prevention counseling to
develop specific prevention goals and strategies for each person (client-centered counseling)
(\textsuperscript{16}). In 1995, after perinatal transmission of HIV was demonstrated to be substantially
reduced by administration of zidovudine to HIV-infected pregnant women and their
newborns, USPHS recommended that all pregnant women be counseled and encouraged to
undergo voluntary testing for HIV (\textsuperscript{17,18}).

In 2001, CDC modified the recommendations for pregnant women to emphasize HIV
screening as a routine part of prenatal care, simplification of the testing process so pretest
counseling would not pose a barrier, and flexibility of the consent process to allow multiple
types of informed consent (11). In addition, the 2001 recommendations for HIV testing in health-care settings were extended to include multiple additional clinical venues in both private and public health-care sectors, encouraging providers to make HIV counseling and testing more accessible and acknowledging their need for flexibility (9). CDC recommended that HIV testing be offered routinely to all patients in high HIV-prevalence health-care settings. In low prevalence settings, in which the majority of clients are at minimal risk, targeted HIV testing on the basis of risk screening was considered more feasible for identifying limited numbers of HIV-infected persons (9).

In 2003, CDC introduced the initiative Advancing HIV Prevention: New Strategies for a Changing Epidemic (19). Two key strategies of this initiative are 1) to make HIV testing a routine part of medical care on the same voluntary basis as other diagnostic and screening tests and 2) to reduce perinatal transmission of HIV further by universal testing of all pregnant women and by using rapid tests during labor and delivery or postpartum if the mother was not screened prenatally (19). In its technical guidance, CDC acknowledged that prevention counseling is desirable for all persons at risk for HIV but recognized that such counseling might not be appropriate or feasible in all settings (20). Because time constraints or discomfort with discussing their patients' risk behaviors caused some providers to perceive requirements for prevention counseling and written informed consent as a barrier (12,21--23), the initiative advocated streamlined approaches.

In March 2004, CDC convened a meeting of health-care providers, representatives from professional associations, and local health officials to obtain advice concerning how best to expand HIV testing, especially in high-volume, high-prevalence acute-care settings. Consultants recommended simplifying the HIV screening process to make it more feasible and less costly and advocated more frequent diagnostic testing of patients with symptoms. In April 2005, CDC initiated a comprehensive review of the literature regarding HIV testing in health-care settings and, on the basis of published evidence and lessons learned from CDC-sponsored demonstration projects of HIV screening in health-care facilities, began to prepare recommendations to implement these strategies. In August 2005, CDC invited health-care providers, representatives from public health agencies and community organizations, and persons living with HIV to review an outline of proposed recommendations. In November 2005, CDC convened a meeting of researchers, representatives of professional health-care provider organizations, clinicians, persons living with HIV, and representatives from community organizations and agencies overseeing care of HIV-infected persons to review CDC's proposed recommendations. Before final revision of these recommendations, CDC described the proposals at national meetings of researchers and health-care providers and, in March 2006, solicited peer review by health-care professionals, in compliance with requirements of the Office of Management and Budget for influential scientific assessments, and invited comment from multiple professional and community organizations. The final recommendations were further refined on the basis of comments from these constituents.

**Rationale for Routine Screening for HIV Infection**

Previous CDC and U.S. Preventive Services Task Force guidelines for HIV testing recommended routine counseling and testing for persons at high risk for HIV and for those in
acute-care settings in which HIV prevalence was $\geq 1\%$ (9,10,24). These guidelines proved difficult to implement because 1) the cost of HIV screening often is not reimbursed, 2) providers in busy health-care settings often lack the time necessary to conduct risk assessments and might perceive counseling requirements as a barrier to testing, and 3) explicit information regarding HIV prevalence typically is not available to guide selection of specific settings for screening (25--29).

These revised CDC recommendations advocate routine voluntary HIV screening as a normal part of medical practice, similar to screening for other treatable conditions. Screening is a basic public health tool used to identify unrecognized health conditions so treatment can be offered before symptoms develop and, for communicable diseases, so interventions can be implemented to reduce the likelihood of continued transmission (30).

HIV infection is consistent with all generally accepted criteria that justify screening: 1) HIV infection is a serious health disorder that can be diagnosed before symptoms develop; 2) HIV can be detected by reliable, inexpensive, and noninvasive screening tests; 3) infected patients have years of life to gain if treatment is initiated early, before symptoms develop; and 4) the costs of screening are reasonable in relation to the anticipated benefits (30). Among pregnant women, screening has proven substantially more effective than risk-based testing for detecting unsuspected maternal HIV infection and preventing perinatal transmission (31--33).

**Rationale for New Recommendations**

Often, persons with HIV infection visit health-care settings (e.g., hospitals, acute-care clinics, and sexually transmitted disease [STD] clinics) years before receiving a diagnosis but are not tested for HIV (34--36). Since the 1980s, the demographics of the HIV/AIDS epidemic in the United States have changed; increasing proportions of infected persons are aged <20 years, women, members of racial or ethnic minority populations, persons who reside outside metropolitan areas, and heterosexual men and women who frequently are unaware that they are at risk for HIV (37). As a result, the effectiveness of using risk-based testing to identify HIV-infected persons has diminished (34,35,38,39).

Prevention strategies that incorporate universal HIV screening have been highly effective. For example, screening blood donors for HIV has nearly eliminated transfusion-associated HIV infection in the United States (40). In addition, incidence of pediatric HIV/AIDS in the United States has declined substantially since the 1990s, when prevention strategies began to include specific recommendations for routine HIV testing of pregnant women (18,41). Perinatal transmission rates can be reduced to $<2\%$ with universal screening of pregnant women in combination with prophylactic administration of antiretroviral drugs (42,43), scheduled cesarean delivery when indicated (44,45), and avoidance of breast feeding (46).

These successes contrast with a relative lack of progress in preventing sexual transmission of HIV, for which screening rarely is performed. Declines in HIV incidence observed in the early 1990s have leveled and might even have reversed in certain populations in recent years (47,48). Since 1998, the estimated number of new infections has remained stable at approximately 40,000 annually (49). In 2001, the Institute of Medicine (IOM) emphasized
prevention services for HIV-infected persons and recommended policies for diagnosing HIV infections earlier to increase the number of HIV-infected persons who were aware of their infections and who were offered clinical and prevention services (37). The majority of persons who are aware of their HIV infections substantially reduce sexual behaviors that might transmit HIV after they become aware they are infected (5). In a meta-analysis of findings from eight studies, the prevalence of unprotected anal or vaginal intercourse with uninfected partners was on average 68% lower for HIV-infected persons who were aware of their status than it was for HIV-infected persons who were unaware of their status (5). To increase diagnosis of HIV infection, destigmatize the testing process, link clinical care with prevention, and ensure immediate access to clinical care for persons with newly identified HIV infection, IOM and other health-care professionals with expertise (25,37,50,51) have encouraged adoption of routine HIV testing in all health-care settings.

Routine prenatal HIV testing with streamlined counseling and consent procedures has increased the number of pregnant women tested substantially (52). By contrast, the number of persons at risk for HIV infection who are screened in acute-care settings remains low, despite repeated recommendations in support of routine risk-based testing in health-care settings (9,10,15,34,53,54). In a survey of 154 health-care providers in 10 hospital EDs, providers reported caring for an average of 13 patients per week suspected to have STDs, but only 10% of these providers encouraged such patients to be tested for HIV while they were in the ED (54). Another 35% referred patients to confidential HIV testing sites in the community; however, such referrals have proven ineffective because of poor compliance by patients (55). Reasons cited for not offering HIV testing in the ED included lack of established mechanisms to ensure follow-up (51%), lack of the certification perceived as necessary to provide counseling (45%), and belief that the testing process was too time-consuming (19%) (54).

With the institution of HIV screening in certain hospitals and EDs, the percentage of patients who test positive (2%--7%) often has exceeded that observed nationally at publicly funded HIV counseling and testing sites (1.5%) and STD clinics (2%) serving persons at high risk for HIV (53,56--59). Because patients rarely were seeking testing when screening was offered at these hospitals, HIV infections often were identified earlier than they might otherwise have been (29). Targeted testing programs also have been implemented in acute-care settings; nearly two thirds of patients in these settings accept testing, but because risk assessment and prevention counseling are time-consuming, only a limited proportion of eligible patients can be tested (29). Targeted testing on the basis of risk behaviors fails to identify a substantial number of persons who are HIV infected (34,35,39). A substantial number of persons, including persons with HIV infection, do not perceive themselves to be at risk for HIV or do not disclose their risks (53,56,59). Routine HIV testing reduces the stigma associated with testing that requires assessment of risk behaviors (60--63). More patients accept recommended HIV testing when it is offered routinely to everyone, without a risk assessment (54,56).

In 1999, to increase the proportion of women tested for HIV, IOM recommended 1) adopting a national policy of universal HIV testing of pregnant women with patient notification (opt-out screening) as a routine component of prenatal care, 2) eliminating requirements for extensive pretest counseling while requiring provision of basic information regarding HIV,
and 3) not requiring explicit written consent to be tested for HIV (12). Subsequent studies have indicated that these policies, as proposed by IOM and other professional organizations (12,64,65), reflect an ethical balance among public health goals, justice, and individual rights (66,67). Rates of HIV screening are consistently higher at settings that provide prenatal and STD services using opt-out screening than at opt-in programs, which require pre-test counseling and explicit written consent (52,68--74). Pregnant women express less anxiety with opt-out HIV screening and do not find it difficult to decline a test (68,74). In 2006, approximately 65% of U.S. adults surveyed concurred that HIV testing should be treated the same as screening for any other disease, without special procedures such as written permission from the patient (75).

Adolescents aged 13--19 years represent new cohorts of persons at risk, and prevention efforts need to be repeated for each succeeding generation of young persons (63). The 2005 Youth Risk Behavior Survey indicated that 47% of high school students reported that they had had sexual intercourse at least once, and 37% of sexually active students had not used a condom during their most recent act of sexual intercourse (76). More than half of all HIV-infected adolescents are estimated not to have been tested and are unaware of their infection (77,78). Among young (aged 18--24 years) men who have sex with men (MSM) surveyed during 2004--2005 in five U.S. cities, 14% were infected with HIV; 79% of these HIV-infected MSM were unaware of their infection (56). The American Academy of Pediatrics recommends that clinicians obtain information from adolescent patients regarding their sexual activity and inform them how to prevent HIV infection (79). Evidence indicates that adolescents prefer to receive this information from their health-care providers rather than from their parents, teachers, or friends (80). However, fewer than half of clinicians provide such guidance (81). Health-care providers' recommendations also influence adolescents' decision to be tested. Among reasons for HIV testing provided by 528 adolescents who had primary care providers, 58% cited their provider's recommendation as their reason for testing (82).

The U.S. Preventive Services Task Force recently recommended that clinicians screen for HIV all adults and adolescents at increased risk for HIV, on the basis that when HIV is diagnosed early, appropriately timed interventions, particularly HAART, can lead to improved health outcomes, including slower clinical progression and reduced mortality (24). The Task Force also recommended screening all pregnant women, regardless of risk, but made no recommendation for or against routinely screening asymptomatic adults and adolescents with no identifiable risk factors for HIV. The Task Force concluded that such screening would detect additional patients with HIV, but the overall number would be limited, and the potential benefits did not clearly outweigh the burden on primary care practices or the potential harms of a general HIV screening program (24,83). In making these recommendations, the Task Force considered how many patients would need to be screened to prevent one clinical progression or death during the 3-year period after screening. On the basis of evidence available for its review, the Task Force was unable to calculate benefits attributable to the prevention of secondary HIV transmission to partners (84). However, a recent meta-analysis indicated that HIV-infected persons reduced high-risk behavior substantially when they became aware of their infection (5). Because viral load is the chief biologic predictor of HIV transmission (85), reduction in viral load through timely initiation
of HAART might reduce transmission, even for HIV-infected patients who do not change their risk behavior (86). Estimated transmission is 3.5 times higher among persons who are unaware of their infection than among persons who are aware of their infection and contributes disproportionately to the number of new HIV infections each year in the United States (87). In theory, new sexual HIV infections could be reduced >30% per year if all infected persons could learn their HIV status and adopt changes in behavior similar to those adopted by persons already aware of their infection (87).

Recent studies demonstrate that voluntary HIV screening is cost-effective even in health-care settings in which HIV prevalence is low (26,27,86). In populations for which prevalence of undiagnosed HIV infection is \( \geq 0.1\% \), HIV screening is as cost-effective as other established screening programs for chronic diseases (e.g., hypertension, colon cancer, and breast cancer) (27,86). Because of the substantial survival advantage resulting from earlier diagnosis of HIV infection when therapy can be initiated before severe immunologic compromise occurs, screening reaches conventional benchmarks for cost-effectiveness even before including the important public health benefit from reduced transmission to sex partners (86).

Linking patients who have received a diagnosis of HIV infection to prevention and care is essential. HIV screening without such linkage confers little or no benefit to the patient. Although moving patients into care incurs substantial costs, it also triggers sufficient survival benefits that justify the additional costs. Even if only a limited fraction of patients who receive HIV-positive results are linked to care, the survival benefits per dollar spent on screening represent good comparative value (26,27,88).

The benefit of providing prevention counseling in conjunction with HIV testing is less clear. HIV counseling with testing has been demonstrated to be an effective intervention for HIV-infected participants, who increased their safer behaviors and decreased their risk behaviors; HIV counseling and testing as implemented in the studies had little effect on HIV-negative participants (89). However, randomized controlled trials have demonstrated that the nature and duration of prevention counseling might influence its effectiveness (90,91). Carefully controlled, theory-based prevention counseling in STD clinics has helped HIV-negative participants reduce their risk behaviors compared with participants who received only a didactic prevention message from health-care providers (90). A more intensive intervention among HIV-negative MSM at high risk, consisting of 10 theory-based individual counseling sessions followed by maintenance sessions every 3 months, resulted in reductions in unprotected sex with partners who were HIV infected or of unknown status, compared with MSM who received structured prevention counseling only twice yearly (91).

Timely access to diagnostic HIV test results also improves health outcomes. Diagnostic testing in health-care settings continues to be the mechanism by which nearly half of new HIV infections are identified. During 2000--2003, of persons reported with HIV/AIDS who were interviewed in 16 states, 44% were tested for HIV because of illness (8). Compared with HIV testing after patients were admitted to the hospital, expedited diagnosis by rapid HIV testing in the ED before admission led to shorter hospital stays, increased the number of patients aware of their HIV status before discharge, and improved entry into outpatient care (92). However, at least 28 states have laws or regulations that limit health-care providers'
ability to order diagnostic testing for HIV infection if the patient is unable to give consent for HIV testing, even when the test results are likely to alter the patient's diagnostic or therapeutic management (93).

Of the 40,000 persons who acquire HIV infection each year, an estimated 40%--90% will experience symptoms of acute HIV infection (94--96), and a substantial number will seek medical care. However, acute HIV infection often is not recognized by primary care clinicians because the symptoms resemble those of influenza, infectious mononucleosis, and other viral illnesses (97). Acute HIV infection can be diagnosed by detecting HIV RNA in plasma from persons with a negative or indeterminate HIV antibody test. One study based on national ambulatory medical care surveys estimated that the prevalence of acute HIV infection was 0.5%--0.7% among ambulatory patients who sought care for fever or rash (98). Although the long-term benefit of HAART during acute HIV infection has not been established conclusively (99), identifying primary HIV infection can reduce the spread of HIV that might otherwise occur during the acute phase of HIV disease (100,101).

Perinatal HIV transmission continues to occur, primarily among women who lack prenatal care or who were not offered voluntary HIV counseling and testing during pregnancy. A substantial proportion of the estimated 144--236 perinatal HIV infections in the United States each year can be attributed to the lack of timely HIV testing and treatment of pregnant women (102). Multiple barriers to HIV testing have been identified, including language barriers; late entry into prenatal care; health-care providers' perceptions that their patients are at low risk for HIV; lack of time for counseling and testing, particularly for rapid testing during labor and delivery; and state regulations requiring counseling and separate informed consent (103). A survey of 653 obstetrical providers in North Carolina suggested that not all health-care providers embrace universal testing of pregnant women; the strength with which providers recommended prenatal testing to their patients and the numbers of women tested depended largely on the providers' perception of the patients' risk behaviors (21). Data confirm that testing rates are higher when HIV tests are included in the standard panel of screening tests for all pregnant women (52,69,104). Women also are much more likely to be tested if they perceive that their health-care provider strongly recommends HIV testing (105). As universal prenatal screening has become more widespread, an increasing proportion of pregnant women who had undiagnosed HIV infection at the time of delivery were found to have seroconverted during pregnancy (106). A second HIV test during the third trimester for women in settings with elevated HIV incidence (≥17 cases per 100,000 person-years) is cost-effective and might result in substantial reductions in mother-to-child HIV transmission (107).

Every perinatal HIV transmission is a sentinel health event, signaling either a missed opportunity for prevention or, more rarely, a failure of interventions to prevent perinatal transmission. When these infections occur, they underscore the need for improved strategies to ensure that all pregnant women undergo HIV testing and, if found to be HIV positive, receive proper interventions to reduce their transmission risk and safeguard their health and the health of their infants.

**Recommendations for Adults and Adolescents**
CDC recommends that diagnostic HIV testing and opt-out HIV screening be a part of routine clinical care in all health-care settings while also preserving the patient's option to decline HIV testing and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. The recommendations are intended for providers in all health-care settings, including hospital EDs, urgent-care clinics, inpatient services, STD clinics or other venues offering clinical STD services, tuberculosis (TB) clinics, substance abuse treatment clinics, other public health clinics, community clinics, correctional health-care facilities, and primary care settings. The guidelines address HIV testing in health-care settings only; they do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans) (9).

Screening for HIV Infection

- In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13--64 years. Health-care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be <0.1%. In the absence of existing data for HIV prevalence, health-care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is <1 per 1,000 patients screened, at which point such screening is no longer warranted.
- All patients initiating treatment for TB should be screened routinely for HIV infection (108).
- All patients seeking treatment for STDs, including all patients attending STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavior risks for HIV infection.

Repeat Screening

- Health-care providers should subsequently test all persons likely to be at high risk for HIV at least annually. Persons likely to be at high risk include injection-drug users and their sex partners, persons who exchange sex for money or drugs, sex partners of HIV-infected persons, and MSM or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.
- Health-care providers should encourage patients and their prospective sex partners to be tested before initiating a new sexual relationship.
- Repeat screening of persons not likely to be at high risk for HIV should be performed on the basis of clinical judgment.
- Unless recent HIV test results are immediately available, any person whose blood or body fluid is the source of an occupational exposure for a health-care provider should be informed of the incident and tested for HIV infection at the time the exposure occurs.

Consent and Pretest Information

- Screening should be voluntary and undertaken only with the patient's knowledge and
understanding that HIV testing is planned.

- Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and to decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended.

- Easily understood informational materials should be made available in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.

- If a patient declines an HIV test, this decision should be documented in the medical record.

Diagnostic Testing for HIV Infection

- All patients with signs or symptoms consistent with HIV infection or an opportunistic illness characteristic of AIDS should be tested for HIV.

- Clinicians should maintain a high level of suspicion for acute HIV infection in all patients who have a compatible clinical syndrome and who report recent high-risk behavior. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection (96).

- Patients or persons responsible for the patient's care should be notified orally that testing is planned, advised of the indication for testing and the implications of positive and negative test results, and offered an opportunity to ask questions and to decline testing. With such notification, the patient's general consent for medical care is considered sufficient for diagnostic HIV testing.

Similarities and Differences Between Current and Previous Recommendations for Adults and Adolescents

Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

- HIV testing must be voluntary and free from coercion. Patients must not be tested without their knowledge.

- HIV testing is recommended and should be routine for persons attending STD clinics and those seeking treatment for STDs in other clinical settings.

- Access to clinical care, prevention counseling, and support services is essential for persons with positive HIV test results.

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Aspects of these recommendations that differ from previous recommendations are as follows:

- Screening after notifying the patient that an HIV test will be performed unless the patient declines (opt-out screening) is recommended in all health-care settings. Specific signed consent for HIV testing should not be required. General informed consent for medical care should be considered sufficient to encompass informed consent for HIV testing.
- Persons at high risk for HIV should be screened for HIV at least annually.
- HIV test results should be provided in the same manner as results of other diagnostic or screening tests.
- Prevention counseling should not be required as a part of HIV screening programs in health-care settings. Prevention counseling is strongly encouraged for persons at high risk for HIV in settings in which risk behaviors are assessed routinely (e.g., STD clinics) but should not have to be linked to HIV testing.
- HIV diagnostic testing or screening to detect HIV infection earlier should be considered distinct from HIV counseling and testing conducted primarily as a prevention intervention for uninfected persons at high risk.

Recommendations for Pregnant Women

These guidelines reiterate the recommendation for universal HIV screening early in pregnancy but advise simplifying the screening process to maximize opportunities for women to learn their HIV status during pregnancy, preserving the woman's option to decline HIV testing, and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. All women should receive HIV screening consistent with the recommendations for adults and adolescents. HIV screening should be a routine component of preconception care, maximizing opportunities for all women to know their HIV status before conception (109). In addition, screening early in pregnancy enables HIV-infected women and their infants to benefit from appropriate and timely interventions (e.g., antiretroviral medications [43], scheduled cesarean delivery [44], and avoidance of breastfeeding* [46]). These recommendations are intended for clinicians who provide care to pregnant women and newborns and for health policy makers who have responsibility for these populations.

HIV Screening for Pregnant Women and Their Infants

Universal Opt-Out Screening

- All pregnant women in the United States should be screened for HIV
infection.

- Screening should occur after a woman is notified that HIV screening is recommended for all pregnant patients and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines (opt-out screening).
- HIV testing must be voluntary and free from coercion. No woman should be tested without her knowledge.
- Pregnant women should receive oral or written information that includes an explanation of HIV infection, a description of interventions that can reduce HIV transmission from mother to infant, and the meanings of positive and negative test results and should be offered an opportunity to ask questions and to decline testing.
- No additional process or written documentation of informed consent beyond what is required for other routine prenatal tests should be required for HIV testing.
- If a patient declines an HIV test, this decision should be documented in the medical record.

Addressing Reasons for Declining Testing

- Providers should discuss and address reasons for declining an HIV test (e.g., lack of perceived risk; fear of the disease; and concerns regarding partner violence or potential stigma or discrimination).
- Women who decline an HIV test because they have had a previous negative test result should be informed of the importance of retesting during each pregnancy.
- Logistical reasons for not testing (e.g., scheduling) should be resolved.
- Certain women who initially decline an HIV test might accept at a later date, especially if their concerns are discussed. Certain women will continue to decline testing, and their decisions should be respected and documented in the medical record.

Timing of HIV Testing

- To promote informed and timely therapeutic decisions, health-care providers should test women for HIV as early as possible during each pregnancy. Women who decline the test early in prenatal care should be encouraged to be tested at a subsequent visit.
- A second HIV test during the third trimester, preferably <36 weeks of gestation, is cost-effective even in areas of low HIV prevalence and may
be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria:


--- Women who receive health care in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened.

--- Women who are known to be at high risk for acquiring HIV (e.g., injection-drug users and their sex partners, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than one sex partner during this pregnancy).

--- Women who have signs or symptoms consistent with acute HIV infection. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection (96).

Rapid Testing During Labor

- Any woman with undocumented HIV status at the time of labor should be screened with a rapid HIV test unless she declines (opt-out screening).
- Reasons for declining a rapid test should be explored (see Addressing Reasons for Declining Testing).
- Immediate initiation of appropriate antiretroviral prophylaxis (42) should be recommended to women on the basis of a reactive rapid test result without waiting for the result of a confirmatory test.

Postpartum/Newborn Testing

- When a woman's HIV status is still unknown at the time of delivery, she should be screened immediately postpartum with a rapid HIV test.
unless she declines (opt-out screening).

- When the mother's HIV status is unknown postpartum, rapid testing of the newborn as soon as possible after birth is recommended so antiretroviral prophylaxis can be offered to HIV-exposed infants. Women should be informed that identifying HIV antibodies in the newborn indicates that the mother is infected.

- For infants whose HIV exposure status is unknown and who are in foster care, the person legally authorized to provide consent should be informed that rapid HIV testing is recommended for infants whose biologic mothers have not been tested.

- The benefits of neonatal antiretroviral prophylaxis are best realized when it is initiated \( \leq 12 \) hours after birth \((110)\).

Confirmatory Testing

- Whenever possible, uncertainties regarding laboratory test results indicating HIV infection status should be resolved before final decisions are made regarding reproductive options, antiretroviral therapy, cesarean delivery, or other interventions.

- If the confirmatory test result is not available before delivery, immediate initiation of appropriate antiretroviral prophylaxis \((42)\) should be recommended to any pregnant patient whose HIV screening test result is reactive to reduce the risk for perinatal transmission.

Similarities and Differences Between Current and Previous Recommendations for Pregnant Women and Their Infants

Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

- Universal HIV testing with notification should be performed for all pregnant women as early as possible during pregnancy.

- HIV screening should be repeated in the third trimester of pregnancy for women known to be at high risk for HIV.

- Providers should explore and address reasons for declining HIV testing.

- Pregnant women should receive appropriate health education, including information regarding HIV and its transmission, as a routine part of prenatal care.

- Access to clinical care, prevention counseling, and support services is essential for women with positive HIV test results.
Aspects of these recommendations that differ from previous recommendations are as follows:

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women. Patients should be informed that HIV screening is recommended for all pregnant women and that it will be performed unless they decline (opt-out screening).
- Repeat HIV testing in the third trimester is recommended for all women in jurisdictions with elevated HIV or AIDS incidence and for women receiving health care in facilities with at least one diagnosed HIV case per 1,000 pregnant women per year.
- Rapid HIV testing should be performed for all women in labor who do not have documentation of results from an HIV test during pregnancy. Patients should be informed that HIV testing is recommended for all pregnant women and will be performed unless they decline (opt-out screening). Immediate initiation of appropriate antiretroviral prophylaxis should be recommended on the basis of a reactive rapid HIV test result, without awaiting the result of confirmatory testing.

Additional Considerations for HIV Screening

Test Results

- Communicating test results. The central goal of HIV screening in health-care settings is to maximize the number of persons who are aware of their HIV infection and receive care and prevention services. Definitive mechanisms should be established to inform patients of their test results. HIV-negative test results may be conveyed without direct personal contact between the patient and the health-care provider. Persons known to be at high risk for HIV infection also should be advised of the need for periodic retesting and should be offered prevention counseling or referred for prevention counseling. HIV-positive test results should be communicated confidentially through personal contact by a clinician, nurse, mid-level practitioner, counselor, or other skilled staff. Because of the risk of stigma and discrimination, family or friends should not be used as interpreters to disclose HIV-positive test results to patients with limited English proficiency. Active efforts are essential to ensure that HIV-infected patients receive their positive test results and linkage to clinical care, counseling, support, and prevention services. If the necessary expertise is not available in the health-care venue in which screening is performed, arrangements should be made to obtain necessary services from another clinical
provider, local health department, or community-based organization. Health-care providers should be aware that the Privacy Rule under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) prohibits use or disclosure of a patient's health information, including HIV status, without the patient's permission.

- Rapid HIV tests. Because of the time that elapses before results of conventional HIV tests are available, providing patients with their test results can be resource intensive and challenging for screening programs, especially in episodic care settings (e.g., EDs, urgent-care clinics, and STD clinics) in which continuing relationships with patients typically do not exist. The use of rapid HIV tests can substantially decrease the number of persons who fail to learn their test results and reduce the resources expended to locate persons identified as HIV infected. Positive rapid HIV test results are preliminary and must be confirmed before the diagnosis of HIV infection is established (111).

- Participants in HIV vaccine trials. Recipients of preventive HIV vaccines might have vaccine-induced antibodies that are detectable by HIV antibody tests. Persons whose test results are HIV positive and who are identified as vaccine trial participants might not be infected with HIV and should be encouraged to contact or return to their trial site or an associated trial site for the confirmatory testing necessary to determine their HIV status.

- Documenting HIV test results. Positive or negative HIV test results should be documented in the patient's confidential medical record and should be readily available to all health-care providers involved in the patient's clinical management. The HIV test result of a pregnant woman also should be documented in the medical record of her infant. If the mother's HIV test result is positive, maternal health-care providers should, after obtaining consent from the mother, notify pediatric care providers of the impending birth of an HIV-exposed infant and of any anticipated complications. If HIV is diagnosed in the infant first, health-care providers should discuss the implications for the mother's health and help her to obtain care.

Clinical Care for HIV-Infected Persons

Persons with a diagnosis of HIV infection need a thorough evaluation of their clinical status and immune function to determine their need for antiretroviral treatment or other therapy. HIV-infected persons should receive or be referred for clinical care promptly, consistent with USPHS guidelines for management of HIV-infected persons
(96). HIV-exposed infants should receive appropriate antiretroviral prophylaxis to prevent perinatal HIV transmission as soon as possible after birth (42) and begin trimethoprim-sulfamethoxazole prophylaxis at age 4--6 weeks to prevent Pneumocystis pneumonia (112). They should receive subsequent clinical monitoring and diagnostic testing to determine their HIV infection status (113).

Partner Counseling and Referral

When HIV infection is diagnosed, health-care providers should strongly encourage patients to disclose their HIV status to their spouses, current sex partners, and previous sex partners and recommend that these partners be tested for HIV infection. Health departments can assist patients by notifying, counseling, and providing HIV testing for partners without disclosing the patient's identity (114). Providers should inform patients who receive a new diagnosis of HIV infection that they might be contacted by health department staff for a voluntary interview to discuss notification of their partners.

Special Considerations for Screening Adolescents

Although parental involvement in an adolescent's health care is usually desirable, it typically is not required when the adolescent consents to HIV testing. However, laws concerning consent and confidentiality for HIV care differ among states (79). Public health statutes and legal precedents allow for evaluation and treatment of minors for STDs without parental knowledge or consent, but not every state has defined HIV infection explicitly as a condition for which testing or treatment may proceed without parental consent. Health-care providers should endeavor to respect an adolescent's request for privacy (79). HIV screening should be discussed with all adolescents and encouraged for those who are sexually active. Providing information regarding HIV infection, HIV testing, HIV transmission, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents as part of primary care (79).

Prevention Services for HIV-Negative Persons

- Risk screening. HIV screening should not be contingent on an assessment of patients' behavioral risks. However, assessment of risk for infection with HIV and other STDs and provision of prevention information should be incorporated into routine primary care of all sexually active persons when doing so does not pose a barrier to HIV testing. Even when risk information is not sought, notifying a patient that routine HIV testing will be performed might result in acknowledgement of risk behaviors and offers an opportunity to discuss HIV infection and how it can be prevented. Patients found to have risk behaviors (e.g., MSM or heterosexuals who have multiple sex partners, persons who have received a recent diagnosis of an STD, persons who exchange sex for money or drugs, or persons who engage in substance abuse) and those who want assistance with changing behaviors should be provided with or referred to HIV risk-reduction services (e.g., drug treatment, STD treatment, and prevention
counseling).

- Prevention counseling. In health-care settings, prevention counseling need not be linked explicitly to HIV testing. However, because certain patients might be more likely to think about HIV and consider their risks at the time of HIV testing, testing might present an ideal opportunity to provide or arrange for prevention counseling to assist with behavior changes that can reduce risks for acquiring HIV infection. Prevention counseling should be offered or made available through referral in all health-care facilities serving patients at high risk for HIV and at facilities (e.g., STD clinics) in which information on HIV risk behaviors is elicited routinely.

HIV/AIDS Surveillance

- Risk-factor ascertainment for HIV-infected persons. CDC recommends that providers ascertain and document all known HIV risk factors (115). Health-care providers can obtain tools and materials to assist with ascertainment and receive guidance on risk factors as defined for surveillance purposes from HIV/AIDS surveillance professionals in their state or local health jurisdiction. This risk-factor information is important for guiding public health decisions, especially for prevention and care, at clinical, local, state, and national levels.
- HIV/AIDS case reporting. All states require that health-care providers report AIDS cases and persons with a diagnosis of HIV infection to the state or local health department. Case report forms are available from the state or local health jurisdiction.
- Pediatric exposure reporting. CDC and the Council for State and Territorial Epidemiologists recommend that all states and territories conduct surveillance for perinatal HIV exposure and contact providers after receiving reports of exposed infants to determine the infant's HIV-infection status. Information concerning dates of maternal HIV tests, receipt of prenatal care, maternal and neonatal receipt of antiretroviral drugs, mode of delivery, and breastfeeding is collected on the pediatric HIV/AIDS case report form (115).

Monitoring and Evaluation

Recommended thresholds for screening are based on estimates of the prevalence of undiagnosed HIV infection in U.S. health-care settings, for which no accurate recent data exist. The optimal frequency for retesting is not yet known. Cost-effectiveness parameters for HIV screening were based on existing program models, all of which include a substantial counseling component, and did not consistently consider secondary infections averted as a benefit of screening. To assess the need for revised thresholds for screening adults and adolescents or repeat screening of pregnant women and to confirm their continued effectiveness, screening programs should monitor the yield of new
diagnoses of HIV infection, monitor costs, and evaluate whether patients with a
diagnosis of HIV infection are linked to and remain engaged in care. With minor
modifications, laboratory information systems might provide a practical alternative for
clinicians to use in determining HIV prevalence among their patients who are screened
for HIV.

Primary Prevention and HIV Testing in Nonclinical Settings

These revised recommendations are designed to increase HIV screening in health-care
settings. Often, however, the population most at risk for HIV includes persons who are
least likely to interact with the conventional health-care system (47,116). The need to
maintain primary prevention activities, identify persons at high risk for HIV who could
benefit from prevention services, and provide HIV testing for persons who are at high
risk for HIV in nonclinical venues remains undiminished. New approaches (e.g.,
enlisting HIV-infected persons and HIV-negative persons at high risk for HIV to recruit
persons from their social, sexual, and drug-use networks for counseling, testing, and
referral) have demonstrated considerable efficacy for identifying persons who were
previously unaware of their HIV infection (117).

Regulatory and Legal Considerations

These public health recommendations are based on best practices and are intended to
comply fully with the ethical principles of informed consent (67). Legislation related to
HIV and AIDS has been enacted in every state and the District of Columbia (118), and
specific requirements related to informed consent and pretest counseling differ among
states (119). Certain states, local jurisdictions, or agencies might have statutory or other
regulatory impediments to opt-out screening, or they might impose other specific
requirements for counseling, written consent, confirmatory testing, or communicating
HIV test results that conflict with these recommendations. Where such policies exist,
jurisdictions should consider strategies to best implement these recommendations within
current parameters and consider steps to resolve conflicts with these recommendations.

Other Guidelines

Issues that fall outside the scope of these recommendations are addressed by other
USPHS guidelines (Box 1). Because concepts relevant to HIV management evolve
rapidly, USPHS updates recommendations periodically. Current updates are available
from the National Institutes of Health at http://AIDSinfo.nih.gov. Additional guidelines
have been published by CDC and the U.S. Department of Health and Human Services,
Office for Civil Rights (Box 2).

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* To eliminate the risk for postnatal transmission, HIV-infected women in the United States should not breastfeed. Support services for use of appropriate breast milk substitutes should be provided when necessary. In international settings, UNAIDS and World Health Organization recommendations for HIV and breastfeeding should be followed (46).

† A second HIV test in the third trimester is as cost-effective as other common health interventions when HIV incidence among women of childbearing age is ≥17 HIV cases per 100,000 person-years (107). In 2004, in jurisdictions with available data on HIV case rates, a rate of 17 new HIV diagnoses per year per 100,000 women aged 15--45 years was associated with an AIDS case rate of at least nine AIDS diagnoses per year per 100,000 women aged 15--45 years (CDC, unpublished data, 2005). As of 2004, the jurisdictions listed above exceeded these thresholds. The list of specific jurisdictions where a second test in the third trimester is recommended will be updated periodically based on surveillance data.

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Box 1

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Box 2
Questions or messages regarding errors in formatting should be addressed to mmwrq@cdc.gov.

Date last reviewed: 9/12/2006
What’s New in the Pediatric Guidelines (Last updated February 12, 2014; last reviewed February 12, 2014)

Key changes made by the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) to update the November 1, 2012, Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection are summarized below. Some content has been reorganized and condensed to enhance usability. Throughout the document, text and references have been updated to include new publications where relevant. The terms “mother-to-child transmission (MTCT)” and “prevention of mother-to-child transmission (PMTCT)” have been replaced with “perinatal transmission” and “prevention of perinatal transmission,” respectively. Minor revisions have been made in toxicity tables and other sections of the document; all changes are highlighted throughout the guidelines. A link to the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children (published November 6, 2013), has been inserted in selected areas of the text to refer readers to more detailed information about use of specific antiretroviral (ARV) agents in the context of hepatitis B, hepatitis C, or tuberculosis coinfection (see the Pediatric Opportunistic Infections Guidelines).

Diagnosis of HIV Infection

- To address the possibility that the sensitivity of diagnostic virologic assays in HIV-exposed infants might be affected by combination ARV prophylaxis, the Panel recommends if the results of prior virologic testing were negative while an infant was receiving prophylaxis, virologic diagnostic testing should be considered 2 to 4 weeks after cessation of ARV prophylaxis for infants receiving combination ARV infant prophylaxis (BIII).

Clinical and Laboratory Monitoring of Pediatric HIV Infection

- Two former sections titled Laboratory Monitoring of Pediatric HIV Infection Prior to Therapy Initiation and Monitoring Children on Antiretroviral Therapy have been combined into a single section with revisions that reflect this modification.

- The Panel now recommends that CD4 T lymphocyte (CD4) cell count/percentage can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy, and who have CD4 levels well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years (BII).

- The Panel has reviewed and updated the schedule for clinical and laboratory monitoring of children before and after initiation of combination antiretroviral therapy (cART) in Table 3.

When to Start Antiretroviral Therapy

- The Panel provides information related to the recent report of “functional cure” in an HIV-infected child in Mississippi, discusses the lack of pharmacokinetic (PK) and safety data for most drugs in preterm infants and infants aged <2 weeks, recommends that providers considering treatment for these groups contact a pediatric HIV expert for guidance, and notes that if early treatment is initiated and a child is shown to be infected, the Panel does not recommend empiric treatment interruption unless the durability of the findings in the Mississippi baby can be replicated. In addition, the Panel recommends initiation of cART in children of all ages with HIV RNA levels >100,000 copies/mL (AII).

What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children

- This section has been reorganized, and some content has been moved to a new, separate section about what drugs should not be started in ARV-naive children.
• Once-daily darunavir in combination with ritonavir is now recommended as a component of a once-daily regimen in adolescents aged ≥12 years.

• Raltegravir, an integrase strand inhibitor (INSTI), is now considered as an agent for Use in Special Circumstances for initial therapy in a cART regimen for ARV-naive pediatric patients despite limited data in children, because of its favorable safety profile, lack of significant drug interactions, and palatability.

• The Panel suggests that clinically stable children with undetectable viral load and stable CD4 counts for more than 6 months can switch from twice-daily to once-daily abacavir as a component of a once-daily regimen.

• The Panel modified its recommendation for fosamprenavir in combination with ritonavir in children aged ≥6 months from “Alternative Option” to “Use in Special Circumstances” due to concerns about the required volume of the liquid formulation and the availability of other Alternative regimens without such problems.

• A section has been added on special considerations for treatment of premature infants and infants younger than age 15 days, discussing lack of PK data to define appropriate dosing in this age group, and consultation with a pediatric expert is recommended if providers consider treating such infants.

What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children

• A new table has been added summarizing the rationale for not recommending specific ARV regimens or components for initial therapy (see Table 8).

Management of Children Receiving Combination Antiretroviral Therapy

• The former section on “Management of Treatment-Experienced Infants, Children, and Adolescents Receiving Antiretroviral Therapy” has been retitled and restructured into 3 sections:
  1) Modifying ARV regimens in children on effective cART for simplification or improved adverse effect profile
  2) Recognizing and managing treatment failure
  3) Considerations about interruptions in therapy.

• New guidance and a new table (Table 12) is provided about modifying ARV regimens for reasons of improved pill burden, palatability, tolerability, and use of once-daily dosing in children with sustained virologic suppression on their current regimen. The Panel now recommends that changing to a new regimen should be considered in children who have sustained virologic suppression on their current regimen, in order to facilitate continued adherence and increase safety (BII).

• The Panel has added a recommendation indicating that, outside of the context of a clinical trial, structured interruptions of cART are not recommended in the clinical care of HIV-infected children (AIII).

Role of Therapeutic Drug Monitoring in the Management of Pediatric HIV Infection

• This section has been expanded to provide graded strength recommendations on evaluating plasma concentrations for ARV treatment-naive and treatment-experienced children.

• Evaluation of plasma concentrations of ARV drugs, while not routinely required in the management of HIV-infected pediatric patients, should be considered in children on ART in the following scenarios: (BII)
  ○ Use of ARV drugs with limited PK data and therapeutic experience in children (e.g., use of efavirenz in children aged <3 years and darunavir with once-daily dosing in children aged <12 years)
• Significant drug-drug interactions and food-drug interactions
• Unexpected suboptimal treatment response (e.g., lack of virologic suppression with history of medical adherence and lack of resistance mutations)
• Suspected suboptimal absorption of the drug
• Suspected dose-dependent toxicity

- Specific recommendations for monitoring plasma concentrations are provided for use of efavirenz in children aged <3 years and darunavir with once-daily dosing in children aged <12 years.

- Evaluation of the genetic G516T polymorphism of drug metabolizing enzyme cytochrome P450 (CYP450) 2B6 is also recommended for children aged <3 years receiving efavirenz because of the significant association of this polymorphism with drug concentrations (AII).

**Antiretroviral Drug Resistance Testing**
- **Table 17**, summarizing recommendations for use of available resistance testing, has been added.

**Pediatric Antiretroviral Drug Information**
- Updates with new pediatric data are provided when relevant to specific drugs. Subheadings have been added to the Pediatric Use section to enhance the ability to locate specific information.

**Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors**
- **Abacavir**: The Panel provides recommendations on once-daily dosing of abacavir in children. In clinically stable children with undetectable viral loads and stable CD4 cell counts for more than 6 months, switching from twice-daily to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose to maximum of 600 mg once daily) is recommended as part of a once-daily regimen.

**Non-Nucleoside Analogue Reverse Transcriptase Inhibitors**
- **Efavirenz**: The Food and Drug Administration (FDA) has approved efavirenz for use in infants and children aged ≥3 months and weighing ≥3.5 kg. However, the Panel recommends that efavirenz generally not be used in children aged 3 months to <3 years because of insufficient data on dosing, and concerns about the potential for underdosing or excessive exposure associated with the CYP 2B6 genotype. Information is provided about use in children aged 3 months to <3 years, including evaluation of the CYP 2B6 genotype prior to dosing and therapeutic drug monitoring. Instructions have been added about the use of capsules as a sprinkle preparation with food or formula.
- **Nevirapine**: The Panel provides information on the newly available 100-mg extended release (XR) tablets and nevirapine XR dosing in children aged ≥6 years. Supporting information and consideration of initiating full-dose nevirapine (rather than lead-in dosing) in children are discussed. The Panel recommends that children aged ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine XR without lead-in dosing as long as plasma RNA is undetectable. A new section has been added to discuss the potential use of nevirapine in HIV-infected infants aged <14 days or in premature infants.

**Protease Inhibitors**
- **Atazanavir**: Modifications have been made in the dosing table because the 250-mg dose is no longer achievable with currently available capsule dose strengths; 100-mg capsules have been discontinued. The panel discusses new dosing recommendations and notes that some experts would increase the atazanavir dose to 300 mg for children weighing ≥35 kg to avoid
underdosing, especially when administered with tenofovir, which decreases plasma atazanavir concentrations.

- **Darunavir:** In February 2013, the FDA approved once-daily dosing of darunavir in children aged >3 years and weight >10 kg, based on population PK modeling. A pediatric trial evaluating once-daily darunavir with ritonavir dosing in children aged 6 to <12 years has not been conducted and no efficacy data have been obtained. Therefore, the Panel recommends that once-daily darunavir with ritonavir should be used only in treatment-naive and treatment-experienced adolescents aged ≥12 years without darunavir resistance-associated mutations. Twice-daily dosing of darunavir with ritonavir should continue to be used in children aged >3 years and <12 years.

**Integrase Strand Transfer Inhibitors**

- **Dolutegravir:** Information has been added on dolutegravir, which is now FDA-approved for use in adults and children aged ≥12 years and weight ≥40 kg who are treatment-naive or treatment-experienced and integrase strand transfer inhibitor (INSTI)-naive. The Panel notes that dolutegravir is not approved for use in children aged <12 years, but that a clinical trial in treatment-experienced children aged <12 years is under way.

- **Raltegravir:** Raltegravir is now available as an oral suspension that has been FDA-approved for use in infants and children aged ≥4 weeks and weighing 3 kg to <20 kg. This formulation is supplied as a single-use packet to be reconstituted and used within 30 minutes of mixing; unused solution should be discarded.
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Members of the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children  (Last updated February 12, 2014; last reviewed February 12, 2014)

These updated Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection were developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) convened by the Office of AIDS Research Advisory Committee (OARAC) and supported by the National Resource Center at the François-Xavier Bagnoud Center (FXBC), Rutgers, The State University of New Jersey; the Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH).

<table>
<thead>
<tr>
<th>Panel Co-Chairs</th>
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<tbody>
<tr>
<td>Peter L. Havens, MS, MD</td>
<td>Medical College of Wisconsin, Children’s Hospital of Wisconsin, Milwaukee, WI</td>
</tr>
<tr>
<td>Russell Van Dyke, MD</td>
<td>Tulane University School of Medicine, New Orleans, LA</td>
</tr>
<tr>
<td>Geoffrey A. Weinberg, MD</td>
<td>University of Rochester School of Medicine and Dentistry, Rochester, NY</td>
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<tr>
<td>Lynne Mofenson, MD</td>
<td>National Institutes of Health, Bethesda, MD</td>
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<th>Members of the Panel</th>
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<tr>
<td>Elaine J. Abrams, MD</td>
<td>Columbia University, New York, NY</td>
</tr>
<tr>
<td>Allison Agwu, MD, SCM</td>
<td>Johns Hopkins School of Medicine, Baltimore, MD</td>
</tr>
<tr>
<td>Ben Banks, MPH, BSW</td>
<td>Ashland, VA</td>
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<tr>
<td>Edmund V. Capparelli,PharmD</td>
<td>University of California–San Diego, La Jolla, CA</td>
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<tr>
<td>Ellen G. Chadwick, MD</td>
<td>Northwestern University, Chicago, IL</td>
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<tr>
<td>Rana Chakraborty, MD, MS, PhD</td>
<td>Emory University School of Medicine, Atlanta, GA</td>
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<td>Diana F. Clarke, PharmD</td>
<td>Boston Medical Center, Boston, MA</td>
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<tr>
<td>Patricia M. Flynn, MD</td>
<td>St. Jude Children’s Research Hospital, Memphis, TN</td>
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<tr>
<td>Marc D. Foca, MD</td>
<td>Columbia University, New York, NY</td>
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<tr>
<td>Paul A. Kroghstad, MD</td>
<td>University of California–Los Angeles, Los Angeles, CA</td>
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<tr>
<td>James B. McAuley, MD, MPH, DTM&amp;H</td>
<td>Rush University Medical Center, Chicago, IL</td>
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<tr>
<td>Ann J. Melvin, MD, MPH</td>
<td>Seattle Children’s Hospital, University of Washington, Seattle, WA</td>
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<td>Mark Mirochnick, MD</td>
<td>Boston University School of Medicine, Boston, MA</td>
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<tr>
<td>Paul Palumbo, MD</td>
<td>Geisel School of Medicine at Dartmouth, Lebanon, NH</td>
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<tr>
<td>Mary E. Paul, MD</td>
<td>Baylor College of Medicine, Houston, TX</td>
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<tr>
<td>Vicki B. Peters, MD</td>
<td>New York City Department of Health and Mental Hygiene, New York, NY</td>
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<tr>
<td>Eva Janzen Powell, BA</td>
<td>Chicago, IL</td>
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<tr>
<td>Natella Rakhmanina, MD, PhD</td>
<td>Children’s National Medical Center, Washington, DC</td>
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<tr>
<td>Theodore D. Ruel, MD</td>
<td>University of California–San Francisco, San Francisco, CA</td>
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<tr>
<td>Richard M. Rutstein, MD</td>
<td>Children’s Hospital of Philadelphia, Philadelphia, PA</td>
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<tr>
<td>Dorothy Shaw, BA</td>
<td>Birmingham, AL</td>
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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection ix

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/2/2014
### Members from the Department of Health and Human Services

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Brian Feit, MPA</td>
<td>Health Resources and Services Administration, Rockville, MD</td>
</tr>
<tr>
<td>Mindy Golatt, MPH, MA, RN, CPNP</td>
<td>Health Resources and Services Administration, Rockville, MD</td>
</tr>
<tr>
<td>Rohan Hazra, MD</td>
<td>National Institutes of Health, Bethesda, MD</td>
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<tr>
<td>Patrick Jean-Philippe, MD</td>
<td>Henry Jackson M. Foundation-Division of AIDS, National Institutes of Health, Bethesda, MD</td>
</tr>
<tr>
<td>Linda Lewis, MD</td>
<td>Food and Drug Administration, Silver Spring, MD</td>
</tr>
<tr>
<td>George K. Siberry, MD, MPH</td>
<td>National Institutes of Health, Bethesda, MD</td>
</tr>
<tr>
<td>Allan W. Taylor, MD, MPH</td>
<td>Centers for Disease Control and Prevention, Atlanta, GA</td>
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### Non-Voting Observer

<table>
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<tr>
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<tr>
<td>Jason Brophy, MD, MSc, DTM&amp;H</td>
<td>Children’s Hospital of Eastern Ontario, Ottawa ON</td>
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### Non-Voting Observers from the François-Xavier Bagnoud Center, School of Nursing, Rutgers, the State University of New Jersey

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<tr>
<td>Carolyn Burr, RN, EdD</td>
<td>François-Xavier Bagnoud Center, Rutgers School of Nursing, Newark, NJ</td>
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<tr>
<td>Deborah Storm, MSN, PhD</td>
<td>François-Xavier Bagnoud Center, Rutgers School of Nursing, Newark, NJ</td>
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## HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children Financial Disclosure

(Last updated December 2013; last reviewed December 2013)

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<th>Name</th>
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<tr>
<td>Abrams, Elaine J.</td>
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<td>Weinberg, Geoffrey A.</td>
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Key to Abbreviations: C = Co-Chair; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; HHS = Member from HHS; M = Member; N/A = Not Applicable; NVO= Non-Voting Observer.
Introduction  (Last updated February 12, 2014; last reviewed February 12, 2014)

These guidelines address the use of combination antiretroviral therapy (cART) for HIV-infected infants, children, and adolescents (through puberty). Included is information on management of adverse events associated with use of antiretroviral (ARV) drugs in children and details on pediatric data related to ARV agents. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, a working group of the Office of AIDS Research Advisory Council (OARAC), reviews new data on an ongoing basis and provides regular updates to the guidelines. The guidelines are available on the AIDSinfo website at http://aidsinfo.nih.gov.

Also available on the AIDSinfo website are separate sets of guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children1 and for the use of ARV agents in HIV-infected (postpubertal) adolescents and adults.2 Because these guidelines are developed for the United States, they may not be applicable in other countries. The World Health Organization (WHO) provides guidelines for resource-limited settings at http://www.who.int/hiv/pub/arv/en.

Advances in medical management, based on results of clinical trials of cART in children, have dramatically reduced morbidity and mortality in HIV-infected children in the United States since the guidelines were first developed in 1993 (with the support of the François-Xavier Bagnoud Center, Rutgers, the State University of New Jersey). HIV mortality has decreased by more than 80% to 90% since the introduction of protease inhibitor (PI)-containing combinations and opportunistic and other related infections have significantly declined in the era of cART.3,4 Resistance testing has enhanced the ability to choose effective initial regimens as well as second- or third-line regimens. Therapeutic strategies continue to focus on timely initiation of ARV regimens capable of maximally suppressing viral replication in order to prevent disease progression, preserve or restore immunologic function, and reduce the development of drug resistance. At the same time, availability of new drugs and drug formulations has led to more potent regimens with lower toxicity, lower pill burdens, and less frequent medication administration, all factors that are associated with better adherence and outcomes. The use of ARV drugs in HIV-infected pregnant women has resulted in a dramatic decrease in the rate of HIV transmission to infants in the United States, to less than 2%. The number of infants with AIDS in the United States continues to decline because of the low rate of new infant HIV infections and the availability of cART to prevent AIDS in HIV-infected infants.5,6 Finally, as a group, children living with HIV infection are growing older, bringing new challenges related to adherence, drug resistance, reproductive health planning, transition to adult medical care, and potential for long-term complications from HIV and its treatments.

The pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of cART are similar for all HIV-infected people, but unique considerations exist for HIV-infected infants, children, and adolescents, including:

• Acquisition of infection through perinatal exposure for most infected children;

• In utero, intrapartum, and/or postpartum neonatal exposure to ARV drugs in most perinatally infected children;

• Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants younger than age 18 months;

• Age-specific differences in interpreting CD4 T lymphocyte (CD4) cell counts;

• Higher viral loads in perinatally-infected infants compared to HIV-infected adolescents and adults;

• Changes in pharmacokinetic (PK) parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
• Differences in the clinical manifestations and treatment of HIV infection secondary to onset of infection in growing, immunologically immature individuals; and

• Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

These recommendations represent the current state of knowledge regarding the use of ARV drugs in children and are based on published and unpublished data regarding the treatment of HIV infection in infants, children, adolescents, and adults, and when no definitive data were available, on the clinical expertise of the Panel members. The Panel intends the guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.

Guidelines Development Process

An outline of the composition of the Panel and the guidelines process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process (page 1 of 2)

<table>
<thead>
<tr>
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<th>Comment</th>
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<tbody>
<tr>
<td>Goal of the Guidelines</td>
<td>Provide guidance to HIV care practitioners on the optimal use of ARV agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States.</td>
</tr>
<tr>
<td>Panel Members</td>
<td>The Panel is composed of approximately 32 voting members who have expertise in management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, ex officio member of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the Panel Roster.</td>
</tr>
<tr>
<td>Financial Disclosure</td>
<td>All members of the Panel submit a financial disclosure statement in writing annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDSinfo website (<a href="http://aidsinfo.nih.gov">http://aidsinfo.nih.gov</a>).</td>
</tr>
<tr>
<td>Users of the Guidelines</td>
<td>Providers of care to HIV-infected infants, children, and adolescents</td>
</tr>
<tr>
<td>Developer</td>
<td>Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC</td>
</tr>
<tr>
<td>Funding Source</td>
<td>Office of AIDS Research, NIH and Health Resources and Services Administration</td>
</tr>
<tr>
<td>Evidence Collection</td>
<td>A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the François-Xavier Bagnoud Center and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.</td>
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<td>Recommendation Grading</td>
<td>Described in Table 2.</td>
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<tr>
<td>Method of Synthesizing Data</td>
<td>Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals endorsed by a consensus of members are included in the guidelines as official Panel recommendations.</td>
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### Table 1. Outline of the Guidelines Development Process (page 2 of 2)

<table>
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<td>Other Guidelines</td>
<td>These guidelines focus on HIV-infected infants, children, and adolescents through puberty. For more detailed discussion of issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of cART in HIV-infected pregnant women and interventions for prevention of perinatal transmission, cART for nonpregnant HIV-infected adults and postpubertal adolescents, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDSinfo website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>).</td>
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<tr>
<td>Update Plan</td>
<td>The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDSinfo website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed, with updates as appropriate, at least once yearly.</td>
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<tr>
<td>Public Comments</td>
<td>A 2-week public comment period follows release of the updated guidelines on the AIDSinfo website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at <a href="mailto:contactus@aidsinfo.nih.gov">contactus@aidsinfo.nih.gov</a>.</td>
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</table>

### Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommendation includes a letter (A, B, or C) that represents the strength of the recommendation and a Roman numeral (I, II, or III) that represents the quality of the evidence that supports the recommendation.

Because licensure of drugs in children often is based on efficacy data from adult trials in addition to safety and PK data in children, recommendations for ARV drugs may need to rely, in part, on data from clinical trials or studies in adults. Pediatric drug approval may be based on evidence from adequate and well-controlled investigations in adults if:

1) The course of the disease and the effects of the drug in the pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients;

2) Supplemental data exist on PKs of the drug in children indicating that systemic exposure in adults and children are similar; and

3) Studies are provided that support the safety of the drug in pediatric patients.7

Studies relating activity of the drug to drug levels (pharmacodynamic data) in children also should be available if there is a concern that concentration-response relationships might be different in children. In many cases, evidence related to use of ARV drugs is substantially greater from adult studies (especially randomized clinical trials) than from pediatric studies. Therefore, for pediatric recommendations, the following rationale has been used when the quality of evidence from pediatric studies is limited:

#### Quality of Evidence Rating I—Randomized Clinical Trial Data

In the absence of large pediatric randomized trials, adult data may be used if there are substantial pediatric data consistent with high-quality adult studies.

- Quality of Evidence Rating I will be used if there are data from large randomized trials in children with clinical and/or validated laboratory endpoints.
• Quality of Evidence Rating I* will be used if there are high-quality randomized clinical trial data in adults with clinical and/or validated laboratory endpoints and pediatric data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes that are consistent with the adult studies. A rating of I* may be used for quality of evidence if, for example, a randomized Phase III clinical trial in adults demonstrates a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

Quality of Evidence Rating II—Nonrandomized Clinical Trials or Observational Cohort Data

In the absence of large, well-designed, pediatric, nonrandomized trials or observational data, adult data may be used if there are sufficient pediatric data consistent with high-quality adult studies.

• Quality of Evidence Rating II will be used if there are data from well-designed nonrandomized trials or observational cohorts in children.

• Quality of Evidence Rating II* will be used if there are well-designed nonrandomized trials or observational cohort studies in adults with supporting and consistent information from smaller nonrandomized trials or cohort studies with clinical outcome data in children. A rating of II* may be used for quality of evidence if, for example, a large observational study in adults demonstrates clinical benefit to initiating treatment at a certain CD4 cell count and data from smaller observational studies in children indicate that a similar CD4 cell count is associated with clinical benefit.

Quality of Evidence Rating III—Expert opinion

The criteria do not differ for adults and children.

In an effort to increase the amount and improve the quality of evidence available for guiding management of HIV infection in children, the discussion of available trials with children and their caregivers is encouraged. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDSinfo website (http://aidsinfo.nih.gov/ClinicalTrials/) or by telephone at 1-800-448-0440.

Table 2. Rating Scheme for Recommendations

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials in children with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>I*: One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints plus accompanying data in children from one or more well-designed, non randomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>II: One or more well-designed, non-randomized trials or observational cohort studies in children with long-term clinical outcomes</td>
</tr>
<tr>
<td></td>
<td>II*: One or more well-designed, non-randomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children from one or more smaller non-randomized trials or cohort studies with clinical outcome data</td>
</tr>
<tr>
<td></td>
<td>III: Expert opinion</td>
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</tbody>
</table>

* Studies that include children or children and adolescents, but not studies limited to postpubertal adolescents

References


In order to best prevent infant HIV infection and start therapy as soon as possible in those who become infected, HIV infection should be identified as early in pregnancy as possible. Universal HIV counseling and voluntary HIV testing are recommended as the standard of care for all pregnant women in the United States by The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel), the U.S. Public Health Service (USPHS), the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force.\(^1-6\) All HIV testing should be performed in a manner consistent with state and local laws. The Centers for Disease Control and Prevention (CDC) recommends the “opt-out” approach, which involves notifying pregnant women that HIV testing will be performed as part of routine care unless they choose not to be tested for HIV. The “opt-in” approach involves obtaining specific consent before testing and has been associated with lower testing rates. The mandatory newborn HIV testing approach involves testing of newborns for perinatal HIV exposure with or without maternal consent.

Early identification of HIV-infected women is crucial for their health and for the care of their children, whether the children are infected or not. Knowledge of antenatal maternal HIV infection enables:

- HIV-infected women to receive appropriate combination antiretroviral therapy (cART) and prophylaxis against opportunistic infections for their own health, which may also decrease risk of transmission to their partners\(^4,7,8\).
• Providing cART to the mother during pregnancy and labor, and antiretroviral (ARV) prophylaxis to the newborn to reduce the risk of perinatal transmission of HIV transmission;6

• Counseling HIV-infected women about the indications for (and potential benefits of) scheduled cesarean delivery to reduce perinatal transmission of HIV;6,9-11

• Counseling HIV-infected women about the risks of HIV transmission through breast milk and that breastfeeding is not recommended for HIV-infected women living in the United States and other countries where safe alternatives to breast milk are available;6

• Initiation of prophylaxis against Pneumocystis jirovecii pneumonia beginning at age 4 to 6 weeks in all HIV-infected infants and in those HIV-exposed infants whose HIV infection status remains indeterminate;13 and

• Early diagnostic evaluation of HIV-exposed infants, as well as testing of partners and other children to permit prompt initiation of cART in infected individuals.1,14

Repeat HIV Testing in the Third Trimester

Repeat HIV testing should be considered for all HIV-seronegative pregnant women. A second HIV test during the third trimester, preferably before 36 weeks’ gestation, is recommended6,15 for women who:

• Are receiving health care in a jurisdiction that has a high incidence of HIV or AIDS in women between ages 15 and 45 or are receiving health care in facilities in which prenatal screening identifies at least 1 HIV-infected pregnant woman per 1,000 women screened (a list of areas where such screening is recommended is found in the 2006 CDC recommendations);

• Are known to be at high risk of acquiring HIV (e.g., those who are injection drug users or partners of injection drug users, exchange sex for money or drugs, are sex partners of HIV-infected individuals, have had a new or more than 1 sex partner during current pregnancy, or have been diagnosed with a new sexually transmitted disease during pregnancy); or

• Have signs or symptoms of acute HIV infection.4,5,16

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. There is evidence that for women, the risk of HIV acquisition is significantly higher during pregnancy than in the postpartum period.17 If acute HIV infection is a possibility, virologic testing with a plasma HIV RNA assay or, if unavailable, an antigen/antibody combination immunoassay should be performed because serologic testing may be negative at this early stage of infection.18

Rapid HIV Testing During Labor in Women with Unknown HIV Status

Use of rapid test kits or an expedited immunoassay to detect HIV infection is recommended to screen women in labor whose HIV status is undocumented and identify HIV exposure in their infants.1,4,5,14,19 Any hospital offering intrapartum care should have rapid or expedited HIV testing available and should have policies and procedures in place to ensure that staff are prepared to provide patient education about rapid or expedited HIV testing, that results are available ideally within one hour, that appropriate ARV medications are available whenever needed, and that follow-up procedures are in place for women found to be HIV-infected and their infants. Rapid tests have been found to be feasible, accurate, timely, and useful both in ensuring prompt initiation of intrapartum and neonatal ARV prophylaxis and in reducing perinatal transmission of HIV.20 Results of rapid tests can be obtained within minutes to a few hours with accuracy comparable to standard enzyme-linked immunosorbent assays (EIA).19,21,22 A single negative rapid test does not need confirmation unless acute HIV infection is a possibility, in which case, a virologic test is necessary.18 A positive rapid HIV test result must be followed by a supplemental test to confirm the presence of HIV infection.22 However, immediate initiation of ARV prophylaxis for prevention of perinatal transmission of HIV is strongly
HIV Counseling and Testing During the Postnatal Period

Women who have not been tested for HIV before or during labor should be offered rapid or expedited testing during the immediate postpartum period or their newborns should undergo rapid or expedited HIV testing with maternal consent (unless state law allows testing without consent). Use of rapid or expedited HIV assays or expedited EIA for prompt identification of HIV-exposed infants is essential because neonatal ARV prophylaxis should be initiated as soon as possible after birth—ideally no more than 12 hours later—to be effective for the prevention of perinatal transmission. When an initial HIV test is positive in mother or infant, initiation of infant ARV prophylaxis and counseling against initiation of breastfeeding is strongly recommended pending results of confirmatory HIV tests. If confirmatory tests are negative and acute HIV infection is excluded, infant ARV prophylaxis can be discontinued. In the absence of ongoing maternal HIV exposure, breastfeeding can be initiated. Mechanisms should be developed to facilitate HIV screening for infants who have been abandoned and are in the custody of the state.

Infant HIV Testing When Maternal HIV Test Results Are Unavailable

When maternal HIV test results are unavailable (e.g., for infants who are in foster care) or their accuracy cannot be evaluated (e.g., for infants adopted from a country where results are not reported in English), HIV antibody testing is indicated to identify HIV exposure in the infant. If antibody testing is positive, further testing is needed to diagnose HIV infection, or in the case of infants aged >18 months, to confirm HIV infection (see Diagnosis of HIV Infection in Infants).

Acute Maternal HIV Infection During Pregnancy or Breastfeeding

The risk of perinatal transmission of HIV is increased in infants born to women who have acute HIV infection during pregnancy or lactation. When acute retroviral syndrome is a possibility in pregnancy or during breastfeeding, maternal testing should include a combination antigen/antibody immunoassay or plasma HIV RNA test, because HIV antibody testing may be negative in early maternal infection. Women with possible acute HIV infection who are breastfeeding should stop breastfeeding immediately until HIV infection is confirmed or excluded. Pumping and temporarily discarding breast milk can be recommended and (if HIV infection is excluded), in the absence of ongoing maternal exposure to HIV, breastfeeding can resume. Care of pregnant or breastfeeding women and their infants identified with acute or early HIV infection should follow guidelines in the Perinatal Guidelines.

Surveillance Reporting of HIV Exposed Infants to Local and State Health Departments

Clinicians should be aware of public health surveillance systems and exposed-infant reporting regulations that may exist in their jurisdictions; this is in addition to mandatory reporting of HIV-infected persons, including infants. Reporting cases allows for appropriate public health functions to be accomplished.

References


**Diagnosis of HIV Infection in Infants and Children**  
(Last updated February 12, 2014; last reviewed February 12, 2014)

<table>
<thead>
<tr>
<th>Panel’s Recommendations</th>
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<tbody>
<tr>
<td>• Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months (AII).</td>
</tr>
<tr>
<td>• HIV DNA polymerase chain reaction and HIV RNA assays are recommended as preferred virologic assays (AII).</td>
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<tr>
<td>• Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months (AII).</td>
</tr>
<tr>
<td>• Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection (BIII).</td>
</tr>
<tr>
<td>• Virologic diagnostic testing should be considered 2 to 4 weeks after cessation of antiretroviral (ARV) prophylaxis for infants receiving combination ARV infant prophylaxis, if the results of prior virologic testing were negative while the infant was receiving prophylaxis (BIII).</td>
</tr>
<tr>
<td>• A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen (AII).</td>
</tr>
<tr>
<td>• Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with one obtained at age ≥1 month and one at age ≥4 months, or 2 negative HIV antibody tests from separate specimens obtained at age ≥6 months (AII).</td>
</tr>
<tr>
<td>• Some experts confirm the absence of HIV infection at 12 to 18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies (BIII).</td>
</tr>
<tr>
<td>• <strong>Screening HIV antibody assays in conjunction with a confirmatory antibody test or virologic detection test</strong> can be used for diagnosis of HIV infection in children with perinatal exposure aged ≥18 months and in children with non-perinatal exposure (see text for special situations) (AII).</td>
</tr>
</tbody>
</table>

**Rating of Recommendations:**  
A = Strong; B = Moderate; C = Optional

**Rating of Evidence:**  
I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

**Diagnostic Testing in Infants with Perinatal HIV-1 (HIV) Exposure**

HIV infection can be definitively diagnosed through use of virologic assays in most non-breastfed HIV-exposed infants by age 1 month and in virtually all infected infants by age 4 months. Tests for antibodies to HIV, including newer tests, do not establish the presence of HIV infection in infants because of transplacental transfer of maternal antibodies to HIV; therefore a virologic test should be used. Positive virologic tests (i.e., nucleic acid amplification tests [NAT]—a class of tests which includes HIV DNA, RNA polymerase chain reaction [PCR] assays, and related RNA qualitative or quantitative assays) indicate likely HIV infection. The first test result should be confirmed as soon as possible by a repeat virologic test on a second specimen because false-positive results can occur with both RNA and DNA assays.

HIV culture is not used for routine HIV diagnostic testing, although it has sensitivity similar to that of HIV DNA PCR. It is more complex and expensive to perform than DNA PCR or RNA assays, requires 2 to 4 weeks for definitive results, and is generally not available outside of research laboratories. Use of the currently approved HIV p24 antigen assay is not recommended for infant diagnosis in the United States because the sensitivity and specificity of the assay in the first months of life are less than that of other HIV virologic tests.
Infants who are found to have positive HIV antibody tests on screening but whose mothers’ HIV status is unknown (see Identification of Perinatal HIV Exposure) should be assumed to be HIV-exposed and undergo the HIV diagnostic testing described here.6

**HIV DNA PCR**

HIV DNA PCR is a sensitive technique used to detect specific HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at 1, 3, and 6 months. The sensitivity of the test performed at birth is 55% but increases to more than 90% by 2 to 4 weeks of age, and 100% at ages 3 months and 6 months.6-9

**HIV RNA Assays**

HIV quantitative RNA assays detect extracellular viral RNA in the plasma. Their specificity (for results ≥5,000 copies/mL) has been shown to be 100% at birth, 1, 3, and 6 months of age and is comparable to HIV DNA PCR.8 HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before they are interpreted as documenting HIV infection in an infant. The sensitivity of HIV RNA assays has been shown to be 25% to 58% during the first weeks of life, 89% at age 1 month, and increases to 90% to 100% by age 2 to 3 months.6-8,10-12 In studies of infants receiving zidovudine or no prophylaxis, HIV RNA assays were found to be as sensitive as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants. An HIV RNA assay can be used as the confirmatory test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting HIV non-subtype B (see HIV Subtype section below). While HIV DNA PCR remains positive in most individuals receiving antiretroviral treatment, HIV RNA assays may be affected by maternal antenatal treatment or infant combination antiretroviral (ARV) prophylaxis.8,13 In one study, the sensitivity of HIV RNA assays was not associated with the type of maternal or infant ARV prophylaxis, but HIV RNA levels at 1 month were lower in infants receiving multidrug prophylaxis (n = 9) compared to levels among infected infants receiving single-drug zidovudine prophylaxis (n = 47) (median HIV RNA 2.5 log copies/mL vs. 5.4 log copies/mL, respectively). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log copies/mL) by age 3 months in both groups after stopping prophylaxis. These data suggest that diagnostic sensitivity of HIV assays may be affected by the type of infant prophylaxis.8 Further studies are necessary to confirm this trend.

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing.6,14-18

**Issues Related to Diagnosis of Group M Non-Subtype B and Group O HIV-1 Infections**

Although HIV-1 Group M subtype B is the predominant viral subtype found in the United States, non-subtype B viruses predominate in other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia. Group O HIV strains are seen in West-Central Africa. Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.19-22 Geographical distribution of HIV groups is available at [http://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp](http://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp).

Currently available HIV DNA PCR tests have decreased sensitivity for detection of non-subtype B HIV, and false-negative HIV DNA PCR test results have been reported in infants infected with non-subtype B HIV.23-25 In an evaluation of perinatally infected infants diagnosed in New York State in 2001 through 2002, 16.7% of infants were infected with a non-subtype B strain of HIV, compared with 4.4% of infants diagnosed between 1998 and 1999.26

Currently available real-time HIV RNA PCR assays have improved sensitivity for detection of non-subtype B HIV infection and the more uncommon Group O strains compared to other RNA assays that do not detect or properly quantify all non-B subtypes and group O HIV27-32 (see HIV RNA Monitoring in Children: [http://aidsinfo.nih.gov/guidelines](http://aidsinfo.nih.gov/guidelines)).
When evaluating an infant whose mother or father (or both) comes from an area endemic for non-subtype B HIV or Group O strains, such as Africa and Southeast Asia, clinicians should consider conducting initial testing using one of the assays more sensitive for non-subtype B viruses, such as one of the real-time PCR assays. In addition, when non-subtype B perinatal exposure is suspected in infants with negative HIV DNA PCR results, repeat testing using one of the newer RNA assays is recommended. The child should undergo close clinical monitoring and HIV serologic testing at age 18 months to definitively rule out HIV infection. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or the Centers for Disease Control and Prevention (CDC) may be able to assist in obtaining referrals for diagnostic testing.

**Issues Related to Diagnosis of HIV-2 Infections**

HIV-2 infection is endemic in Angola; Mozambique; West African countries including Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and in parts of India.33,34 It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions;35,36 HIV-2 is rare in the United States. HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic, who are HIV-1 antibody-positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot and HIV-1 RNA viral loads at or below the limit of detection.37,38 This pattern of HIV testing can also be seen in patients who have a false-positive HIV-1 test. HIV-1 and HIV-2 coinfections may also occur, further complicating the diagnosis.

The majority of commercially available HIV screening antibody tests can detect both HIV-1 and HIV-2 but cannot distinguish between the two viruses. The only Food and Drug Administration (FDA)-approved antibody test that distinguishes between HIV-1 and HIV-2 is the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test. If HIV-2 is suspected, infection can be confirmed using a supplemental test such as an HIV-2 immunoblot or HIV-2-specific Western blot. HIV-2 immunoblots are available through commercial labs; however, none are FDA-approved for HIV-2 diagnosis. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by their public health laboratory or the CDC.

Infants born to HIV-2-infected mothers should be tested for HIV-2 infection with HIV-2-specific virologic assays (HIV-2 DNA PCR testing) at time points similar to those used for HIV-1 testing. HIV-2 virologic assays are not commercially available, but the National Perinatal HIV Hotline (1-888-448-8765) can provide a list of sites that perform this testing. Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.34,39,41

**Timing of Diagnostic Testing in Infants with Known Perinatal HIV Exposure**

Virologic diagnostic testing of an HIV-exposed infant should be performed at age 14 to 21 days, at age 1 to 2 months, and at age 4 to 6 months. Virologic diagnostic testing should be considered at birth for infants at high risk of HIV infection and 2 to 4 weeks after discontinuation of prophylaxis for infants receiving combination neonatal ARV regimens (see below).

Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples, regardless of a child’s age. A positive HIV antibody test with confirmatory Western blot (or immunofluorescent antibody [IFA] assay) at age ≥18 months confirms HIV infection, except in occasional late seroreverters (see the Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations section below).1

HIV infection can be presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥14 days and one at age ≥4 weeks) or one negative virologic test at age ≥8 weeks, or one
negative HIV antibody test at age ≥6 months.1,6 *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at age 4 to 6 weeks until they are determined to be HIV-uninfected or presumptively uninfected.42,43 Thus, initiation of PCP prophylaxis can be avoided or discontinued if an infant has negative virologic tests at ages 2 weeks and ≥4 weeks, or if virologic testing is negative at age ≥8 weeks.

**Definitive** exclusion of HIV infection in a non-breastfed infant is based on 2 or more negative virologic tests, one at age ≥1 month and one at age ≥4 months, or 2 negative HIV antibody tests from separate specimens obtained at age ≥6 months. For both presumptive and definitive exclusion of HIV infection, a child must have no other laboratory (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and not be breastfeeding. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody-negative status.

**Virologic Testing at Birth (Optional)**

Virologic testing at birth should be considered for newborns at high risk of perinatal HIV transmission, such as infants born to HIV-infected mothers who did not receive prenatal care or prenatal ARVs, were diagnosed with acute HIV infection during pregnancy, or who had HIV viral loads ≥1,000 copies/mL close to the time of delivery.44 As many as 30% to 40% of HIV-infected infants can be identified by age 48 hours.6 Prompt diagnosis is critical to allow for discontinuing ARV prophylaxis and instituting early ARV therapy (see When to Initiate Therapy). Blood samples from the umbilical cord should not be used for diagnostic evaluations because of the potential for contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection during the intrauterine period from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection.45 Some researchers have proposed that infants with early infection may have more rapid disease progression than those with late infection and, therefore, should receive more aggressive therapy.45,46 However, data from prospective cohort studies have demonstrated that although early differences in HIV RNA levels were present between infants with a positive HIV culture within 48 hours of birth and those with a first positive culture after age 7 days, these differences were no longer statistically significant after age 2 months.47 HIV RNA levels after the first month of life were more predictive of rapid disease progression than the time at which HIV culture tests were positive.47,48

**Virologic Testing at Age 14 to 21 Days**

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks6 and early identification of infection would permit discontinuation of neonatal ARV prophylaxis and further evaluation for initiation of ARV therapy (see Infants Younger than Age 12 Months and Table 5 in When to Initiate).

**Virologic Testing at Age 1 to 2 Months**

Infants with negative virologic tests before age 1 month should be retested at age 1 to 2 months. Most HIV-exposed neonates will receive 6 weeks of neonatal ARV prophylaxis. Although the use of antepartum, intrapartum, and neonatal zidovudine single-drug prophylaxis did not delay detection of HIV by culture in infants in Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 or the sensitivity and predictive values of many virologic assays,6,10-12,49 this may not always apply to current combination prenatal and neonatal ARV regimens if the test is obtained while the infant is receiving combination neonatal ARV prophylaxis.8 Virologic diagnostic testing for infants receiving combination ARV infant prophylaxis should be considered 2 to 4 weeks after cessation of prophylaxis if prior negative diagnostic testing was performed during the period of prophylaxis. In such situations, the test recommended at age 1 to 2 months can be delayed until after cessation of ARV prophylaxis.
An infant with two negative virologic tests, one at age ≥14 days and one at age ≥1 month, can be viewed as presumptively uninfected and will not need PCP prophylaxis, assuming the child has not had a positive virologic test, CD4 immunosuppression, or clinical evidence of HIV infection.

**Virologic Testing at Age 4 to 6 Months**

HIV-exposed children who have had negative virologic assays at age 14 to 21 days and at age 1 to 2 months, have no clinical evidence of HIV infection, and are not breastfed should be retested at age 4 to 6 months for definitive exclusion of HIV infection.

**Antibody Testing at Age 6 Months and Older**

Two or more negative HIV antibody tests performed in non-breastfed infants at age ≥6 months can also be used to definitively exclude HIV infection in HIV-exposed children with no clinical or virologic laboratory evidence of HIV infection.

**Antibody Testing at Age 12 to 18 Months to Document Seroreversion**

Some experts confirm the absence of HIV infection in infants with negative virologic tests (when there has not been prior confirmation of two negative antibody tests) by repeat serologic testing between 12 and 18 months of age to confirm that maternal HIV antibodies transferred in utero have disappeared. In a recent study, the median age at seroreversion was 13.9 months. Although the majority of HIV-uninfected infants will serorevert by age 15 to 18 months, there are reports of late seroreversion after 18 months (see below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.

**Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations**

- Late seroreversion up to age 24 months
- Postnatal HIV infection in HIV-exposed children with prior negative virologic tests for whom there are additional HIV transmission risks
- HIV-2 and non-subtype B HIV-1

Non-breastfed, perinatally HIV-exposed infants with no other HIV transmission risk and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies for up to age 24 months (these infants are called late seroreverters). In one study 14% seroreverted after age 18 months. These children may have positive enzyme-linked immunosorbent assay (EIA) results but indeterminate confirmatory antibody tests (Western Blot or IFA). In such cases, repeat antibody testing at a later time would document seroreversion.

In contrast to late seroreverters, in rare situations, postnatal HIV infections have been reported in HIV-exposed infants who had prior negative HIV virologic tests. This occurs in infants who become infected through an additional risk after completion of testing (see **Diagnostic Testing in Children with Non-Perinatal HIV Exposure**). If a confirmatory HIV antibody test is positive at age 18 months, repeated virologic testing will distinguish between residual antibodies in uninfected, late seroreverting children and true infection.

Postnatal HIV exposure can occur if an HIV-infected mother breastfeeds her infant. Typical scenarios in the United States include women who have not been adequately counseled about infant feeding, women who breastfeed despite being counseled not to do so, and women who learn of their HIV diagnosis only after initiating breastfeeding. Diagnostic testing to rule out acquisition of HIV through breast milk will only be accurate after breastfeeding has completely ceased. The timing of testing in such situations is discussed below in **Diagnostic Testing in Children with Non-Perinatal HIV Exposure**.

Another example where there can be postnatal HIV exposure is when an HIV-infected caregiver premasticates or prechews solid food before feeding it to an infant. This practice has been documented to result in HIV transmission. In such exposed children, both screening EIA and confirmatory antibody tests (EIA, Western Blot or IFA) may be positive at 18 months. Another study documented very rare cases of late postnatal
Children with non-subtype B HIV-1 infection and children with HIV-2 infection may have persistent positive EIA tests and indeterminate confirmatory antibody tests.\textsuperscript{23-25,60} Situations in which such infections may be suspected and the diagnostic approach to them are discussed above in Issues Related to Diagnosis of Group M Non-Subtype B and Group O HIV-1 Infections and Issues Related to Diagnosis of HIV-2 Infection.

**Diagnostic Testing in Children with Non-Perinatal HIV Exposure**

Breastfeeding is a known route of HIV transmission. Infants who are breastfed by HIV-infected women, including those diagnosed with acute HIV infection during breastfeeding or who breastfed before knowing their HIV diagnosis should undergo immediate HIV virologic testing and breastfeeding should be discontinued. Follow-up virologic testing should be performed at 4 to 6 weeks, 3 and 6 months after breastfeeding cessation if the initial tests are negative.\textsuperscript{61-63} HIV antibody testing of an infant to assess for HIV exposure would not be helpful if the mother acquired HIV infection after giving birth. In that situation, an infant would be HIV antibody-negative but still at risk of acquiring HIV infection through breastfeeding and counseling to cease breastfeeding should be provided.

Perinatal HIV acquisition accounts for the majority of HIV infections in children, but providers may need to evaluate children exposed to HIV through other routes, such as sexual abuse, or because they were adopted from countries in which parenteral exposure to HIV via contaminated blood products is a possibility. In such cases, maternal HIV status may be negative or unknown. Receipt of solid food premasticated or prechewed by an HIV-infected caregiver also has been documented to be associated with risk of HIV transmission.\textsuperscript{41,54-58} Finally, acquisition of HIV is possible through accidental needlesticks or behavioral risks, such as sexual activity or injection drug use in older children.

Screening HIV antibody assays in conjunction with a confirmatory antibody test or virologic detection test should be performed on children who are suspected to have HIV infection because of clinical or laboratory findings consistent with HIV. Additional virologic testing may be necessary if acute HIV infection or end-stage AIDS is suspected because antibody testing can be negative in these situations.

**References**


Clinical and Laboratory Monitoring of Pediatric HIV Infection  (Last updated February 12, 2014; last reviewed February 12, 2014)

Laboratory monitoring of HIV-infected children poses unique and challenging issues. In particular, normal ranges and the value of CD4 T lymphocyte (CD4) cell count and plasma HIV-1 RNA concentration (viral load) for prediction of risk of disease progression varies significantly by age. This section will address immunologic, virologic, and general laboratory monitoring of HIV-infected children, relevant to both those who are and are not receiving combination antiretroviral therapy (cART).

Immunologic Monitoring in Children: General Considerations

Clinicians interpreting CD4 cell count and percentage in children must consider age as a factor. CD4 cell count and percentage values in healthy infants who are HIV-uninfected are considerably higher than values observed in uninfected adults and slowly decline to adult values by age 5 years. In children younger than age 5 years, the absolute CD4 cell count tends to vary more with age than does CD4 percentage. Therefore, in HIV-infected children younger than age 5 years, CD4 percentage has generally been preferred for monitoring immune status, whereas absolute CD4 cell count has been the preferred option for children aged ≥5 years, although CD4 cell count can be used in younger children if CD4 percentage is not available. An analysis from the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) found that CD4 percentage provided little or no additional prognostic value compared with CD4 cell count regarding short-term disease progression in children aged <5 years as well as in older children, and either or both can be used in decisions on when to initiate cART (see When to Initiate).

In HIV-infected children, as in infected adults, the CD4 cell count and percentage decline as HIV infection progresses and patients with lower CD4 cell count/percentage values have a poorer prognosis than patients.
with higher values (see Tables A-C in Appendix C: Supplemental Information).

The prognostic value of CD4 cell count and percentage, and plasma viral load was assessed in a large individual patient meta-analysis (HPPMCS), which incorporated clinical and laboratory data from 17 pediatric studies and included 3,941 HIV-infected children receiving either no therapy or only zidovudine monotherapy. The analysis looked at the short-term (12-month) risk of developing AIDS or dying based on a child’s age and selected values of CD4 cell count or percentage and plasma viral load at baseline (see Figures A and B in Appendix C: Supplemental Information). In a separate analysis of this dataset, predictive value of CD4 cell count for risk of death or AIDS/death in HIV-infected children aged 5 years or older was similar to that observed in young adults, with an increase in the risk of mortality when CD4 cell count fell below 350 cells/mm³ (see Figure C and Table B in Appendix C: Supplemental Information).

The risk of disease progression associated with a specific CD4 cell count or percentage varies with the age of the child. Infants in the first year of life experience higher risks of progression or death than older children for any given CD4 stratum. For example, comparing a 1-year-old child with a CD4 percentage of 25% to a 5-year-old child with the same CD4 percentage, there is an approximately fourfold increase in the risk of AIDS and six fold increase in the risk of death in the 1-year-old child (see Figures A and B in Appendix C: Supplemental Information). Children aged 5 years or older have a lower risk of progression than younger children, with the increase in risk of AIDS or death corresponding to CD4 cell count more similar to those in young adults (see Figure C and Table B in Appendix C: Supplemental Information). In the HPPMCS, there were no deaths among children aged 5 years or older with CD4 cell count >350 cells/mm³, although in younger children there continued to be a significant risk of death even with CD4 cell count >500 cells/mm³ (see Table B in Appendix C: Supplemental Information).

These risk profiles contribute to the rationale for recommendations on when to initiate therapy in a treatment-naive HIV-infected child (see When to Initiate). A website using the meta-analysis from the HPPMCS is available to estimate the short-term risk of progression to AIDS or death in the absence of effective cART according to age and the most recent CD4 percentage/absolute CD4 cell count or HIV-1 RNA viral load measurement (http://hppmcs.org).

Measurement of CD4 cell count and percentage can be associated with considerable intrapatient variation. Mild intercurrent illness or the receipt of vaccinations can produce a transient decrease in CD4 cell count and percentage, thus, CD4 cell count/percentage are best measured when patients are clinically stable. No decision about therapy should be made in response to a change in CD4 cell count/percentage until the change has been substantiated by at least a second determination, with a minimum of 1 week between measurements.

**HIV RNA Monitoring in Children: General Considerations**

Quantitative HIV-1 RNA assays measure the plasma concentration of HIV RNA as copies/mL, commonly referred to as the plasma viral load. During the period of primary infection in adults and adolescents, in the absence of therapy, plasma viral load initially rises to high peak levels and then declines by as much as 2 to 3 log₁₀ copies to reach a stable lower level (the virologic set point) approximately 6 to 12 months after acute infection. In infected adults, the stable lower level (or viral set point) correlates with the subsequent risk of disease progression or death in the absence of therapy.

The pattern of change in plasma viral load in untreated perinatally infected infants differs from that in infected adults and adolescents. High plasma viral load persists in untreated infected children for prolonged periods. In one prospective study of infants with perinatal infection born prior to antiretroviral (ARV) availability in children, plasma viral loads generally were low at birth (i.e., <10,000 copies/mL), increased to high values by age 2 months (most infants had values >100,000 copies/mL, ranging from undetectable to nearly 10 million copies/mL), and then decreased slowly, with a mean plasma viral load during the first year of life of 185,000 copies/mL. After the first year of life, plasma viral load slowly declined over the next few
Viral load during the first 12 to 24 months after birth showed an average decline of approximately 0.6 log_{10} copies/mL per year, followed by an average decline of 0.3 log_{10} copies/mL per year until age 4 to 5 years. This pattern probably reflects the lower efficiency of an immature but developing immune system in containing viral replication and possibly the rapid expansion of HIV-susceptible cells that occurs with somatic growth.17

High plasma viral load (i.e., >299,000 copies/mL) in infants younger than age 12 months has been correlated with disease progression and death, but the range of plasma viral loads overlap considerably in young infants who have rapid disease progression and those who do not.11,13 Plasma viral load >100,000 copies/mL in older children also has been associated with high risk of disease progression and mortality, particularly if CD4 percentage is <15% (see Table C in Appendix C: Supplemental Information).15,16 The most robust data set available to elucidate the predictive value of plasma viral load for disease progression in children was assembled in the HPPMCS4 (see Immunologic Monitoring in Children: General Considerations) in children on no therapy or only zidovudine monotherapy, which showed that the risk of clinical progression to AIDS or death dramatically increases when viral load exceeds 100,000 copies (5.0 log_{10} copies)/mL; at lower values, only younger children show much variation in risk (see Figures D and E and Table A in Appendix C: Supplemental Information). At any given viral load, infants younger than aged 1 year were at higher risk of progression than older children, although these differences were less striking than those observed for the CD4 percentage data.

Despite data indicating that high plasma viral load is associated with disease progression, the predictive value of specific HIV RNA concentrations for disease progression and death for an individual child is moderate.15 Plasma viral load may be difficult to interpret during the first year of life because values are high and are less predictive of disease progression risk than in older children.12 In both HIV-infected children and adults, CD4 cell count or percentage and plasma viral load are independent predictors of disease progression and mortality risk, and use of the two markers together more accurately defines prognosis.15,16,18,19

Methodological Considerations in Interpretation and Comparability of HIV RNA Assays

Several different methods can be used for quantitating HIV RNA, each of which has a different level of sensitivity. Although the results of the assays are correlated, the absolute HIV RNA copy number obtained from a single specimen tested by two different assays can differ by twofold (0.3 log_{10} copies/mL) or more.20,21

Six Food and Drug Administration (FDA)-approved viral load assays using one of four different methodologies currently exist:

- HIV-1 reverse transcriptase (RT) quantitative polymerase chain reaction (PCR) assays: the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics), for which the lower limit of quantification differs between the “ultrasensitive” assay (<50 copies/mL) and the “regular sensitivity” assay (<400 copies/mL); the AmplicPrep/TaqMan HIV-1 Test, including the COBAS automated format (Roche Diagnostics); and the Real Time HIV-1 Assay (Abbott Molecular Incorporated);

- HIV-1 nucleic acid sequence-based amplification test (NucliSENS EasyQ® HIV-1 v2.0, bioMerieux);

- HIV-1 in vitro signal amplification, branched chain nucleic acid probe assay (VERSANT HIV-1 RNA 3.0 Assay [bDNA], Siemens); and

- Aptima HIV-1 RNA Qualitative assay (Gen-Probe Inc., San Diego, CA), primarily used for HIV diagnosis, as well as detection of less than full viral suppression during therapy.

The lower limits of quantification of the assays differ (less than 40 copies/mL for the Abbott Real Time HIV-1 test, less than 20 copies/mL for the AmplicPrep/TaqMan HIV-1 Test/Version 2, less than 50 copies/mL for the Amplicor HIV-1 Monitor Test, less than 20 copies/mL for the NucliSENS EasyQ® HIV-1 v2.0, and less than 50 copies/mL for the VERSANT assay). Use of ultrasensitive viral load assays is recommended to...
confirm that cART is producing maximal suppression of viremia. Because of the variability among assays in techniques and quantitative HIV RNA measurements, if possible, a single HIV RNA assay method should be used consistently to monitor an individual patient.22-24

The predominant HIV-1 subtype in the United States is subtype B—the subtype for which all initial assays were targeted. Current kit configurations for all companies have been designed to detect and quantitate essentially all viral subtypes, with the exception of the uncommon O subtypes.25,26 This is important for many regions of the world where non-B subtypes are predominant as well as for the United States, where a small subset of individuals are infected with non-B viral subtypes.22,27-31 It is particularly relevant for children who are born outside the United States or to foreign-born parents. Choice of HIV RNA assay, particularly for young children, may be influenced by the amount of blood required for the assay. The NucliSENS assay requires the least blood (100 µL of plasma), followed by the RT-PCR assays such as the Amplicor HIV-1 Monitor (200 µL of plasma) and VERSANT assays (1 mL of plasma).

Biologic variation in plasma viral load within one person is well documented. In adults, repeated measurement of plasma viral load using the same assay can vary by as much as threefold (0.5 log10 copies/mL) in either direction over the course of a day or on different days.18,21 This biologic variation may be greater in infected infants and young children. This inherent biologic variability must be considered when interpreting changes in plasma viral load in children. Thus, on repeated testing, only differences greater than fivefold (0.7 log10 copies/mL) in infants younger than age 2 years and greater than threefold (0.5 log10 copies/mL) in children aged 2 years and older should be considered reflective of plasma viral load changes that are biologically and clinically substantial.

No clinical decisions should be made as a result of a change in plasma viral load unless the change is confirmed by a second measurement. Interpretation of plasma viral load for clinical decision making should be done by or in consultation with an expert in pediatric HIV infection because of the complexities of HIV RNA testing and the age-related changes in plasma viral load in children.

Based on accumulated experience with currently available assays, viral suppression is currently defined as a plasma viral load below the detection limit of the assay used (generally <20 to 75 copies/mL). This definition of suppression has been much more thoroughly investigated in HIV-infected adults than in HIV-infected children (see the Adult and Adolescent Antiretroviral Guidelines).32 Temporary viral load elevations (“blips”) between the level of detection and 500 copies/mL often are detected in adults33 and children on cART and should not be considered to represent “virologic failure” as long as the values return to below the level of detection at the time of repeat testing. For definitions and management of virologic treatment failure, see Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy. These definitions of viral suppression and virologic failure are recommended for clinical use. Research protocols or surveillance programs may use different definitions.

**Clinical and Laboratory Monitoring of Children with HIV Infection**

Table 3 provides one proposed general monitoring schedule, which should be adjusted based on the specific cART regimen a child is receiving.

**Entry into Care—Baseline Evaluation**

At entry into care, HIV-infected children should have a complete age-appropriate medical history, physical examination, and laboratory evaluation (see Table 3). This should include a general medical and social history (e.g., immunizations, nutrition, physical and social environment), evaluation for HIV-specific physical conditions (e.g., growth delay, microcephaly, motor or cognitive neurologic problems), evaluation for HIV-associated laboratory abnormalities (e.g., anemia, leukopenia, thrombocytopenia, elevated glucose, transaminases or creatinine, hypoalbuminemia), and assessment of presence or risk of opportunistic infections (see the Pediatric Opportunistic Infections Guidelines).
Laboratory confirmation of HIV infection should be obtained if available documentation is incomplete (see **Diagnosis of HIV Infection**). CD4 cell count and percentage, as well as plasma HIV RNA measurements (i.e., viral load), should be obtained at entry into care to help guide decisions about timing of cART initiation (see **When to Initiate**). Genotype resistance testing should be performed, even if cART is not initiated immediately. For patients previously treated with ARV drugs, resistance evaluation requires a complete ARV history (see **Antiretroviral Drug-Resistance Testing**).

**Monitoring of Children Not Receiving Antiretroviral Therapy**

Children not receiving cART should be evaluated every 3 to 4 months with measurement of CD4 cell count and percentage, and plasma viral load; evaluation of growth and development for signs of HIV-associated change; and laboratory evaluation for HIV-associated conditions including anemia, leukopenia, thrombocytopenia, elevated glucose, transaminases, or creatinine, and hypoalbuminemia. Urinalysis should be obtained every 6 to 12 months to monitor for HIV-associated nephropathy. Opportunistic infection monitoring should follow guidelines appropriate for the child's exposure history and clinical setting (see the **Pediatric Opportunistic Infections Guidelines**).

More frequent evaluation may be necessary for children experiencing virologic, immunologic, or clinical deterioration or to confirm an abnormal value.

**Initiation of Combination Antiretroviral Therapy—Overview**

Readiness for ARV adherence should be assessed prior to starting cART. If abacavir is being considered as part of the regimen, HLA-B*5701 testing should be sent prior to initiation of that ARV, and an alternative ARV should be used if HLA-B*5701 is positive (see **Abacavir** in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if not already performed (see **Antiretroviral Drug-Resistance Testing**).

Children who start cART or who change to a new regimen should be followed to assess effectiveness, tolerability, and side effects of the regimen and to evaluate medication adherence. Frequent patient visits and intensive follow-up during the initial months after a new ARV regimen is started are necessary to support and educate the family. The first few weeks of cART can be particularly difficult for children and their caregivers; they must adjust their schedules to allow for consistent and routine administration of medication doses. Children may also experience side effects of medications, and both children and their caregivers need assistance to determine whether the effects are temporary and tolerable or are more serious or long-term and require a visit to the clinician. It is critical that providers speak to caregivers and children in a supportive, non-judgmental manner using layman’s terms. This promotes honest reporting and ensures dialogue between providers and both children and their caregiver(s), even when medication adherence is reported to be inconsistent.

**Monitoring of Children Receiving Antiretroviral Therapy**

**Evaluations at Initiation of cART**

At the time of cART initiation, CD4 cell count and percentage and plasma viral load should be measured to establish a baseline to monitor cART benefit. To set the baseline for monitoring cART toxicity (see **Management of Medication Toxicity or Intolerance**), complete blood count (CBC) and differential, serum chemistries (including electrolytes, creatinine, glucose, hepatic transaminases), urinalysis, and serum lipids (cholesterol, triglycerides) should be measured. CBC allows monitoring of zidovudine-associated anemia, leukopenia, and macrocytosis (see **Zidovudine** in Appendix A: Pediatric Antiretroviral Drug Information). Electrolytes with anion gap might help identify nucleoside reverse transcriptase inhibitor (NRTI)-associated lactic acidosis. With use of tenofovir disoproxil fumarate, creatinine may increase, phosphate decrease, and proteinuria can occur (see **Tenofovir** in Appendix A: Pediatric Antiretroviral Drug Information). Use of protease inhibitors may be associated with hyperglycemia. Hepatic transaminases (alanine aminotransferase and aspartate aminotransferase) increase with many ARV drugs. Bilirubin should be measured prior to starting atazanavir because that drug causes an increase in indirect bilirubin (see **Atazanavir** in Appendix A: Pediatric Antiretroviral Drug Information).
Some practitioners measure baseline creatine kinase before starting zidovudine (see Zidovudine in Appendix A: Pediatric Antiretroviral Drug Information) or raltegravir (see Raltegravir in Appendix A: Pediatric Antiretroviral Drug Information). For further details of adverse effects associated with a particular ARV, see Tables 11a-11l in Management of Medication Toxicity or Intolerance.

Within 1 to 2 Weeks of Initiation of cART

Within 1 to 2 weeks of initiating therapy, children should be evaluated either in person or by phone to identify clinical side effects and to support adherence. Many clinicians plan additional contacts (in person or by telephone) with children and caregivers to support adherence during the first few weeks of therapy.

2 to 4 Weeks after Initiation of cART

While data are limited on which to base an exact recommendation about precise timing, most experts recommend laboratory testing at 2 to 4 weeks (and not more than 8 weeks) after initiation of cART to assess virologic response and laboratory toxicity. Laboratory chemistry tests to measure are regimen-specific (see above). Evaluation of hepatic transaminases is recommended at 2 weeks and 4 weeks for patients starting treatment that includes nevirapine (see Nevirapine in Appendix A: Pediatric Antiretroviral Drug Information). Plasma viral load monitoring is important as a marker of response to cART because a fall in viral load suggests medication adherence, administration of appropriate doses, and viral drug susceptibility. Some experts favor measuring viral load at 2 weeks to ensure that viral load is declining. Because of higher baseline viral load in infants and young children, the decline in viral load after cART initiation may be slower than in adults. A significant decrease in viral load in response to cART should be observed by 4 to 8 weeks of therapy.

Routine Testing for Patients Receiving Combination Antiretroviral Therapy

After the initial phase of cART initiation, regimen adherence, effectiveness (CD4 cell count and percentage and plasma viral load), and toxicities (history, physical, and laboratory testing as above) should be assessed every 3 to 4 months in children receiving cART. Children who develop symptoms of toxicity should have appropriate laboratory evaluations (such as evaluation of serum lactate in a child receiving NRTIs who develops symptoms suspicious for lactic acidosis). If laboratory evidence of toxicity is identified, testing should be performed more frequently until the toxicity resolves.

Testing for Patients Who are Stable on Long-Term cART

Some experts monitor CD4 cell count and percentage less frequently (e.g., every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years. Recent studies have critically evaluated the frequency of laboratory monitoring in both adults and children, particularly CD4 cell count and plasma viral load. These studies support less frequent monitoring in stable patients in whom viral suppression has been sustained for at least a year.34-39 Some clinicians find value in visits every 3 months even when lab testing is not performed in order to review adherence and update dosing for interim growth.

Testing at the Time of Switching cART

When a switch in regimen is made to simplify cART, labs appropriate to the toxicity profile of the new regimen should be measured at baseline, with follow up including plasma viral load at 4 weeks (and not more than 8 weeks) after the switch, to ensure efficacy of the new regimen. If regimen is switched because of cART failure (see Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy) resistance testing should be performed while a patient is still receiving the failing regimen to optimize the chance of identifying resistance mutations because resistant strains may revert to wild type within a few weeks of stopping ARV drugs (see Antiretroviral Drug-Resistance Testing).
Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and after Initiation of Combination Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Entry Into Care</th>
<th>Pre-Therapy</th>
<th>cART Initiation</th>
<th>Weeks 1-2 on Therapy</th>
<th>Weeks 2-4 on Therapy</th>
<th>Every 3-4 Months</th>
<th>Only Required Every 6-12 Months</th>
<th>ARV Switch</th>
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<tr>
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<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

1. See text for details of appropriate tests to send.
2. Readiness for ARV adherence is assessed prior to starting cART. If abacavir is being considered as part of the regimen, send HLA-B*5701 testing prior to initiation of that ARV, and choose an alternative ARV if HLA-B*5701 is positive (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if not already performed (see Antiretroviral Drug-Resistance Testing). Send tests appropriate to the toxicities expected from each patient’s cART regimen and history (see text).
3. If cART is initiated within 30 to 45 days of a pre-therapy lab result, repeat testing may not be necessary.
4. CD4 cell count and percentage can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years.
5. If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with tenofovir, more frequent urinalysis is considered.

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, CBC = complete blood count

References


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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General Considerations

Antiretroviral (ARV) treatment of pediatric HIV infection has steadily improved with the introduction of potent combination drug regimens that effectively suppress viral replication in most patients, resulting in a lower risk of failure due to development of drug resistance. Currently, combination antiretroviral treatment (cART) regimens including at least three drugs from at least two drug classes are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children.1-5 In the United States and the United Kingdom, significant declines (81%–93%) in mortality have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of highly active combination regimens;6-8 significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period.4,7 As a result, some perinatally HIV-infected children are now living into the third and fourth decades of life, and potentially, beyond.

The increased survival of HIV-infected children is associated with challenges in selecting successive new ARV drug regimens. In addition, therapy is associated with short- and long-term toxicities, which can be recognized in childhood or adolescence9-12 (see Management of Medication Toxicity or Intolerance). ARV drug-resistant virus can develop during cART because of poor adherence, a regimen that is not potent, or a combination of these factors which results in incomplete viral suppression. In addition, primary drug resistance may be seen in ARV-naive children who have become infected with a resistant virus.13-15 Thus, decisions about when to start therapy (see When to Initiate), what drugs to choose in ARV-naive children (see What to Start) and how to best treat ARV-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV infection should be directed by or made in consultation with a specialist in pediatric and adolescent HIV infection. Treatment of ARV-naive children (when and what to start), when to change therapy, and treatment of ARV-experienced children will be discussed in separate sections of the guidelines.

Several factors need to be considered in making decisions about initiating and changing cART in children, including:

• Severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or AIDS-defining illnesses (see Centers for Disease Control and Prevention (CDC) pediatric clinical staging system for HIV http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm),16 degree of CD4 T lymphocyte (CD4) immunosuppression, and level of HIV plasma viremia;

• Availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child’s age group;

• Potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the cART regimen;

• Effect of initial regimen choice on later therapeutic options;

• A child’s cART history;

• Presence of ARV drug-resistant virus;

• Presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect drug choice;

• Potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a child; and
• The ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child’s individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most ARV drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting PK and safety data from Phase I/II trials in children. In addition, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Panel reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

**Goals of Antiretroviral Treatment**

Although there is a single case report of “functional cure” in an HIV-infected child treated with a cART regimen initiated at age 30 hours, current cART does not eradicate HIV infection in the majority of perinatally infected infants because of the long half-life of latently infected CD4 cells. Some data suggest that the half-life of intracellular HIV proviral DNA is even longer in infected children than in adults (median 14 months vs. 5–10 months, respectively). Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of cART for HIV-infected children and adolescents include:

• Reducing HIV-related mortality and morbidity;
• Restoring and/or preserving immune function as reflected by CD4 cell measures;
• Maximally and durably suppressing viral replication;
• Preventing emergence of viral drug-resistance mutations;
• Minimizing drug-related toxicity;
• Maintaining normal physical growth and neurocognitive development;
• Improving quality of life;
• Reducing the risk of sexual transmission to discordant partners in adolescents who are sexually active; and
• Reducing the risk of perinatal transmission in adolescent females who become pregnant.

Strategies to achieve these goals require complex balancing of sometimes competing considerations.

**Use and Selection of cART**

The treatment of choice for HIV-infected children is a regimen containing at least three drugs from at least two classes of ARV drugs. The Panel has recommended several preferred and alternative regimens (see What to Start). The most appropriate regimen for an individual child depends on multiple factors as noted above. A regimen that is characterized as an alternative choice may be a preferred regimen for some patients.

**Drug Sequencing and Preservation of Future Treatment Option**

The choice of ARV treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in ARV drug regimens can rapidly exhaust treatment options and should be avoided. Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Current recommendations for initial therapy are to use two classes of drugs (see What to Start), thereby sparing three classes of drugs for later use.
Maximizing Adherence

As discussed in Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents, poor adherence to prescribed regimens can lead to subtherapeutic levels of ARV medications, which enhances the risk of development of drug resistance and likelihood of virologic failure. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with a child’s caregiver and the child (when age appropriate) before the decision to initiate therapy is made. Participation by the caregiver and child in the decision-making process is crucial. Potential problems should be identified and resolved before starting therapy, even if this delays initiation of therapy. In addition, frequent follow-up is important to assess virologic response to therapy, drug intolerance, viral resistance, and adherence. Finally, in patients who experience virologic failure, it is critical to fully assess adherence before making changes to the cART regimen.

Table 4. 1994 Revised HIV Pediatric (Age <13 Years) Classification System: Clinical Categories*

<table>
<thead>
<tr>
<th>Category N: Not Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category A: Mildly Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with two or more of the following conditions but none of the conditions listed in Categories B and C:</td>
</tr>
<tr>
<td>• Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral = 1 site)</td>
</tr>
<tr>
<td>• Hepatomegaly</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Dermatitis</td>
</tr>
<tr>
<td>• Parotitis</td>
</tr>
<tr>
<td>• Recurrent or persistent upper respiratory infection, sinusitis, or otitis media</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category B: Moderately Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following:</td>
</tr>
<tr>
<td>• Anemia (&lt;8 g/dL), neutropenia (&lt;1,000 cells/mm$^3$), or thrombocytopenia (&lt;100,000 cells/mm$^3$) persisting ≥30 days</td>
</tr>
<tr>
<td>• Bacterial meningitis, pneumonia, or sepsis (single episode)</td>
</tr>
<tr>
<td>• Candidiasis, oropharyngeal (i.e., thrush) persisting for &gt;2 months in children aged &gt;6 months</td>
</tr>
<tr>
<td>• Cardiomyopathy</td>
</tr>
<tr>
<td>• Cytomegalovirus infection with onset before age 1 month</td>
</tr>
<tr>
<td>• Diarrhea, recurrent or chronic</td>
</tr>
<tr>
<td>• Hepatitis</td>
</tr>
<tr>
<td>• Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than 2 episodes within 1 year)</td>
</tr>
<tr>
<td>• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month</td>
</tr>
<tr>
<td>• Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome</td>
</tr>
<tr>
<td>• Leiomyosarcoma</td>
</tr>
<tr>
<td>• Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex</td>
</tr>
<tr>
<td>• Nephropathy</td>
</tr>
<tr>
<td>• Nocardiosis</td>
</tr>
<tr>
<td>• Fever lasting &gt;1 month</td>
</tr>
<tr>
<td>• Toxoplasmosis with onset before age 1 month</td>
</tr>
<tr>
<td>• Varicella, disseminated (i.e., complicated chickenpox)</td>
</tr>
</tbody>
</table>
### Table 4. 1994 Revised HIV Pediatric (Age <13 Years) Classification System: Clinical Categories*

**Category C: Severely Symptomatic**

Children who have any condition listed in the 1987 surveillance case definition for AIDS (below), with the exception of LIP, which is a Category B condition:

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least 2 culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy—at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings:
  - Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests
  - Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children aged <2 years)
  - Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- HSV infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child aged >1 month
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- *Mycobacterium tuberculosis*, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jirovecii* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at age >1 month
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the findings:
  - Persistent weight loss >10% of baseline; or
  - Downward crossing of at least two of the following percentile lines on the weight-for-age chart (such as 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; or
  - <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart plus
  - Chronic diarrhea (that is, ≥2 loose stools per day for >30 days) or documented fever (for ≥30 days, intermittent or constant)


### References

1. Lindsey JC, Malee KM, Brouwers P, Hughes MD, Team PCS. Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy.

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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When to Initiate Therapy in Antiretroviral-Naive Children  
(Last updated February 12, 2014; last reviewed February 12, 2014)

Overview

The decision about when to initiate combination antiretroviral therapy (cART) in asymptomatic HIV-infected older children, adolescents, and adults continues to generate controversy among HIV experts. Aggressive therapy in the early stages of HIV infection has the potential to control viral replication before the evolution of HIV in that individual into a diverse and potentially more pathogenic quasispecies. Initiation of therapy at higher CD4 T lymphocyte (CD4) cell counts has been associated with fewer drug resistance mutations at virologic failure in adults. Early therapy also slows immune system destruction and preserves immune function, preventing clinical disease progression. Ongoing viral replication may be associated with persistent inflammation and development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of replication may reduce the occurrence of these non-AIDS complications. Conversely, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, may result in reduced evolution of drug-resistant virus due to a lack of drug selection pressure, improved adherence to the therapeutic regimen due to perceived need when the patient becomes symptomatic, and reduced or delayed adverse effects of cART. Because therapy in children is initiated at a young age and will likely be life-long, concerns about adherence and toxicities are particularly important.

The Department of Health and Human Services (HHS) Adult and Adolescent Antiretroviral Guidelines Panel (the Panel) has recommended initiation of therapy for all adults with HIV infection, with the proviso that the strength of the recommendations is dependent on the pre-treatment CD4 cell count. Randomized clinical trials have provided definitive evidence of benefit with initiation of therapy in adults with CD4 cell counts <350 cells/mm³. Observational cohort data have demonstrated the benefit of treatment in adults with CD4 cell counts between 350 and 500 cells/mm³ in reducing morbidity and mortality; therefore, adult treatment guidelines recommend initiation of lifelong cART for individuals with CD4 cell counts ≤500 cells/mm³. For adults with CD4 counts >500 cell/mm³, observational data are less conclusive regarding the potential survival benefit of early treatment. The recommendation for initiation of therapy at CD4 counts >500/mm³ (BIII evidence) in adults is based on accumulating data that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, the availability of more effective cART regimens with improved tolerability, and evidence that effective cART reduces sexual HIV transmission. However, the Adult Guidelines Panel acknowledges that the amount of data supporting earlier initiation of therapy decreases as the CD4 cell count increases above 500 cells/mm³, and that concerns remain over the unknown overall benefit, long-term risks, cumulative additional costs, and potential for decreased medication adherence associated with earlier treatment in asymptomatic patients.
Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive, HIV-Infected Infants and Children

**Panel’s Recommendations**

- Combination antiretroviral therapy (cART) should be initiated in all children with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions) (AI*).
- cART should be initiated in HIV-infected infants aged <12 months regardless of clinical status, CD4 T lymphocyte (CD4) percentage or viral load (AI for infants aged <12 weeks and AII for infants aged ≥12 weeks to 12 months).
- cART should be initiated in HIV-infected children aged ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
  - Ages 1 to <3 years
    - With CD4 count <1000 cells/mm³ or CD4 percentage <25% (AII)
  - Ages 3 to <5 years
    - With CD4 cell count <750 cells/mm³ or CD4 percentage <25% (AII)
  - Age ≥5 years
    - With CD4 cell count <350 cells/mm³ (AI*)
    - With CD4 cell count 350–500 cells/mm³ (BII*)
- cART should be considered for HIV-infected children aged ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
  - Ages 1 to <3 years
    - With CD4 cell count ≥1000 cells/mm³ or CD4 percentage ≥25% (BIII)
  - Ages 3 to <5 years
    - With CD4 cell count ≥750 cells/mm³ or CD4 percentage ≥25% (BIII)
  - Age ≥5 years
    - With CD4 cell count >500 cells/mm³ (BIII)
- cART should be initiated in HIV-infected children aged ≥1 year with confirmed plasma HIV RNA levels >100,000 copies/mL (AII).
- Issues associated with adherence should be assessed and discussed with an HIV-infected child’s caregivers before initiation of therapy (AIII). Patients/caregivers may choose to postpone therapy, and on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Infants Younger Than Age 12 Months

The Children with HIV Early Antiretroviral Therapy (CHER) Trial, a randomized clinical trial in South Africa, demonstrated that initiating triple-drug, cART before age 12 weeks in asymptomatic perinatally infected infants with normal CD4 percentage (>25%) resulted in a 75% reduction in early mortality, compared with delaying treatment until the infants met clinical or immune criteria. Most of the deaths in the infants in the delayed treatment arm occurred in the first 6 months after study entry. A substudy of this trial also found that infants treated early had significantly better gross motor and neurodevelopmental profiles than those in whom therapy was deferred. Because the risk of rapid progression is so high in young infants and based on the data in young infants from the CHER study, the Panel recommends initiating therapy for all infants aged <12 months regardless of clinical status, CD4 percentage, or viral load (Table 5). Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with an HIV-infected infant’s caregivers.
However, given the high risk of disease progression and mortality in young HIV-infected infants, it is important to expedite this assessment in infants aged <12 months.

The risk of disease progression is inversely correlated with the age of a child, with the youngest infants at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in older infected infants; by age 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.\(^{19}\) In the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger children than in older children at any given level of CD4 percentage, particularly for infants aged <12 months.\(^{20}\) Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. No specific “at-risk” viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections can occur in young infants with normal CD4 cell counts.\(^{20}\)

Identification of HIV infection during the first few months of life permits clinicians to initiate cART during the initial phases of primary infection. Data from a number of observational studies in the United States and Europe suggest that infants who receive early treatment are less likely to progress to AIDS or death than those who start therapy later.\(^{2,21-24}\) A study of 195 South African children initiating cART aged <24 months found that infants treated by age 6 months achieved target growth milestones more rapidly than children who initiated therapy between ages 12 and 24 months.\(^{25}\) Several small studies have demonstrated that, despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.\(^{26,27}\) In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication. Some of these infants have become HIV seronegative. Although there is a single case report of “functional cure” in an HIV-infected child treated with a cART regimen initiated at age 30 hours, discussed below, current cART does not eradicate HIV infection in the majority of perinatally infected infants because of the long half-life of latently infected CD4 cells.\(^{28,29}\)

A recent report of a “functional cure” in an HIV-infected child in Mississippi has generated discussion about early initiation of cART in newborn infants with high-risk HIV exposure. This newborn, born to a mother who did not receive antenatal or perinatal cART, was treated with a 3-drug cART regimen at ages 30 hours through 18 months, after which cART was discontinued against medical advice. Follow-up evaluations off cART showed no evidence of virologic rebound by standard clinical assays, and although a scant amount of HIV nucleic acid was detected, replication-competent virus was not.\(^{30}\) This experience has prompted increasing support for initiation of treatment in the first weeks of life, as soon as the diagnosis is made. However, because of limited safety and pharmacokinetic data and experience with antiretroviral (ARV) drugs in infants aged <2 to 4 weeks, drug and dose selection in this age group is challenging (see What to Start). If early treatment is initiated, the Panel does not recommend empiric treatment interruption until the durability of the findings in the Mississippi baby can be studied and replicated in other children.

Virologic suppression may take longer to achieve in young children than in older children or adults.\(^{31,32}\) Possible reasons for the slower response in infants include higher virologic set points in young infants, inadequate ARV drug levels, and poor adherence because of the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70% to 80% have been reported in HIV-infected infants initiating therapy at age <12 months.\(^{2,33,34}\) In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at age <6 months, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.\(^{2}\) More rapid viral suppression in young infants may also be important in reducing the long-lived HIV reservoir; a study of 17 HIV-infected infants initiating lopinavir/ritonavir-based cART before age 6 months demonstrated that time to the first HIV viral load <400 copies/mL was correlated with the size of the long-lived HIV reservoir (i.e., the resting memory CD4 T-cell pool).\(^{35}\)
Information on appropriate drug dosing in infants younger than 3 to 6 months is limited. Hepatic and renal functions are immature in newborns undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children.\(^{36}\) When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, ARV drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. Frequent follow-up and continued assessment and support of adherence are especially important when treating young infants (see Adherence).

Finally, the possibility of long-term toxicities (e.g., lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, mitochondrial dysfunction) with prolonged therapy is a concern.\(^{37}\)

**Children Aged 1 Year and Older**

Disease progression is less rapid in children aged ≥1 year.\(^{19}\) Children with clinical AIDS or significant symptoms (Clinical Category C or B—see Table B in Appendix C: Supplemental Information)\(^{38}\) are at high risk of disease progression and death. The Panel recommends treatment for all such children, regardless of immunologic or virologic status. However, children aged ≥1 year who have mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than children with more severe clinical symptoms.\(^{39}\) It should also be noted that some Clinical Category B conditions, such as a single episode of serious bacterial infection, may be less prognostic of the risk of disease progression. Consideration of CD4 cell count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, the strength of recommendations to initiate cART in asymptomatic individuals is based primarily on risk of disease progression, as determined by baseline CD4 cell count.\(^{9}\) In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 cell counts <350 cells/mm\(^3\). In HIV-infected adults in Haiti, a randomized clinical trial found significant reductions in mortality and morbidity with initiation of treatment when CD4 cell counts fell to <350 cells/mm\(^3\), compared with deferring treatment until CD4 cell counts fell to <200 cells/mm\(^3\).\(^{10}\) In observational data in adults, a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting treatment between 1995 and 2003, the risk of AIDS or death was significantly less in adults who started treatment with CD4 cell counts of 200 to 350 cells/mm\(^3\) compared with those who started therapy at CD4 cell counts <200 cells/mm\(^3\).\(^{40}\)

The Cochrane Collaboration\(^{41}\) recently published a review on the effectiveness of cART in HIV-infected children aged <2 years based on data from published randomized trials of early versus deferred cART\(^{17,42}\). The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that data supporting universal initiation of treatment between ages 1 and 2 years are less compelling.

The Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) trial was designed to investigate the impact on AIDS-free survival and neurodevelopment of deferral of cART in children aged >1 year.\(^{43}\) This multicenter, open-label trial randomized 300 HIV-infected children aged >1 year (median 6.4 years) to immediate initiation of cART or deferral until the CD4 percentage was <15%. The median baseline CD4 percentage was 19% (IQR 16–22%) and 46% of children in the deferred group started cART during the study. AIDS-free survival at week 144 was 98.7% (95% CI 94.7–99.7) in the deferred group and 97.9% (93.7–99.3) in the immediate therapy group (\(P = 0.6\)), and immediate cART did not significantly improve neurodevelopmental outcomes.\(^{44}\) However, because of the low event rate, the study was underpowered to detect a difference between the two groups. This study population likely had a selection bias toward relatively slowly progressive disease because it enrolled children who had survived a median of 6 years without cART. The limited enrollment of children aged <3 years poses restrictions on its value for recommendations in that age group.

No randomized trial data exist to address the comparative efficacy of starting versus deferring treatment at higher CD4 thresholds in HIV-infected adults or children. Two observational studies in adults—the ART Cohort Collaboration (ART-CC) and North American AIDS Cohort Collaboration on Research and Design (NA-
ACCORD)—suggest a higher rate of progression to AIDS or death in patients deferring treatment until the CD4 count is <350 cells/mm³ compared with patients starting cART at CD4 cell counts of 351 to 500 cells/mm³.11,12 The NA-ACCORD study demonstrated a benefit of starting treatment at CD4 cell counts >500 cell/mm³ compared with starting cART at CD4 cell counts below this threshold;11 however, the ART-CC cohort found no additional benefit for patients starting cART with CD4 cell counts >450 cells/mm³.12 In a third observational study of 5,162 patients with CD4 cell counts between 500 and 799 cells/mm³, patients who started cART immediately did not experience a significant reduction in progression to AIDS or death (HR: 1.10, 95% CI: 0.67 to 1.79) or death alone (HR: 1.02, 95% CI: 0.49 to 2.12), compared with those who deferred therapy.14 There are no similar observational data analyses for HIV-infected children.

In children, the prognostic significance of a specific CD4 percentage or count varies with age.20,45 In data from the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count in children aged 1 to 4 years than in children aged ≥5 years (see Figures A and B and Tables A and B in Appendix C: Supplemental Information). Data from the HIV Paediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful prognostic marker for disease progression in children aged ≥5 years, with risk of progression similar to that observed in adults (see Table B in Appendix C: Supplemental Information).20,46 For children aged 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (see Table A in Appendix C: Supplemental Information).

Because the CD4 percentage is more consistent than the naturally declining CD4 cell count in the first years of life, it has been used preferentially to monitor immunologic status in children aged <5 years of age. However, an analysis of more than 21,000 pairs of CD4 measurements from 3,345 children aged <1 to 16 years in the HIV Paediatric Prognostic Markers Collaborative Study found that CD4 cell counts and percentages were frequently discordant around established World Health Organization (WHO) and the Pediatric European Network for Treatment of AIDS (PENTA) thresholds for initiation of cART (14% and 21%, respectively).47 Furthermore, CD4 cell counts were found to provide greater prognostic value over CD4 percentage for short-term disease progression for children aged <5 years as well as in older children. For example, the estimated hazard ratio for AIDS or death at the 10th centile of CD4 cell count (compared with the 50th centile) was 2.2 (95% confidence interval [CI]) 1.4, 3.0) for children aged 1 to 2 years versus 1.2 (CI 0.8, 1.6) for CD4 percentage. Therefore, the updated pediatric guidelines include CD4 cell count thresholds (which differ for children aged 1 to <3, 3 to 5, and ≥5 years due to age-related changes in absolute CD4 cell count) as well as CD4 percentage thresholds for all children aged >12 months. In the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count.45 Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality and lower neurocognitive performance;51 similar findings have been reported in adults.52-54 Similarly, in the HIV Paediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children aged >1 year when HIV RNA levels were ≥100,000 copies/mL (see Figures D and E and Table A in Appendix C: Supplemental Information).45 For example, the estimated 1-year risk of death was 2 to 3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared with 10,000 copies/mL and 8 to 10 times higher with plasma HIV RNA >1,000,000 copies/mL. Therefore, the Panel recommends that children of all ages with HIV RNA levels >100,000 copies/mL initiate cART.

As with data in adults, data from pediatric studies suggest that improvement in immunologic parameters is better in children when treatment is initiated at higher CD4 percentage/count levels.32,55-59 In a study of 1,236 perinatally infected children in the United States, only 36% of those who started treatment with CD4 percentage <15% and 59% of those starting with CD4 percentage 15% to 24% achieved CD4 percentage >25% after 5 years of therapy.60 Younger age at initiation of therapy has also been associated with improved
immune response and with more rapid growth reconstitution. In addition, the PREDICT Study demonstrated improved height z-scores in the early treatment arm compared with no improvement in the deferred arm. Given that disease progression in children aged ≥5 years is similar to that in adults, and observational data in adults show decreased risk of mortality with initiation of therapy when CD4 cell count is <500 cells/mm³, most experts feel that recommendations for asymptomatic children in this age range should be similar to those for adults. However, there are no conclusive pediatric data to address the optimal CD4 cell count threshold for initiation of therapy in older children; additional research studies are needed to answer this question in children more definitively. The HHS Adult Treatment Guidelines Panel has moved to endorse initiating cART in all HIV-infected adults regardless of CD4 cell count, using varying strengths of evidence to support different CD4 cell count thresholds and incorporating compelling data demonstrating that cART is effective in preventing secondary transmission of HIV. However, prevention of sexual transmission of HIV is not a significant consideration for children aged <13 years. Comparative studies on the impact of treatment versus treatment delay at specific higher CD4 cell counts have not been performed in children, and observational adult studies have produced conflicting results. Drug choices are more limited in children than in adults and adequate data to address the potential long-term toxicities of prolonged cART in a developing child are not yet available. Some studies have shown that a small proportion of perinatally infected children may be long-term nonprogressors, with no immunologic or clinical progression by age 10 years despite receiving no cART. Medication adherence is the core requirement for successful virologic control, but enforcing consistent adherence in childhood is often challenging. Incomplete adherence leads to the selection of viral resistance mutations but forced administration of ARVs to children may result in treatment aversion or fatigue, which occurs among many perinatally infected children during adolescence. The relative benefits of initiating cART in asymptomatic children with low viral burdens and high CD4 cell counts must be weighed against these potential risks.

The Panel recommends that cART should be initiated in all children who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B condition: single episode of serious bacterial infection [Table 4 in Goals of Antiretroviral Treatment]), regardless of CD4 percentage/count or HIV RNA level. The Panel also recommends that children of all ages with HIV RNA levels >100,000 copies/mL initiate cART regardless of CD4 count or symptoms.

The Panel also generally recommends treatment for all children aged ≥1 year with no or mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of bacterial infection [Table 4 in Goals of Antiretroviral Treatment]), with the strength of recommendation differing based on age and CD4 count/percentage. Providers may choose to postpone therapy, and, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors. Note that the Panel’s recommendations which permit optional deferral of therapy for healthy children ≥1 year of age are different from the 2013 WHO guidelines, which recommend initiation of therapy for all children <5 years of age, reflecting different approaches in resource-limited settings.

Treatment is strongly recommended regardless of HIV RNA level for children aged 1 to <3 years with CD4 cell counts <1000/mm³ or percentage <25%, and for children aged 3 to <5 years with CD4 cell counts <750 cells/mm³ or percentage <25%, based on observational pediatric data. Treatment should also be considered for children aged 1 to <3 years with CD4 cell counts ≥1000/mm³ and percentage ≥25% and for children aged 3 to <5 years with CD4 cell counts ≥750 cells/mm³ and percentage ≥25%, although the strength of the recommendation is lower because of limited data. For children aged ≥5 years with no or minimal symptoms, treatment is recommended if CD4 cell counts are ≤500 cells/mm³, regardless of HIV RNA level. The evidence for this recommendation is strongest for children with CD4 cell counts <350 cells/mm³. For children with CD4 cell counts 350 to 500 cells/mm³, the recommendation is based on observational data in adults and hence the evidence base is not as strong; this recommendation should not prohibit research studies in children designed to answer this question more definitively. Treatment should also be considered for children who are asymptomatic or have mild symptoms...
with CD4 counts >500 cells/mm³, although the strength of the recommendation is lower because of limited data.

In general, except in infants and children with advanced HIV infection, cART does not need to be started immediately. Before initiating therapy, it is important to take time to educate caregivers (and older children) about regimen adherence and to anticipate and resolve any barriers that might diminish adherence. This is particularly true for children aged ≥5 years given their lower risk of disease progression and the higher CD4 cell count threshold now recommended for initiating therapy.

If therapy is deferred, the health care provider should closely monitor a child’s virologic, immunologic, and clinical status (see Clinical and Laboratory Monitoring). Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL);
- CD4 count or percentage values approaching the age-related threshold for treatment;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

**Table 5. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children**

Table 5 provides general guidance rather than absolute recommendations for individual patients. Factors to be considered in decisions about initiation of therapy include risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with a child (if age appropriate) and the caregiver. Patients/caregivers may choose to postpone therapy and, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 Months</td>
<td>Regardless of clinical symptoms, immune status, or viral load</td>
<td>Treat (AI for &lt;12 weeks of age; AII for ≥12 weeks)</td>
</tr>
</tbody>
</table>
| 1 to <3 Years | AIDS or significant HIV-related symptoms  
CD4 cell count <1000 cells/mm³ or CD4 percentage <25%,*  
Asymptomatic or mild symptoms and CD4 cell count ≥1000 cells/mm³ or percentage ≥25%  | Treat (AI*)  
Treat (AII)  
Consider Treatment(d) (BIII) |
| 3 to <5 Years | AIDS or significant HIV-related symptoms  
CD4 cell count <750 cells/mm³ or CD4 percentage <25%,*  
Asymptomatic or mild symptoms and CD4 cell count ≥750 cells/mm³ or percentage ≥25%  | Treat (AI*)  
Treat (AII)  
Consider Treatment(d) (BIII) |
| ≥5 Years | AIDS or significant HIV-related symptoms  
CD4 cell count ≤500 cells/mm³  
Asymptomatic or mild symptoms and CD4 cell count >500 cells/mm³  | Treat (AI*)  
Treat (AI* for CD4 cell count <350 cells/mm³ and BII* for CD4 cell count 350–500 cells/mm³)  
Consider Treatment (BIII) |
| All Ages | HIV RNA levels >100,000 copies/mL                                           | Treat (AII)         |
References


Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children

Panel’s Recommendations

• The Panel recommends initiating combination antiretroviral therapy (cART) in treatment-naive children using one of the following preferred agents plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone combination:
  ◦ For neonates/infants aged ≥42 weeks postmenstrual and ≥14 days postnatal to children <3 years: ritonavir-boosted lopinavir (AI);
  ◦ For children aged 3 years to <6 years: efavirenz or ritonavir-boosted lopinavir (AI*);
  ◦ For children aged ≥6 years: ritonavir-boosted atazanavir or efavirenz or ritonavir-boosted lopinavir (AI*).

• The Panel recommends the following preferred dual-NRTI backbone combinations:
  ◦ For children of any age: zidovudine plus (lamivudine or emtricitabine) (AI*);
  ◦ For children aged ≥3 months: abacavir plus (lamivudine or emtricitabine) (AI) or zidovudine plus (lamivudine or emtricitabine) (AI*);
  ◦ HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 (AI*);
  ◦ For adolescents at Tanner Stage 4 or 5: abacavir plus (lamivudine or emtricitabine) (AI) or tenofovir disoproxil fumarate (tenofovir) plus (lamivudine or emtricitabine) (AI*) or zidovudine plus (lamivudine or emtricitabine) (AI*).

• Table 6 provides a list of Panel-recommended alternative and acceptable regimens.

• Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing (AIII).

• For children aged <42 weeks postmenstrual or <14 days postnatal, data are currently inadequate to provide recommended dosing to allow the formulation of an effective, complete cART regimen (see Special Considerations section).

• Alternative regimens may be preferable for some patients based on their individual characteristics and needs.

• Both emtricitabine and lamivudine, and tenofovir have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection the reader should access the Pediatric Opportunistic Infections Guidelines.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Criteria Used for Recommendations

In general, the Panel recommendations are based on reviews of pediatric and adult clinical trial data published in peer-reviewed journals (the Panel may also review data prepared by manufacturers for Food and Drug Administration [FDA] review and data presented in abstract format at major scientific meetings). Few randomized, Phase III clinical trials of combination antiretroviral therapy (cART) in pediatric patients exist that provide direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic (PK) trials and non-randomized, open-label studies. In general, even in studies in adults, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 T lymphocyte (CD4) cell count and HIV RNA levels. The Panel continually modifies
recommendations on optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities are recognized.

Information considered by the Panel for recommending specific drugs or regimens includes:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., powders), volume of syrups, and pill size and number of pills;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

The Panel classifies recommended drugs or drug combinations into one of several categories as follows:

- **Preferred:** Drugs or drug combinations are designated as preferred for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies demonstrate that safety and efficacy are suggested using surrogate markers; additional considerations are listed above.

- **Alternative:** Drugs or drug combinations are designated as alternatives for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared with preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.

- **Use in Special Circumstances:** Some drugs or drug combinations are recommended for use as initial therapy only in special circumstances when preferred or alternative drugs cannot be used.

**Factors to Consider When Selecting an Initial Regimen**

A cART regimen for children should generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one active drug from the following classes: non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI), generally boosted with low-dose ritonavir. Although integrase strand transfer inhibitors (INSTIs) or CCR5 antagonists may be considered for first-line treatment of adults, there are insufficient data to recommend these agents as preferred agents for initial therapy in children at this time.

Choice of a regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Table 7. In addition, because cART will most likely need to be administered lifelong, considerations related to the choice of initial antiretroviral (ARV) regimen should also include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens; differing formulations; palatability problems; and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after assessment and counseling of caregivers about adherence to therapy.

**Choice of NNRTI- Versus PI-Based Initial Regimens**

Preferred regimens for initial therapy include both NNRTI- and protease inhibitor (PI)-based regimens. The selection of a NNRTI- or PI-based regimen should be based on patient characteristics, especially age, and preferences, results of viral drug resistance testing, and information cited below.
Recent clinical trial data in children provide some guidance for choosing between a NNRTI-based regimen and a PI-based regimen for initial therapy. The P1060 study compared a nevirapine-based regimen to a lopinavir-based regimen in HIV-infected infants and children aged 2 months to 35 months in 6 African countries and India. Infants and children in this study were stratified at entry based on prior maternal or infant exposure to peripartum single-dose nevirapine prophylaxis or no exposure, and randomized to receive either zidovudine, lamivudine, and nevirapine or zidovudine, lamivudine, and ritonavir-boosted lopinavir (lopinavir boosted with low-dose ritonavir). Median age was 0.7 years in the single-dose nevirapine-exposed and 1.7 years in the nevirapine-unexposed children. Among infants and children with prior exposure to nevirapine, 39.6% of children in the nevirapine group reached a study endpoint of death, virologic failure, or toxicity by Week 24 compared with 21.7% of children in the ritonavir-boosted lopinavir group. Among infants and children with no prior nevirapine exposure, 40.1% of children treated with nevirapine met a study endpoint after 24 weeks in the study compared with 18.4% of children who received ritonavir-boosted lopinavir. Based on these data, a PI-based regimen containing ritonavir-boosted lopinavir is the preferred initial regimen for HIV-infected children aged <3 years.

A comparison of a PI-based regimen and a NNRTI-based regimen was also undertaken in HIV-infected treatment-naive children aged 30 days to <18 years in PENPACT-1 (PENTA 9/PACTG 390) (the study did not dictate the specific NNRTI or PI drug initiated). In the PI-based group, 49% of children received ritonavir-boosted lopinavir and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. Efavirenz was recommended only for children aged ≥3 years. After 4 years of follow-up, 73% of children randomized to PI-based therapy and 70% randomized to NNRTI-based therapy remained on their initial cART regimen. In both groups, 82% of children had viral loads <400 copies/mL, suggesting that selection of a NNRTI or a PI did not influence outcome. Although the age of participants overlapped somewhat between P1060 and PENPACT-1 (in PENPACT-1, the lowest quartile was aged <2.8 years), PENPACT-1 generally enrolled older children.

Recent data from PROMOTE-pediatrics trial also demonstrated comparable virologic efficacy among children randomized to receive either a NNRTI or ritonavir-boosted lopinavir-based cART. Children were aged 2 months to <6 years, with a median of 3.1 years (intermediate between P1060 and PENPACT 1). Children had no perinatal exposure to nevirapine and could be cART-naive or currently receiving cART with HIV RNA level <400 copies/mL at enrollment. In the NNRTI arm, children <3 years of age received nevirapine and those aged ≥3 years primarily received efavirenz. Among 185 children randomized to ritonavir-boosted lopinavir- (n = 92) or NNRTI- (n = 93) based cART, the proportion with HIV RNA level <400 copies/mL at 48 weeks was 80% in the ritonavir-boosted lopinavir arm versus 76% in the NNRTI-arm, a difference of 3.8% (95% CI: -8.9% to +17).

With regard to virologic suppression, the results of the P1060 study suggest that a PI-based regimen containing ritonavir-boosted lopinavir should be the preferred initial regimen for children aged <3 years. However, in both single-dose nevirapine-exposed and -unexposed children in the P1060 study, participants receiving the nevirapine-based regimen demonstrated better immunologic response and growth than those receiving a ritonavir-boosted lopinavir-based regimen, although these differences did not achieve statistical significance. Similarly, in the NEVEREST study, children switched to a nevirapine regimen showed better immune and growth responses than those continuing a ritonavir-boosted lopinavir regimen. Based on these findings, the potential for improved lipid profiles with nevirapine use, and the poor palatability of liquid ritonavir-boosted lopinavir, liquid nevirapine remains an acceptable alternative for infants who were not exposed to peripartum single-dose nevirapine or infant nevirapine prophylaxis and who cannot tolerate ritonavir-boosted lopinavir. In children aged ≥3 years, either a NNRTI-based or a PI-based regimen is acceptable.

**Summary: NNRTI-Based Regimens (One NNRTI + Two-NRTI Backbone)**

**Efavirenz (aged ≥3 months), etravirine (aged ≥6 years) and nevirapine (aged ≥15 days) have an FDA-approved pediatric indication for treatment of HIV infection. In the United States, nevirapine is the only NNRTI approved for initial therapy in children.**
available in a liquid formulation. Efavirenz capsules can be opened and sprinkled on age-appropriate food. This administration procedure has recently been approved by the FDA for use in children as young as age 3 months who weigh at least 3.5 kg. However, at this time, there are concerns regarding variable PK of the drug in the very young and the committee does not endorse its use for infants and children aged 3 months to 3 years at this time. Additional data about the PK in children in this age group are awaited. Advantages and disadvantages of different NNRTI drugs are delineated in Table 7. Use of NNRTIs as initial therapy preserves the PI class for future use and confers lower risk of dyslipidemia and fat maldistribution than use of some agents in the PI class. In addition, for children taking solid formulations, NNRTI-based regimens generally have a lower pill burden than PI-based regimens. The major disadvantages of the current NNRTI drugs FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance, and cross resistance to other NNRTIs is common. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all NNRTI drugs, but is most frequent with nevirapine, at least in HIV-infected adults. Like PIs, NNRTIs have the potential to interact with other drugs also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted PI regimens.

Efavirenz, in combination with 2 NRTIs, is the preferred NNRTI for initial therapy of children aged ≥3 years based on clinical trial experience in adults and children. Nevirapine is considered as a component of an alternative NNRTI-based regimen because of its association with the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare but potentially life-threatening hepatitis,7,8 and conflicting data about virologic efficacy compared to preferred regimens.

Currently, there are insufficient data to recommend etravirine or rilpivirine-based regimens as initial therapy in children. Etravirine is currently FDA-approved only for treatment-experienced adults and it is unlikely that it will be investigated in treatment-naive children.

Preferred NNRTI

Efavirenz as Preferred NNRTI (For Children Aged ≥3 Years) (AI*)

In clinical trials in HIV-infected adults, efavirenz in combination with two NRTIs has been associated with excellent virologic response. Efavirenz-based regimens have proven virologically superior or non-inferior to a variety of regimens including those containing ritonavir-boosted lopinavir, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.9-16

Efavirenz in combination with two NRTIs or with a NRTI and a PI has been studied in HIV-infected children17-23 with results comparable to those seen in adults. For children aged ≥3 years who are unable to swallow pills, efavirenz capsules can be opened and sprinkled on age-appropriate food. Bioequivalence data based on bioavailability and PK support this option.24

The major limitations of efavirenz are central nervous system (CNS) side effects in both children and adults; reported adverse effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after initiating efavirenz. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the occurrence was more frequent in adults with higher levels of drug.25-28 In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than adults.21,23 In addition, first-trimester exposure to efavirenz is potentially teratogenic (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Although emerging information about the use of efavirenz in pregnancy is reassuring, alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman’s health (BIII).
Alternative NNRTI

Nevirapine as Alternative NNRTI (AI)

Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Nevirapine in combination with two NRTIs or with a NRTI and a PI has been studied in HIV-infected children.

Randomized clinical trials in adults have not demonstrated virologic inferiority for a nevirapine-based regimen compared to either efavirenz or atazanavir-based regimens. In the 2NN trial, virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine vs. 62% of those receiving efavirenz). Similarly, in the ARTEN trial, cART-naive participants were randomized to nevirapine 200 mg twice daily, nevirapine 400 mg once daily, or ritonavir-boosted atazanavir all in combination with tenofovir disoproxil fumarate (tenofovir)/emtricitabine. By 48 weeks, similar proportions of subjects in each group had at least 2 consecutive plasma HIV RNA levels <50 copies/mL (66.8% for nevirapine vs. 65.3% for atazanavir/ritonavir).

In the P1060 trial of children aged <3 years, a nevirapine-based regimen was less effective compared to a ritonavir-boosted lopinavir regimen, regardless of prior history of maternal nevirapine exposure. In PENPACT-I and PROMOTE-pediatrics, there was no difference in virologic suppression between NNRTI-based and PI-based regimens (see Choice of NNRTI- Versus PI- Based Initial Regimens). However, interpretation of these studies is complicated by the fact that the children in P1060 were younger than those in PROMOTE-pediatrics and PENPACT-I. Furthermore efavirenz was allowed in PROMOTE-pediatrics and PENPACT-I and was preferentially prescribed to older children. In addition, in the PROMOTE-pediatrics study, both ARV-naive and experienced but virologically suppressed children were enrolled. Comparisons of a nevirapine-based regimen and an efavirenz-based regimen in children in non-randomized studies have suggested that efavirenz is more effective. An analysis of children and adults starting first-line cART in Uganda demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years). Few had been exposed to peripartum nevirapine. In addition, a recent report of 804 children aged 3 to 16 years who received either efavirenz (n = 421) or nevirapine (n = 383) in the Botswana national treatment program demonstrated increased rates of virologic failure (including both failure to suppress and rebound) among those receiving nevirapine (OR = 2.0, 95% CI 1.4–2.7). Time to virologic failure also favored an efavirenz regimen.

In addition to concerns about virologic efficacy, adult randomized clinical trials have demonstrated higher rates of toxicity and drug discontinuation in the nevirapine arms. In the 2NN study, serious hepatic toxicity was more frequent in the nevirapine arm than in the efavirenz arm (hepatic laboratory toxicity in 8%–14% of those on nevirapine, compared with 5% on efavirenz). In the ARTEN trial, more participants in the nevirapine arms discontinued study drugs because of adverse events (13.6% vs. 2.6%, respectively) or lack of efficacy (8.4% vs. 1.6%, respectively). Data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 cell counts and in women, particularly women with CD4 cell counts >250 cells/mm³ and men with CD4 cell counts >400 cells/mm³. In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults. Although there is limited evidence in children of hepatic toxicity associated with CD4 count, overall toxicity has been reported to be more frequent among children with CD4 percentage ≥15% at therapy initiation. The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown. Efavirenz use in this situation has been well tolerated in the very limited number of patients in whom it has been reported but this substitution should be attempted with caution.

Because of the greater potential for toxicity and possibly increased risk of virologic failure, nevirapine-based regimens are considered an alternative rather than the preferred NNRTI in children aged ≥3 years. In children aged <3 years, nevirapine is considered an alternative because of increased risk of virologic failure compared to a PI ritonavir-boosted lopinavir regimen.
Nevirapine should not be used in postpubertal adolescent girls with CD4 cell counts >250/mm³ because of the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk. Nevirapine also should be used with caution in children with elevated pretreatment liver function tests.

**PI-Based Regimens (PIs [Boosted or Unboosted] Plus Two-NRTI Backbone)**

**Summary: PI-Based Regimens**

Nine PIs are currently FDA-approved for use in adults and seven are approved for use in children. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. However, because PIs are metabolized via hepatic enzymes, the drugs have potential for multiple drug interactions. They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider in selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), age of the child, and availability of data in children. (Table 7 lists the advantages and disadvantages of PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug).

Ritonavir is a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme and can be used in low doses as a PK booster when coadministered with some PIs, increasing drug exposure by prolonging the half-life of the boosted PI. Currently only ritonavir-boosted lopinavir is available as a coformulated product. When ritonavir is used as a PI booster with other PIs, two agents must be administered. In addition, the use of low-dose ritonavir increases the potential for hyperlipidemia and drug-drug interactions.

The Panel recommends either atazanavir with low-dose ritonavir or coformulated ritonavir-boosted lopinavir as the preferred PI for initial therapy in children based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, availability of appropriate dosing information, and experience as initial therapy in both resource-rich and resource-limited areas. Ritonavir-boosted darunavir is considered an alternative PI regimen. Several regimens including unboosted atazanavir in adolescents aged ≥13 years, ritonavir-boosted fosamprenavir in children aged ≥6 months, and nelfinavir are considered appropriate for use in special circumstances when preferred and alternative drugs are not available or are not tolerated.

**Preferred PIs**

**Atazanavir with Low-Dose Ritonavir as Preferred PI (for Children ≥6 Years) (AI*)**

Atazanavir is a once-daily PI that was FDA-approved in March 2008 for use in children aged ≥6 years. It has efficacy equivalent to efavirenz-based and ritonavir-boosted-lopinavir-based combination therapy when given in combination with 2 NRTIs in treatment-naive adults. Seventy-three percent of 48 treatment-naive South African children achieved viral load <400 copies/mL by 48 weeks when given atazanavir with or without low-dose ritonavir in combination with 2 NRTIs. Among 43 treatment-naive children aged 6 to18 years in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 51% and 47% achieved viral load <400 copies/mL and <50 copies/mL, respectively, by 96 weeks. When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children aged ≥6 years and in ARV-naive adults appears to be associated with fewer PI-resistance mutations at virologic failure compared with atazanavir given without ritonavir boosting. The main adverse effect associated with ritonavir-boosted atazanavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher with low-dose ritonavir boosting than with atazanavir alone.
Lopinavir with Low-Dose Ritonavir as Preferred PI (for Infants with a Postmenstrual Aged ≥42 Weeks and Postnatal Age ≥14 Days) (AI)

In clinical trials of treatment-naive adults, regimens containing ritonavir-boosted lopinavir plus 2 NRTIs have been demonstrated to be comparable to a variety of other regimens including atazanavir, darunavir (at 48 weeks), fosamprenavir, ritonavir-boosted saquinavir, and efavirenz. Ritonavir-boosted lopinavir was demonstrated to have superior virologic activity when compared to nelfinavir.\textsuperscript{11,45,47,55-60} Ritonavir-boosted lopinavir has been studied in both ARV-naive and -experienced children and has demonstrated durable virologic activity and low toxicity (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).\textsuperscript{1,61-67} In addition, dosing and efficacy data in infants as young as age 25 days are available.\textsuperscript{64,68} Post-marketing reports of ritonavir-boosted lopinavir-associated cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported, predominantly in preterm neonates. These reports have resulted in a change in ritonavir-boosted lopinavir labeling including a recommendation to not administer the combination to neonates until they reach a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days. In addition, although once-daily ritonavir-boosted lopinavir is FDA-approved for initial therapy in adults,\textsuperscript{69} PK data in children do not support a recommendation for once-daily dosing in children.\textsuperscript{70,71}

Alternative PI

Darunavir with Low-Dose Ritonavir Administered Once Daily as Alternative PI (For Children Aged ≥12 Years) or Twice Daily (For Children Aged ≥3 to 12 Years) (AI*)

Darunavir combined with low-dose ritonavir is FDA-approved for ARV-naive and -experienced adults and for ARV-naive and -experienced children aged ≥3 years. In a randomized, open-label trial in adults, darunavir/ritonavir (800/100 mg once daily) was found to be non-inferior to ritonavir-boosted lopinavir (once or twice daily) when both boosted PIs were administered in combination with tenofovir/emtricitabine. Adverse events were also less common in the darunavir/ritonavir group (\textit{P} <0.01).\textsuperscript{55,72} Unfortunately, there is limited information about the use of darunavir combined with low-dose ritonavir as part of an initial therapy regimen for HIV-infected children. To date the only clinical trial of darunavir with low-dose ritonavir as initial therapy is a study of once-daily ritonavir-boosted darunavir in treatment-naive adolescents aged 12 to 18 years (mean age, 14.6 years). After 24 weeks of treatment, 11 of 12 subjects had HIV-1 RNA <50 copies/mL and the agents were well tolerated.\textsuperscript{73,74} Data in treatment-experienced children have also demonstrated that the regimen is effective and well-tolerated. In a study of treatment-experienced children (aged 6–17 years), DELPHI, twice-daily ritonavir-boosted-darunavir-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks.\textsuperscript{75} In another study of treatment-experienced pediatric subjects (aged 3 to <6 years and weight ≥10 kg to <20 kg), ARIEL, 57% of subjects had HIV-1 RNA <50 copies/mL and 81% were less than 400 copies/mL after 24 weeks of treatment.\textsuperscript{76} Twenty children completed the trial; 1 stopped prematurely because of vomiting. Based on data from these studies and the findings of high potency and low toxicity in adults, ritonavir-boosted darunavir is recommend as an alternative agent for initial therapy in HIV-infected children. Some experts, however, would only recommend ritonavir-boosted darunavir for treatment-experienced children and reserve its use for patients with resistant mutations to other PIs.

As noted above, ritonavir-boosted darunavir is approved for once-daily use in adults and children. In addition to the DELPHI study noted above, a PK study of 24 patients, aged 14 to 23 years, receiving once-daily darunavir demonstrated darunavir exposure similar to that in adults receiving once-daily therapy although there was a trend toward lower exposures in those aged <18 years.\textsuperscript{77} Also, in the ARIEL study, 10 treatment-experienced children were switched from twice daily dosing to once-daily dosing after 24 weeks of therapy. PK studies were performed after 2 weeks of once-daily dosing and demonstrated darunavir mean area under the curve (AUC) 24-hour equivalent to 128% of the adult AUC 24 hour.\textsuperscript{78} Based on these findings, the FDA has approved use of once-daily darunavir in children. At this time, the Panel recommends that once-daily
dosing of ritonavir-boosted darunavir as alternative initial therapy be considered only in treatment-naive adolescents aged >12 years. Additional experience with once-daily dosing of ritonavir-boosted darunavir in children aged ≥3 years through age 12 years is awaited. Also, if darunavir resistance-associated substitutions are present (V11I, V32I, L33F, I47V, 150V, I54L, I54M, T74P, L76V, I84V, and L89V), once-daily administration should not be used. If ritonavir-boosted darunavir is used as alternative therapy in children aged <12 years or if any of these resistance-associated substitutions are present, the Panel recommends twice-daily dosing.

PIs for Use in Special Circumstances

**Atazanavir without Ritonavir Boosting in Children Aged ≥13 Years (BII*)**

Although unboosted atazanavir is FDA-approved for treatment-naive adolescents aged ≥13 years who weigh >39 kg and are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m² basis) are required in adolescents than in adults to achieve adequate drug concentrations53 (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information on dosing used in IMPAACT/PACTG P1020A). If using unboosted atazanavir in treatment-naive patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because this combination demonstrated inferior virologic response in adults in ACTG 5175. Also, unboosted atazanavir should not be used in combination with tenofovir because concomitant administration results in lower atazanavir exposure. If didanosine, emtricitabine, and atazanavir are used in combination, patients should be instructed to take didanosine and atazanavir at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach. The complexity of this regimen argues against its use.

**Fosamprenavir with Low-Dose Ritonavir as Alternative PI (for Children Aged ≥6 Months) (AI*)**

Fosamprenavir (the prodrug of amprenavir) is available in a pediatric liquid formulation and a tablet formulation. In an adult clinical trial, fosamprenavir with low-dose ritonavir was demonstrated to be noninferior to ritonavir-boosted lopinavir.57 In June 2007, fosamprenavir suspension was FDA-approved for use in pediatric patients aged ≥2 years. The approval was based on 2 open-label studies in pediatric patients aged 2 to 18 years.80,81 PK, safety and efficacy were assessed in an international study of PI-naive and -experienced pediatric patients, aged 4 weeks to 2 years. Overall, fosamprenavir was well tolerated except for vomiting and effective in suppressing viral load and increasing CD4 cell count (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). These data supported FDA approval for use in PI-naive children as young as 4 weeks who were born at ≥38 weeks’ gestation and had attained a postnatal age of 28 days. Young infants, however, demonstrated low drug exposure. Fosamprenavir should always be used in combination with low-dose ritonavir boosting and only for children aged ≥6 months. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

**Nelfinavir for Children Aged ≥2 Years (BI*)**

Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children aged ≥2 years in special circumstances. The pediatric experience with nelfinavir-based regimens in ARV-naive and -experienced children is extensive, with follow-up in children receiving the regimen for as long as 7 years. The drug has been well tolerated—diarrhea is the primary adverse effect; however, in clinical studies the virologic potency of nelfinavir has varied greatly, with reported rates of virologic suppression ranging from 26% to 69% (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naive pediatric patients. In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus 80% of children with therapeutic nelfinavir troughs (>0.8 mg/L). The interpatient variability in plasma concentrations is great in children, with lower levels in younger children. The optimal dose of nelfinavir in younger children, particularly in those aged <2 years, has not been well defined. These data, combined with data in adults showing inferior potency of nelfinavir compared with other PIs and efavirenz, balanced against the advantage of a PI that is not coadministered with low-dose ritonavir for boosting, make nelfinavir an agent for use in special circumstances.
circumstances in treatment-naive children aged ≥2 years and not recommended for treatment of children aged <2 years.

Nelfinavir is currently available only as tablets, which can be dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable PK parameters in a study in adults.95

**Integrase Strand Transfer Inhibitor (INSTI)-Based Regimens (INSTIs Plus Two-NRTI Backbone)**

**Summary: INSTI-Based Regimens**

**INSTIs for Use in Special Circumstances**

Dolutegravir has recently been approved by the FDA for use in children aged 12 years and greater and weighing at least 40 kg. The approval was supported by data from a study of 23 treatment experienced but INSTI-naive children and adolescents.96 The drug has a very favorable safety profile and can be dosed once daily in treatment of INSTI-naive patients.

Raltegravir is FDA-approved for treatment of HIV-1-infected children aged ≥2 years and weight ≥10 kg. It is available in film-coated tablets and chewable tablets. However, these two formulations are not bio-equivalent, thus they require different dosing and are not interchangeable. Oral granules for suspension are currently under investigation. Safety and efficacy data are promising, but at this time, there are no data on raltegravir use as initial therapy in HIV-infected children. However, because of its favorable safety profile, lack of significant drug interactions, and palatability, raltegravir may be considered as initial therapy in special circumstances.97,98

**Selection of Dual-NRTI Backbone as Part of Initial Combination Therapy**

**Summary: Selection of Dual-NRTI Backbone Regimen**

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, 7 NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, and tenofovir) are FDA-approved for use in children aged <13 years. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; emtricitabine in combination with stavudine or didanosine; and tenofovir in combination with lamivudine or emtricitabine.19,51,83,89,99-107 Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 7.

In the dual-NRTI regimens listed below, lamivudine and emtricitabine are interchangeable. Both lamivudine and emtricitabine are well tolerated with few adverse effects. Although there is less experience in children with emtricitabine than with lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir or tenofovir or zidovudine). The main advantage of emtricitabine over lamivudine is that it can be administered once daily. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine, and improved susceptibility to zidovudine, stavudine, and tenofovir based on decreased viral fitness.108,109

**Preferred Dual-NRTI Regimens (in Alphabetical Order)**

**Abacavir in Combination with Lamivudine or Emtricitabine (for Children ≥ 3 Months) (AI)**

Abacavir in combination with lamivudine has been shown to be as potent as or possibly more potent than zidovudine in combination with lamivudine in both children and adults.110,111 In 5 years of follow-up, abacavir plus lamivudine maintained significantly better viral suppression and growth in children than did zidovudine plus lamivudine and zidovudine plus abacavir.111 However, abacavir/lamivudine or emtricitabine has the potential for abacavir-associated life-threatening HSRs in a small proportion of patients. Abacavir
hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see Appendix A: Pediatric Antiretroviral Drug Information); however, in the United States, the prevalence of HLA-B*5701 is much lower in African Americans and Hispanics (2%–2.5%) than in whites (8%). Pretreatment screening for HLA-B*5701 before initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir HSRs in HIV-infected adults (from 7.8% to 3.4%). Before initiating abacavir-based therapy in HIV-infected children, genetic screening for HLA-B*5701 should be performed and children who test positive for HLA-B*5701 should not receive abacavir (AII*).

An advantage of an abacavir regimen is the potential to switch to once-daily dosing in children with undetectable plasma RNA after approximately 24 weeks of therapy. Three small studies have now demonstrated equivalent drug exposure following a change from a twice-daily to a once-daily dosing regimen in children aged ≥3 months who had undetectable or low, stable plasma RNA after a variable period of twice-daily abacavir dosing. Two of the three demonstrated continued virologic suppression and one did not assess viral suppression. Recently, the ARROW trial reported findings from 669 HIV-infected children who had been receiving abacavir and lamivudine twice daily for 36 weeks and were randomized to either continue twice-daily dosing or change to once-daily dosing. At 48 weeks, once-daily abacavir was non-inferior to twice-daily dosing in terms of viral suppression; therefore, the Panel suggests that in clinically stable patients with undetectable plasma RNA and stable CD4 cell counts for more than 6 months, switching from twice-daily to once-daily dosing of abacavir is recommended as part of a once-daily regimen.

Tenofovir in Combination with Lamivudine or Emtricitabine (for Adolescents, Tanner Stage 4 or 5) (AI*)

Tenofovir is FDA-approved for use in children and adolescents aged ≥2 years. Because of decreases in bone mineral density (BMD) observed in adults and children receiving tenofovir, the Panel has opted to consider use of tenofovir based on Tanner stage. We have reserved our strongest recommendation in support of using tenofovir for adolescents who are in the late stages of or who have completed puberty (Tanner stages 4 and 5). Tenofovir can be used in younger children after weighing potential risks of decreased BMD versus benefits of therapy. In comparative clinical trials in adults, tenofovir when used with lamivudine or emtricitabine as a dual-NRTI backbone was superior to zidovudine used with lamivudine and efavirenz in viral efficacy. In ACTG 5202, adults who had a screening HIV-1 RNA ≥100,000 copies/mL receiving tenofovir/emtricitabine as part of a cART regimen had a longer time to virologic failure and to first adverse event compared to those assigned to abacavir/lamivudine. However, this has not been demonstrated in other comparative trials or in a meta-analysis.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an oral sprinkle/granule formulation. The use of tenofovir in pediatric patients aged 2 years to <18 years is approved by the FDA based on data from 2 randomized studies. In study 321, 87 treatment-experienced subjects aged 12 to <18 years, were randomized to receive tenofovir or placebo plus optimized background regimen for 48 weeks. Although there was no difference in virologic response between the two groups, the safety and PKs of tenofovir in children in the study were similar to those in adults receiving tenofovir. In study 352, 92 treatment-experienced children, aged 2 years to <18 years with virologic suppression on stavudine- or zidovudine-containing regimens were randomized to either replace stavudine or zidovudine with tenofovir or continue their original regimen. After 48 weeks, 89% of subjects receiving tenofovir and 90% of subjects continuing their original regimen had HIV-1 RNA concentrations <400 copies/mL. Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents Tanner Stage 4 or 5 (AI*). The fixed-dose combination of tenofovir and emtricitabine and the fixed-dose triple combination of tenofovir, emtricitabine, and efavirenz both allow for once-daily dosing, which may help improve adherence in older adolescents.

In some, but not all, studies, decreases in BMD have been observed in both adults and children taking tenofovir for 48 weeks. At this time, data are insufficient to recommend use of tenofovir as part of a preferred regimen for initial therapy in infected children in Tanner Stages 1 through 3, for whom the risk of bone toxicity may be greatest (see Appendix A: Pediatric Antiretroviral Drug Information for more detailed pediatric information). It is important to note that although decreases in BMD are observed, the...
Renal toxicity has been reported in children receiving tenofovir. Given the potential for bone and renal toxicity, tenofovir may be more useful for treatment of children in whom other ARV drugs have failed than for initial therapy of treatment-naive younger children. Numerous drug-drug interactions with tenofovir and other ARV drugs, including didanosine, ritonavir-boosted lopinavir, atazanavir, and tipranavir, complicate appropriate dosing of tenofovir.

Both emtricitabine and lamivudine, and tenofovir have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and interactions of ARV drugs with treatment for Hepatitis C and tuberculosis the reader should access the Pediatric Opportunistic Infections Guidelines.

### Zidovudine in Combination with Lamivudine or Emtricitabine (AI*)

The most extensive experience in children is with zidovudine in combination with lamivudine. Data on the safety of this combination in children are extensive and the combination is generally well tolerated. The major toxicities associated with zidovudine/lamivudine are bone marrow suppression, manifested as macrocytic anemia and neutropenia and an association with lipoatrophy; minor toxicities include gastrointestinal toxicity and fatigue. In addition, the combination of zidovudine and lamivudine is acceptable in infants less than 3 months of age.

### Alternative Dual-NRTI Regimens

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine (BII), didanosine in combination with lamivudine or emtricitabine (BI*) and tenofovir in combination with lamivudine or emtricitabine in children and adolescents who are Tanner Stage 3 (as opposed to Tanner Stages 4 and 5, where this is a preferred dual-NRTI regimen) (BI*). There is considerable experience with use of these dual-NRTI regimens in children, and in a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities. However, zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in a European pediatric study. The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naive children aged 3 to 21 years, long-term virologic suppression was achieved with a once-daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who must be fed frequently and it may decrease medication adherence in older children because of the complexity of the regimen. A comparison of didanosine given with or without food in children found that systemic exposure was similar but with slower and more prolonged absorption with food. To improve adherence, some practitioners recommend administration of didanosine without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferable to administer didanosine under fasting conditions when possible.

### Dual-NRTI Regimens for Use in Special Circumstances

The dual-NRTI combinations of stavudine with lamivudine or emtricitabine in children of any age are recommended for use in special circumstances. Stavudine is recommended for use only in special circumstances because the ARV is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs. Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than children receiving zidovudine-containing combinations. In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive abacavir or tenofovir, stavudine may be preferable to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

In children aged ≥2 years and those who are prepubertal or in the early stages of puberty (Tanner Stages 1 and 2), tenofovir in combination with lamivudine or emtricitabine is also recommended for use in special circumstances. As discussed above, the use of tenofovir during puberty when bone toxicity may be greatest may require caution. However, tenofovir may be a reasonable choice for initial therapy in children with demonstrated resistance to other NRTIs, coinfection with hepatitis B virus, or in those desiring a once-daily NRTI where abacavir is not an option. The Panel awaits additional safety data, especially with the recently licensed powder formulation, before providing a broader recommendation in younger children.
Both emtricitabine and lamivudine, and tenofovir have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection the reader should access the Pediatric Opportunistic Infections Guidelines.

Special Considerations

Treatment of Premature Infants and Infants Younger than Age 15 days

For infants aged <15 days and for premature infants (until 42 weeks’ corrected gestational age) we currently do not have sufficient PK data to allow the formulation of an effective, complete cART regimen.

Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of ARV drugs. Reports of cardiovascular, renal, and CNS toxicity associated with ritonavir-boosted lopinavir in young infants preclude the administration of this agent in the first 2 weeks of life. The IMPAACT network is planning a study of early treatment of infants. Based on PK modeling, an investigational dose of 6 mg/kg of nevirapine administered twice daily to full-term infants will be tested. Providers considering treatment of infants aged < 2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will have to include weighing the risks and benefits of using unapproved ARV drug dosing, and incorporate case-specific factors such as exposure to perinatal ARV prophylaxis.

Table 6. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 1 of 2)

A cART regimen in treatment-naive children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI (generally with low-dose ritonavir boosting) plus a 2-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Table 7).

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
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<tbody>
<tr>
<td>Children aged ≥14 days to &lt;3 yearsa</td>
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<tr>
<td>Children aged ≥3 years to &lt;6 years</td>
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<td>Children aged ≥6 years</td>
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<tr>
<th>Alternative Regimens</th>
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<tr>
<td>Children aged &gt;14 days</td>
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<td>Children aged ≥3 years to &lt;12 years</td>
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<td>Children aged ≥12 years</td>
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<table>
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<tr>
<th>Regimens for Use in Special Circumstances</th>
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<tbody>
<tr>
<td>Children aged ≥6 months&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children aged ≥2 years</td>
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<tr>
<td>Children ≥12 years</td>
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<tr>
<td>Treatment-naive adolescents aged ≥13 years and weighing &gt;39 kg</td>
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<tr>
<td>Treatment-naive adolescents aged ≥13 years and weighing &gt;39 kg</td>
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Table 6. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 2 of 2)

<table>
<thead>
<tr>
<th>Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs</th>
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<tbody>
<tr>
<td><strong>Children of any age</strong></td>
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<tr>
<td><strong>Children aged ≥3 months</strong></td>
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<tr>
<td><strong>Adolescents at Tanner Stage 4 or 5</strong></td>
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<tr>
<th>Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs</th>
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<tbody>
<tr>
<td><strong>Children aged ≥2 weeks</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Children ≥3 months</strong></td>
</tr>
<tr>
<td><strong>Children at Tanner Stage 3 and adolescents</strong></td>
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<thead>
<tr>
<th>2-NRTI Regimens for Use in Special Circumstances</th>
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<tr>
<td>d4T plus (3TC or FTC)</td>
</tr>
<tr>
<td>TDF plus (3TC or FTC) (prepubertal children aged ≥2 years and adolescents, Tanner Stage 1 or 2)</td>
</tr>
</tbody>
</table>

- LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and postnatal age ≥14 days.
- EFV should be used only in children aged ≥3 months with weight ≥3.5 kg but is not recommended as initial therapy in children aged ≥3 months to 3 years. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.
- NVP should not be used in postpubertal girls with CD4 count >250/mm$^3$, unless the benefit clearly outweighs the risk. NVP is FDA approved for treatment of infants aged ≥15 days.
- DRV once daily should not be used if resistance-associated substitutions are present (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V).
- FPV with low-dose RTV should only be administered to infants born at ≥38 weeks’ gestation who have attained a postnatal age of 28 days and to infants born before 38 weeks’ gestation who have reached a postmenstrual age of 42 weeks.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, cART = combination antiretroviral therapy, d4T = stavudine, ddl = didanosine, DRV = darunavir, DTG = dolutegravir, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV/r = fixed-dose formulation ritonavir-boosted lopinavir, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, TDF = tenofovir, ZDV = zidovudine
### Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 1 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **NNRTIs**<br>In Alphabetical Order | NNRTI Class Advantages: | • Long half-lives.  
• Less dyslipidemia and fat maldistribution than PIs.  
• PI-sparing.  
• Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens. | NNRTI Class Disadvantages: | • Single mutation can confer resistance, with cross resistance between EFV and NVP.  
• Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with nevirapine).  
• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4). |
| EFV | • Potent ARV activity.  
• Once-daily administration.  
• Can give with food (but avoid high-fat meals).  
• Capsules can be opened and added to food. | • Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects).  
• Rash (generally mild).  
• No commercially available liquid.  
• Limited data on dosing for children aged <3 years.  
• No data on dosing for children aged <3 months.  
• Use with caution in adolescent females of childbearing age. | |
| NVP | • Liquid formulation available.  
• Dosing information for young infants available.  
• Can give with food.  
• Extended-release formulation is available that allows for once-daily dosing in older children. | • Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen.  
• Higher incidence of rash/HSR than other NNRTIs.  
• Higher rates of serious hepatic toxicity than EFV.  
• Decreased virologic response compared with EFV.  
• Generally need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for autoinduction of NVP metabolism and is associated with a lower incidence of toxicity.  
• Twice-daily dosing necessary in children with BSA < 0.58 m². | |
| **PIs**<br>In Alphabetical Order | PI Class Advantages: | • NNRTI-sparing.  
• Clinical, virologic, and immunologic efficacy well documented.  
• Resistance to PIs requires multiple mutations.  
• When combined with dual NRTI backbone, targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes). | PI Class Disadvantages: | • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance.  
• Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4).  
• Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations.  
• Poor palatability of liquid preparations, which may affect adherence to treatment regimen.  
• Many PIs require low-dose ritonavir boosting resulting in associated drug interactions. |
### Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 2 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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</table>
| PIs       | ATV/r        | • Once-daily dosing.  
• ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters). | • No liquid formulation.  
• Food effect (should be administered with food).  
• Indirect hyperbilirubinemia common but asymptomatic.  
• Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG).  
• RTV component associated with large number of drug interactions (see RTV). |
|           | ATV          | • Once-daily dosing.  
• Less effect on TG and total cholesterol levels than other PIs. | • No liquid formulation.  
• Food effect (should be administered with food).  
• Indirect hyperbilirubinemia common but asymptomatic.  
• Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG).  
• May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations.  
• Unboosted ATV cannot be used with TDF. |
|           | DRV/r        | • Effective in PI-experienced children when given with low-dose RTV boosting.  
• Can be used once daily in children aged ≥12 years. | • Pediatric pill burden high with current tablet dose formulations.  
• No liquid formulation.  
• Food effect (should be given with food).  
• Must be given with RTV boosting to achieve adequate plasma concentrations.  
• Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown.  
• RTV component associated with large number of drug interactions (see RTV).  
• Can only be used once daily in absence of certain PI-associated resistance mutations. |
|           | FPV/r        | • Oral prodrug of APV with lower pill burden.  
• Pediatric formulation available, which should be given to children with food. | • Skin rash.  
• More limited pediatric experience than preferred PI.  
• Must be given with food to children.  
• RTV component associated with large number of drug interactions (see RTV).  
• Contains sulfa moiety. Potential for cross-sensitivity between FPV and other drugs in sulfonamide class is unknown.  
• Should only be administered to infants born at ≥38 weeks’ gestation and who have attained a postnatal age of 28 days. |
Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 3 of 4)

<table>
<thead>
<tr>
<th>ARV Class In Alphabetical Order, continued</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **PIs**                                   | LPV/r        | • Coformulated liquid and tablet formulations.  
• Tablets can be given without regard to food but may be better tolerated when taken with meal or snack. | • Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone.  
• Food effect (liquid formulation should be administered with food).  
• RTV component associated with large number of drug interactions (see RTV).  
• Should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age ≥ 14 days.  
• Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG). |
| **NFV**                                   |              | • Can give with food.  
• Simplified 2-tablet (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate. | • Diarrhea.  
• Food effect (should be administered with food).  
• Appropriate dosage for younger children not well defined.  
• Adolescents may require higher doses than adults.  
• Less potent than boosted PIs. |

| **INSTI**                                 | Integrase Inhibitor Class Advantages:  
• Susceptibility of HIV to a new class of ARVs. | Integrase Inhibitor Class Disadvantages:  
• Limited data on pediatric dosing or safety. |
| **DTG**                                   |              | • Once daily administration.  
• Can give with food. | • Limited data on pediatric dosing or safety.  
• Drug interactions with EFV, FPV/r, TPV/r and rifampin necessitating twice daily dosing. |
| **RAL**                                   |              | • Susceptibility of HIV to a new class of ARVs.  
• Can give with food.  
• Available in a chewable tablet. | • Limited data on pediatric dosing or safety.  
• Potential for rare systemic allergic reaction or hepatitis. |

| **Dual-NRTI Pairs In Alphabetical Order**  | ABC plus (3TC or FTC) | Palatable liquid formulations.  
• Can give with food.  
• ABC and 3TC are coformulated as a single pill for older/larger patients. | Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. |
|                                           | d4T plus (3TC or FTC) | • Extensive pediatric experience.  
• Palatable liquid formulations.  
• Can give with food.  
• FTC is available as a palatable liquid formulation administered once daily. | • d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipodystrophy, peripheral neuropathy, hyperlipidemia. |
Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (see Appendix A: Pediatric Antiretroviral Drug Information for more information) (page 4 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual-NRTI Pairs</td>
<td>ddI plus (3TC or FTC)</td>
<td>• Delayed-release capsules of ddI may allow once-daily dosing in children aged ≥ 6 years, weighing ≥20 kg, and able to swallow pills and who can receive adult dosing along with once-daily FTC. • FTC available as a palatable liquid formulation administered once daily.</td>
<td>• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be coadministered with FTC or 3TC). • Limited pediatric experience using delayed-release ddI capsules in younger children. • Pancreatitis, neurotoxicity with ddI.</td>
</tr>
<tr>
<td></td>
<td>TDF plus (3TC or FTC)</td>
<td>• Resistance slow to develop. • Once-daily dosing for TDF. • Less mitochondrial toxicity than other NRTIs. • Can give with food. • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced strength tablets and oral powder for use in younger children.</td>
<td>• Limited pediatric experience. • Potential bone and renal toxicity, may be less in postpubertal children. • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV.</td>
</tr>
<tr>
<td></td>
<td>ZDV plus (3TC or FTC)</td>
<td>• Extensive pediatric experience. • ZDV and 3TC are coformulated as single pill for older/larger patients. • Palatable liquid formulations. • Can give with food. • FTC is available as a palatable liquid formulation administered once daily.</td>
<td>• Bone marrow suppression with ZDV. • Lipoatrophy with ZDV.</td>
</tr>
<tr>
<td></td>
<td>ZDV plus ABC</td>
<td>• Palatable liquid formulations. • Can give with food.</td>
<td>• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. • Bone marrow suppression and lipoatrophy with ZDV.</td>
</tr>
<tr>
<td></td>
<td>ZDV plus ddI</td>
<td>• Extensive pediatric experience. • Delayed-release capsules of ddI may allow once-daily dosing of ddI in older children able to swallow pills and who can receive adult doses.</td>
<td>• Bone marrow suppression and lipoatrophy with ZDV. • Pancreatitis, neurotoxicity with ddI. • ddI liquid formulation is less palatable than 3TC or FTC liquid formulation. • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue.</td>
</tr>
</tbody>
</table>

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, ATV/r=atazanavir/ritonavir, d4T = stavudine, DRV/r=darunavir/ritonavir, ddl = didanosine, EFV=efavirenz, FPV/r=fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = ritonavir-boosted lopinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PK = pharmacokinetic, RAL = raltegravir, TDF = tenofovir, ZDV = zidovudine
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*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*  
*G-19*

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection


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What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children

Many additional antiretroviral agents (ARVs) and combinations are available; some are not recommended for initial therapy, although they may be used in treatment-experienced children. This section describes ARV drugs and drug combinations that are not recommended or for which data are insufficient to recommend use for initial therapy in ARV-naive children.

Not Recommended

These include drugs and drug combinations that are not recommended for initial therapy in ARV-naive children because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism. These drugs and drug combinations are listed in Table 8.

Insufficient Data to Recommend

Drugs and drug combinations approved for use in adults that have insufficient, limited, and/or no pharmacokinetic (PK) or safety data in children cannot be recommended as initial therapy in children. However, these drugs and drug combinations may be appropriate for consideration in management of treatment-experienced children (see Management of Children Receiving Antiretroviral Therapy). These drugs are also listed in Table 8.

Antiretroviral Drugs and Combinations Not Recommended for Initial Therapy

In addition to the regimens listed below, several ARVs—including unboosted atazanavir in adolescents aged <13 years, nelfinavir and tenofovir disoproxil fumarate (tenofovir) in children aged <2 years, unboosted darunavir, once-daily dosing of lopinavir/ritonavir, and full-dose ritonavir—are not recommended for use as initial therapy.

Enfuvirtide-Based Regimens

Enfuvirtide, a fusion inhibitor, is Food and Drug Administration (FDA)-approved for use in combination with other ARV drugs to treat children aged ≥6 years who have evidence of HIV replication despite ongoing antiretroviral therapy (i.e., treatment-experienced children on non-suppressive regimens). Enfuvirtide is not recommended as initial therapy because the drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%).

Fosamprenavir without Ritonavir Boosting

Fosamprenavir without ritonavir boosting has been studied in children aged ≥2 years but is not recommended because the volume of fosamprenavir oral suspension necessary to administer in the absence of ritonavir boosting is prohibitive. In addition, low levels of exposure may result in selection of resistance mutations that are associated with darunavir resistance.

Indinavir-Based Regimens

Although adequate virologic and immunologic responses have been observed with indinavir-based regimens in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis have been reported in pediatric patients using indinavir.1-4 The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults.1,4 Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy in children.

Regimens Containing Only NRTIs

In adult trials, regimens containing only nucleoside reverse transcriptase inhibitors (NRTIs) have shown less potent virologic activity when compared with more potent non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based regimens. These include studies of zidovudine plus abacavir plus...
lamivudine, stavudine plus didanosine plus lamivudine, stavudine plus lamivudine plus abacavir, didanosine plus stavudine plus abacavir, tenofovir plus abacavir plus lamivudine, and tenofovir plus didanosine plus lamivudine. Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited; in small observational studies, response rates of 47% to 50% have been reported. In a study of the triple-NRTI regimen abacavir, lamivudine, and zidovudine in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining a viral load of <400 copies/mL at 48 weeks of treatment. Therefore, regimens containing only NRTIs are not recommended. A possible exception to this recommendation is the treatment of young children (aged <3 years) with concomitant HIV infection and tuberculosis in whom a nevirapine based regimen is not acceptable. For these children where treatment choices are limited, the World Health Organization recommends the use of a triple-NRTI regimen.

Regimens Containing Three Drug Classes
Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI). Although efavirenz plus nelfinavir plus one or two NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naive children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options.

Regimens Containing Three NRTIs and a NNRTI
Data are currently insufficient to recommend a regimen of three NRTIs plus a NNRTI in young infants. A recent review of 9 cohorts from 13 European countries suggested superior responses to this 4-drug regimen when compared to boosted PI or 3-drug NRTI regimens. There has been speculation that poor tolerance and adherence to a PI-based regimen may account for differences. The ARROW trial conducted in Uganda and Zimbabwe randomized 1,206 children (median age 6 years) to a standard NNRTI-based 3-drug regimen versus 4-drug regimen (3 NRTIs and a NNRTI). After a 36-week induction period, the children on the four-drug regimen were continued on a dual NRTI plus NNRTI or an all NRTI-based regimen. Although early benefits in CD4 T lymphocyte (CD4) improvement and virologic control were observed in the four-drug arm, these benefits were not sustained after de-intensification to the three-NRTI arm. Furthermore, after a median of 3.7 years on therapy, children in the initial 4-drug arm that changed to an all NRTI-based regimen had significantly poorer virologic control. Based on demonstrated benefits of recommended three-drug regimens and lack of additional efficacy data on the four-drug regimen, the Panel does not currently recommend this regimen.

Saquinavir with Low-Dose Ritonavir
A saquinavir/ritonavir-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naive adults. However, saquinavir is not recommended for initial therapy in children because the agent is not available in a pediatric formulation and dosing and outcome data on saquinavir use in children are limited.

Stavudine in Combination with Didanosine
The dual-NRTI combination of stavudine/didanosine is not recommended for use as initial therapy because of greater toxicity when used in combination. In small pediatric studies, stavudine/didanosine demonstrated virologic efficacy and was well tolerated. However, in studies in adults, stavudine plus didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine plus lamivudine. In addition, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy.

Tipranavir-Based Regimens
This agent has been studied in treatment-experienced children and adults. Tipranavir is a PI licensed for use in children age ≥2 years. Tipranavir-based regimens are not recommended because higher doses of ritonavir
to boost tipranavir must be used and rare, but serious, cases of intracranial hemorrhage have been reported.

**Not Recommended for Initial Therapy for Children Because of Insufficient Data**

A number of ARV drugs and drug regimens are not recommended for initial therapy of ARV-naive children or for specific age groups because of insufficient pediatric data. These include the dual-NRTI backbone combinations abacavir/didanosine, abacavir/tenofovir, and didanosine/tenofovir. In addition, several new agents appear promising for use in adults but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (CCR5 antagonist), elvitegravir (ISTI), and etravirine and rilpivirine (both NNRTIs). Additionally, there are dosing schedules that may not be recommended in certain age groups based on insufficient data. As new data become available, these agents may be considered as recommended agents or regimens. These are summarized below and also listed in Table 8.

**Darunavir with Low-Dose Ritonavir when Administered Once Daily (for Children Aged ≥3 to 12 Years)**

Data are limited on PK of once-daily ritonavir-boosted darunavir in young children. While modeling studies identified a once-daily dosing regimen now approved by the FDA, the Panel is concerned about the lack of efficacy data for persons aged ≥3 to <12 years treated with once-daily ritonavir-boosted darunavir. Therefore once-daily dosing for initial therapy is not recommended in this age group. For children age ≥3 to <12 years, twice-daily darunavir boosted with ritonavir is an alternate PI regimen. For patients who have undetectable viral load on twice-daily therapy with darunavir boosted with ritonavir, practitioners can consider changing to once-daily treatment to enhance ease of use and support adherence.

**Dolutegravir for Children Aged <12 Years**

Dolutegravir is an integrase strand transfer inhibitor (INSTI) that has recently been approved by the FDA for use in children aged 12 years and older and weighing at least 40 kg. At this time there is no information about its use in children aged <12 years but a clinical trial in treatment-experienced children aged <12 years is under way.

**Efavirenz for Children Aged ≥3 Months to 3 Years**

Efavirenz is FDA-approved for use in children as young as age 3 months who weigh at least 3.5 kg. Concerns regarding variable PK of the drug in the very young have resulted in a recommendation to not use efavirenz in children under age 3 years at this time (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). However, should efavirenz be considered, CYP2B6 genotyping that predicts efavirenz metabolic rate should be performed, if available. Therapeutic drug monitoring can also be considered.

**Elvitegravir-Based Regimens**

Elvitegravir is an INSTI only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate, and is FDA-approved for use as combination antiretroviral therapy (cART) in HIV-1-infected cART-naive adults. It is not FDA-approved for use in children aged <18 years. There are no data on its use in individuals younger than age 18 years, and it cannot be considered for use as initial therapy for children at this time (see http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf).

**Etravirine-Based Regimens**

Etravirine is an NNRTI that has been studied in treatment-experienced children 6 years of age and older. It is associated with multiple interactions with other ARVs, including ritonavir-boosted tipranavir, ritonavir-boosted fosamprenavir, ritonavir-boosted atazanavir, and unboosted PIs, and must be administered twice daily. Studies in treatment-experienced younger children are under way. It is unlikely that etravirine will be studied in treatment-naive children.
Rilpivirine-Based Regimens

Rilpivirine is currently available both as a single-agent formulation and a once-daily, fixed-dose combination tablet containing emtricitabine and tenofovir. An ongoing study is assessing the safety and efficacy in adolescents aged 12 to 18 years. In adult studies, reduced viral suppression was observed in patients with initial HIV RNA >100,000 copies/mL.

Maraviroc-Based Regimens

Maraviroc is an entry inhibitor that has been used infrequently in children. A dose finding study in children aged 2 to 18 years is currently under way. The drug has multiple drug interactions and must be administered twice daily. In addition, tropism assays must be performed prior to use to ensure the presence of only CCR5-tropic virus.

Antiretroviral Drug Regimens that Should Never be Recommended

Several ARV drugs and drug regimens should never be recommended for use in therapy of children or adults. These are summarized in Table 9. Clinicians should be aware of the components of fixed-drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Table 8. ART Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children

<table>
<thead>
<tr>
<th>Regimen or ARV Component</th>
<th>Rationale for Being Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unboosted ATV-containing regimens in children aged &lt;13 years and/or weight &lt;39 kg</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td>DRV-based regimens once-daily in children ≥3 to 12 years</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Unboosted DRV</td>
<td>Use without ritonavir has not been studied</td>
</tr>
<tr>
<td>Dual (full-dose) PI regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Dual NRTI combination of ABC plus ddl</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Dual NRTI combination of ABC plus TDF</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Dual NRTI combination of d4T plus ddl</td>
<td>Significant toxicities</td>
</tr>
<tr>
<td>Dual NRTI combination of TDF plus ddl</td>
<td>Increase in concentrations; high rate of virologic failure</td>
</tr>
<tr>
<td>EFV-based regimens for children aged &lt;3 years</td>
<td>Appropriate dose not determined</td>
</tr>
<tr>
<td>ENF-containing regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Injectable preparation</td>
<td></td>
</tr>
<tr>
<td>ETV-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>EVG-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>FPV without RTV boosting</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td>Medication burden</td>
<td></td>
</tr>
<tr>
<td>IDV-based regimens</td>
<td>Renal toxicities</td>
</tr>
<tr>
<td>LPV/r dosed once daily</td>
<td>Reduced drug exposure</td>
</tr>
<tr>
<td>MVC-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>NFV-containing regimens for children aged &lt;2 years</td>
<td>Appropriate dose not determined</td>
</tr>
<tr>
<td>Regimens containing only NRTIs</td>
<td>Inferior virologic efficacy</td>
</tr>
<tr>
<td>Regimens containing three drug classes</td>
<td>Insufficient data to recommend</td>
</tr>
</tbody>
</table>
Table 8. ART Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children (page 2 of 2)

<table>
<thead>
<tr>
<th>Regimen or ARV Component</th>
<th>Rationale for Being Not Recommended</th>
</tr>
</thead>
</table>
| Full-dose RTV or use of RTV as the sole PI | GI intolerance  
Metabolic toxicity |
| Regimens containing three NRTIs and an NNRTI | Insufficient data to recommend |
| RPV-based regimens | Insufficient data to recommend |
| SQV-based regimens | Limited dosing and outcome data burden |
| TDF-containing regimens in children aged <2 years | Potential bone toxicity  
Appropriate dose has yet to be determined |
| TPV-based regimens | Increased dose of RTV for boosting  
Reported cases of intracranial hemorrhage |

Key to Abbreviations:  
ABC = abacavir, ATV = atazanavir, d4T=stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz,  
ETV = etravirine, EVG = elvitegravir, FPV = fosamprenavir, IDV = indinavir, LPV/r = ritonavir-boosted lopinavir, MVC = maraviroc,  
NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide, TDF = tenofovir disoproxil fumarate, RPV = rilpivirine,  
TPV = tipranavir

Table 9. ART Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children (page 1 of 2)

<table>
<thead>
<tr>
<th>Regimen/Component</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ART Regimens Never Recommended for Children</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| One ARV drug alone (monotherapy) | • Rapid development of resistance  
• Inferior antiviral activity compared with combination including ≥3 ARV drugs | • HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV  
• 3TC or FTC interim “bridging regimen” in special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence |
| Two NRTIs alone | • Rapid development of resistance  
• Inferior antiviral activity compared with combination including ≥3 ARV drugs | • Not recommended for initial therapy.  
• For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment. |
| TDF plus ABC plus (3TC or FTC) as a triple-NRTI regimen | • High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults. | • No exceptions |
| TDF plus ddI plus (3TC or FTC) as a triple-NRTI regimen | • High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults. | • No exceptions |
| **ARV Components Never Recommended as Part of an ARV Regimen for Children** | | |
| ATV plus IDV | • Potential additive hyperbilirubinemia | • No exceptions |
| Dual-NRTI combinations | • Enhanced toxicity | • No exceptions |
| Dual-NRTI combinations:  
• 3TC plus FTC | • Similar resistance profile and no additive benefit | • No exceptions |
| • d4T plus ZDV | • Antagonistic effect on HIV | • No exceptions |
### Table 9. ART Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children (page 2 of 2)

<table>
<thead>
<tr>
<th>Regimen/Component</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV Components Never Recommended as Part of an ARV Regimen for Children, continued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured</td>
<td>• Potential for teratogenicity</td>
<td>• When no other ARV option is available and potential benefits outweigh risks</td>
</tr>
<tr>
<td>NVP in adolescent girls with CD4 count &gt;250 cells/mm³ or adolescent boys with CD4 count &gt;400 cells/mm³</td>
<td>• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups</td>
<td>• Only if benefit clearly outweighs risk</td>
</tr>
<tr>
<td>Unboosted SQV, DRV, or TPV</td>
<td>• Poor oral bioavailability</td>
<td>No exceptions</td>
</tr>
<tr>
<td>Unboosted SQV, DRV, or TPV</td>
<td>• Inferior virologic activity compared with other PIs</td>
<td></td>
</tr>
</tbody>
</table>

**Key to Abbreviations:** 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, IDV = indinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

### References


Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents  (Last updated February 12, 2014; last reviewed February 12, 2014)

**Panel’s Recommendations**

- Combination antiretroviral therapy (cART) regimens must be individually tailored to the adolescent (AIII).
- Appropriate dosing of cART for adolescents may be complex, not always predictable, and dependent upon multiple factors, including body mass and composition and pubertal development (AII).
- Effective and appropriate methods should be selected to reduce the likelihood of unintended pregnancy and to prevent secondary transmission of HIV to sexual partners (AII).
- Providers should be aware of potential interactions between cART and hormonal contraceptives that could lower contraceptive efficacy (AII*).
- Alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens do not compromise the woman’s health (BIII). Adolescent females who require treatment with efavirenz should undergo pregnancy testing before initiation of treatment and receive counseling about potential fetal risk and desirability of avoiding pregnancy while receiving efavirenz-containing regimens (AIII).
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings (AIII).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

**Background**

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive combination antiretroviral therapy (cART) history. Adolescents with non-perinatally acquired HIV infection generally follow a clinical course similar to that in adults. Because non-perinatally infected adolescents may be at the initial stages of their HIV disease, they may be potential candidates for early intervention and treatment.

**Dosing of Antiretroviral Therapy for HIV-Infected Adolescents**

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics (PK), which is especially important for drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some protease inhibitors [PIs]) are administered to children at higher weight- or surface area-based doses than would be predicted by direct extrapolation of adult doses. This is based upon reported PK data indicating more rapid drug clearance in children. With unboosted PI usage, continued use of these pediatric weight- or surface-area-based doses as a child grows during adolescence can result in medication doses that are higher than the usual adult doses. Data suggesting optimal doses for every ARV drug in adolescents are not available. Appendix A: Pediatric Antiretroviral Drug Information includes a discussion of data relevant to...
adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available.

**Adolescent Contraception, Pregnancy, and Antiretroviral Therapy**

HIV-infected adolescents may be sexually active. Reproductive plans including preconception care, contraception methods, and safer sex techniques for prevention of secondary HIV transmission should be discussed regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use) for additional information please see the [Perinatal Guidelines—Reproductive Options for HIV-Concordant and Serodiscordant Couples](http://www.hiv-druginteractions.org/).

The possibility of an unplanned pregnancy should also be considered when selecting a cART regimen for an adolescent female. The most vulnerable period in fetal organogenesis is the first trimester, often before pregnancy is recognized. Concerns about specific ARV drugs and birth defects should be promptly addressed to preclude misinterpretation or lack of adherence by adolescents with unexpressed plans for pregnancy. For additional information please see the [Perinatal Guidelines](http://www.hiv-druginteractions.org/). Alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman’s health.

**Contraceptive-Antiretroviral Drug Interactions**

Several PI and non-nucleoside reverse transcriptase inhibitor drugs alter metabolism of oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the Adult and Adolescent Antiretroviral Guidelines) (http://www.hiv-druginteractions.org/). These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related adverse effects. Some newer agents, such as integrase inhibitors (specifically raltegravir), appear to have no interaction with estrogen-based contraceptives. Providers should be aware of these drug interactions and consider alternative or additional contraceptive methods for patients receiving cART.

Whether interactions with cART would compromise the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone acetate [DMPA]) is unknown because these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered in women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional adverse effects, and no clinically significant changes in ARV drug levels. At this time, concerns about loss of bone mineral density (BMD) with long-term use of DMPA with or without cART (specifically tenofovir) should not preclude use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility. However, more active monitoring of BMD in young women on DMPA may need to be considered. Minimal information exists about drug interactions with use of newer hormonal contraceptive methods (e.g., the patch and vaginal ring). Women with HIV can use all available contraceptive methods, including intrauterine devices (IUD). Adolescents who want to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with cART use during pregnancy (see the [Perinatal Guidelines](http://www.hiv-druginteractions.org/)).

**HIV-Infected Pregnant Adolescents and Outcomes**

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of perinatal transmission and maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different for pregnant women than for nonpregnant females. Details regarding choice of cART regimen in pregnant HIV-infected women, including adolescents, are provided in the [Perinatal Guidelines](http://www.hiv-druginteractions.org/). Although information is limited about the pregnancies of adolescents who were HIV-infected perinatally, perinatal HIV transmission outcomes in this population appear similar to those in...
adult cohorts; however, there may be differences in pregnancy-related morbidities. Kenny et al reported pregnancy outcomes from the United Kingdom and Ireland in a group of 30 adolescents who were perinatally HIV-infected or who acquired HIV infection at a young age. Few of these pregnancies were planned and in many cases, the partner was unaware of the mother’s HIV status. Rates of elective termination, miscarriage, and prematurity were high. The rate of prematurity was twice that in the general adolescent population of Europe. Many of the women had an AIDS diagnosis before pregnancy, but only one infant was HIV-infected. Although the rate of perinatal transmission is reassuring, this study highlights some of the major challenges in caring for pregnant, perinatally HIV-infected youth.

Comparisons of pregnancy incidence and outcomes between perinatally infected and non-perinatally infected youth are few and may offer special insight into the effects of prolonged HIV infection on pregnancy-related sequelae. Agwu et al retrospectively evaluated pregnancies at four clinics. Non-perinatally infected youth were more likely to have one or more pregnancies despite similar age at first pregnancy between groups. They also appeared to have more premature births and spontaneous abortions, but that is tempered by the fact that the perinatally infected youth were more likely to have an elective termination. The perinatal transmission rate for the entire cohort was 1.5%. Similar results were found in several other studies. However, in a single-center review of perinatal versus non-perinatal birth outcomes, infants born to women with perinatal HIV infection were more likely to be small for gestational age.

**Transition of Adolescents into Adult HIV Care Settings**

Facilitating a smooth transition of adolescents with chronic health conditions from their pediatric/adolescent medical home to adult care can be difficult and is especially challenging for HIV-infected adolescents. Transition is described as “a multifaceted, active process that attends to the medical, psychosocial, and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system.” Care models for children and adolescents with perinatally acquired HIV tend to be family-centered, consisting of a multidisciplinary team that often includes pediatric or adolescent physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, more intimate settings. Although expert care is also provided under the adult HIV care medical model, an adolescent may be unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers with whom he or she often does not have a long-standing relationship. Providing an adolescent and an adult medical care provider with support and guidance regarding expectations for each partner in the patient-provider relationship may be helpful. In this situation, it may also be helpful for a pediatric and an adult provider to share joint care of a patient for a period of time. Providers should also have a candid discussion with a transitioning adolescent to understand what qualities the adolescent considers most important in an adult care setting (e.g., confidentiality, small clinic size, after-school appointments). Some general guidelines about transitional plans and who might benefit most from them are available. Pediatric and adolescent providers should have a formal plan to transition adolescents to adult care.

Outcomes are variable in young adult patients transitioned to adult care. In a recent study, 10% of 18-year-olds were lost to follow-up with care at an adult HIV site associated with a greater likelihood of attrition. Definitions of “successful transition” have ranged from the ability to maintain a certain level of follow-up in the new clinic, to laboratory measures of stability, to comparisons of younger and older adult patients. Factors that should be taken into consideration during transition include social determinants such as developmental status, behavioral/mental health issues, housing, family support, employment, recent discharge from foster care, peer pressure, illicit drug use, and incarceration. Currently there is no definitive model of transition to adult care, but in one study, adherence to medical visits just prior to the transition was predictive of successful transfer. Psychiatric comorbidities and their effective management also predict adherence to medical care and therapy.
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31. Agwu A. Factors associated with falling out of care for older adolescents in the HIV research network. 19th International AIDS Conference; 2012; Washington, DC.

32. Arazi-Caillaud SE, Mecikovsky D. Transition of HIV-Infected Adolescents to Adult HIV Care: 2 Years of Follow-up, Abstract CDB426.IAS; July 17-20, 2011; Rome, Italy.


Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents  (Last updated February 12, 2014; last reviewed February 12, 2014)

Background

Adherence to combination antiretroviral therapy (cART) is a principal determinant of virologic suppression. Prospective adult and pediatric studies have established a direct correlation between risk of virologic failure and the proportion of missed doses of antiretroviral (ARV) drugs. Based on early work in HIV-infected adults treated with unboosted protease inhibitor (PI)-based regimens, adherence has been the threshold associated with complete viral suppression. More recent studies from adult populations suggest that the relationship between ARV adherence and viral suppression may vary with individual drug, drug class, and pattern of adherence. Viral suppression may be achieved with lower levels of adherence to boosted PI and non-nucleoside reverse transcriptase inhibitor regimens. In patients who achieve virologic suppression, the longer the duration of suppression the lower the level of adherence necessary to prevent viral rebound. Different patterns of inadequate adherence (intermittent missed doses, treatment interruptions) may have a differential impact on regimen efficacy, depending on the drug combination.

Poor adherence can result in sub-therapeutic plasma ARV drug concentrations, facilitating development of drug resistance to one or more drugs in a given regimen, and possibly cross-resistance to other drugs in the same class. Multiple factors (including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance) influence the adherence-resistance relationship. In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens in patients who develop multidrug-resistant HIV and for increasing the risk of secondary transmission.

Poor adherence to ARVs is commonly encountered in the treatment of HIV-infected children and adolescents. Multiple studies have reported that less than 50% of children and/or caretakers reported full adherence to prescribed regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), ARV regimens, and study characteristics. A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial and behavioral characteristics of

Panel’s Recommendations

- Strategies to maximize adherence should be discussed before initiation of combination antiretroviral therapy (cART) and again before changing regimens (AIII).
- Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence (AIII).
- At least one method of measuring adherence to cART should be used in addition to monitoring viral load (AII).
- When feasible, a once-daily antiretroviral regimen should be utilized (AI*).
- To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care (AI*).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents
children and parents have been associated with adherence; however, no consistent predictors of either good or poor adherence in children have been consistently identified. Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment. These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to ensure adherence education, support, and assessment as integral components of care.

**Specific Adherence Issues in Children**

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient and family factors, and characteristics of health care providers. The limited availability of palatable formulations for young children is especially problematic. Furthermore, infants and children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex, multidrug regimen requires evaluation of the caregivers and their environments, as well as the ability and willingness of a child to take the drug. Barriers faced by adult caregivers that can contribute to non-adherence in children include forgetting doses, changes in routine, being too busy, and child refusal. Some caregivers may place too much responsibility for managing medications on older children before they are developmentally able to undertake such tasks, whereas others themselves face health and adherence challenges related to HIV infection or other medical conditions. Other barriers to adherence include caregivers’ unwillingness to disclose HIV infection status to the child and/or others, reluctance of caregivers to fill prescriptions locally, hiding or relabeling of medications to maintain secrecy within the household, avoidance of social support, and a tendency for doses to be missed if the parent is unavailable. Adherence may also be jeopardized by social issues within a family (e.g., substance abuse, unstable housing, and involvement with the criminal justice system).

**Specific Adherence Issues in Adolescents**

HIV-infected adolescents also face specific adherence challenges. Several studies have identified pill burden as well as lifestyle issues (i.e., not having medications on hand when away from home, change in schedule) as significant barriers to effective adherence. Denial and fear of their HIV infection are common in adolescents, especially youth who have been recently diagnosed; this may lead to refusal to initiate or continue cART. Distrust of the medical establishment, misinformation about HIV, and lack of knowledge about the availability and effectiveness of ARV treatments can also be barriers to linking adolescents to care, retaining them in care, and maintaining them on successful cART.

Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they often have long histories of inadequate adherence. Regimen fatigue also has been identified as a barrier to adherence in adolescents. HIV-infected adolescents often have low self-esteem, unstructured and chaotic lifestyles, concomitant mental illnesses, and cope poorly with their illness. Depression, alcohol or substance abuse, poor school attendance, psychiatric disorders and advanced HIV disease have been associated with nonadherence. A review of published papers on adherence among HIV-infected youth suggests that depression and anxiety are consistently associated with poorer adherence. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties include adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and youth who are homeless and have no place to store medicine. When recommending treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ARV regimen with a realistic assessment of existing and potential support systems to facilitate adherence.

**Adherence Assessment and Monitoring**

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom cART initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may influence adherence by children and parents.
their families and can be used to identify individual needs for intervention. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain a patient’s explicit agreement with the treatment plan, including strategies to support adherence. It is also important to alert patients to minor side effects of ARVs, such as nausea, headaches, and abdominal discomfort that may recede over time or respond to change in diet or timing of medication administration.

Adherence is difficult to assess accurately; different methods of assessment have yielded different results (and each approach has limitations). Patients, caregivers, and health care providers often overestimate adherence. Use of multiple methods to assess adherence is recommended. Viral load response to a new regimen is often the most accurate indication of adherence. Other measures include quantitative self report of missed doses by caregivers and children or adolescents (i.e., focusing on missed doses during a recent 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Caregivers may report number of doses taken more accurately than doses missed. Targeted questions about stress, pill burden, and daily routine are recommended. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports. Electronic monitoring devices (e.g., Medication Event Monitoring System [MEMS] caps) which are equipped with a computer chip that records each opening of a medication bottle are primarily used in research studies, but have been shown to be useful tools to measure adherence in some settings. Mobile phone technologies (e.g., interactive voice response, SMS text messaging), are being evaluated to quantify missed doses and provide real-time feedback on adherence to caregivers, but studies in the pediatric population are in the pilot phase. Home visits can play an important role in assessing adherence. In some cases, suspected non-adherence is confirmed only when dramatic clinical responses to cART occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma ARV concentrations or therapeutic drug monitoring may be useful measures in situations where non-adherence is suspected. Drug concentrations in hair are currently being studied as an alternative method to measure adherence.

Adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both HIV-infected children and their caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources.

**Strategies to Improve and Support Adherence**

Intensive follow-up is required, particularly during the first few months after therapy is initiated. Patients should be seen frequently—as often as weekly during the first month of treatment—to assess adherence and determine the need for strategies to improve and support adherence. Strategies include the development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (e.g., associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers—rather than one specific intervention—may be most effective. Programs designed for administration of directly observed combination therapy to adults, in either the clinic or at home, have demonstrated successful results in both the United States and in international, resource-poor settings. Modified directly observed therapy (m-DOT), where one dose is administered in a supervised setting and the remaining doses are self-administered, appears to be both feasible and acceptable. However, a recent meta-analysis of 10 randomized clinical trials evaluating DOT to promote adherence in adults found that it was no more effective than self-administered treatment. In another meta-analysis of DOT studies, DOT was found to have a demonstrated effect on virologic, immunologic, and adherence outcomes, but efficacy of the strategy was not supported when the analysis was
restricted to randomized controlled trials. Table 10 summarizes some of the strategies that can be used to support and improve adherence to ARV medications.

**Regimen-Related Strategies**

ARV regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects. When non-adherence occurs, addressing medication-related issues (e.g., side effects), may result in improvement. If a regimen is overly complex, it can be simplified. For example, when the burden of pills is great, one or more drugs can be changed to a **fixed-drug combination** resulting in a regimen with fewer pills. When feasible, a once-daily regimen should be recommended. Several studies in adults have demonstrated better adherence with once-daily versus twice-daily ARV regimens.

When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can sometimes be masked with a small amount of flavoring syrup or food (see Appendix A: Pediatric Antiretroviral Drug Information) or a child can be taught to swallow pills in order to overcome medication aversion.

Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup.

**Patient/Family-Related Strategies**

The primary approach taken by the clinical team to promote medication adherence in children is patient and caregiver education. Educating families about adherence should begin before ARV medications are initiated or changed and should include a discussion of the goals of therapy, the reasons for making adherence a priority, and the specific plans for supporting and maintaining a child’s medication adherence. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

A number of behavioral tools can be used to integrate taking medications into an HIV-infected child’s daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives for taking medications, can be effective tools to promote adherence. Training children to swallow pills has been associated with improved adherence at 6 months post-training in a small study of children aged 4 to 21 years. Availability of mental health services and the treatment of mental health disorders may facilitate adherence to complex ARV regimens. A gastrostomy tube should be considered for nonadherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications.

Directly observed dosing of ARV medications has been implemented in adults, adolescents, and children, using home nursing services as well as daily medication administration in the clinic setting.

Other strategies to support adherence that have been employed in the clinical setting include setting patients’ cell phone alarms to go off at medication times; using beepers or pagers as an alarm; sending SMS text-message reminders; conducting motivational interviews; providing pill boxes and other adherence support tools, particularly for patients with complex regimens; and delivering medications to the home. Two randomized clinical trials in adults have demonstrated that SMS text-messaging, at weekly intervals, is associated with improved adherence outcomes. In a pilot study evaluating peer support and pager messaging in an adult population, peer support was associated with greater self-reported adherence post-intervention; however, the effect was not sustained at follow-up. Although pager messaging was not associated with reported adherence, improved biologic outcomes were measured. A study evaluating the efficacy of a 4-session, individual, clinic-based motivational interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months in youth taking cART. However, reduction in viral load was not maintained at 9 months.
Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with patients’ families. This process begins early in a provider’s relationship with a family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important. Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child-centered and includes caregivers in adherence support also has been shown to improve treatment outcomes.

Table 10. Strategies to Improve Adherence to Antiretroviral Medications

<table>
<thead>
<tr>
<th>Initial Intervention Strategies</th>
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<tbody>
<tr>
<td>• Establish trust and identify mutually acceptable goals for care.</td>
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<tr>
<td>• Obtain explicit agreement on need for treatment and adherence.</td>
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<tr>
<td>• Identify depression, low self-esteem, substance abuse, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat mental health issues before starting antiretroviral (ARV) drugs, if possible.</td>
</tr>
<tr>
<td>• Identify family, friends, health team members, and others who can support adherence.</td>
</tr>
<tr>
<td>• Educate patient and family about the critical role of adherence in therapy outcome.</td>
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<tr>
<td>• Specify the adherence target: ≥95% of prescribed doses.</td>
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<tr>
<td>• Educate patient and family about the relationship between partial adherence and resistance.</td>
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<tr>
<td>• Develop a treatment plan that the patient and family understand and to which they feel committed.</td>
</tr>
<tr>
<td>• Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.</td>
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<th>Medication Strategies</th>
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<tr>
<td>• Choose the simplest regimen possible, reducing dosing frequency and number of pills.</td>
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<tr>
<td>• Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities.</td>
</tr>
<tr>
<td>• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).</td>
</tr>
<tr>
<td>• Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects.</td>
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<tr>
<td>• Simplify food requirements for medication administration.</td>
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<tr>
<td>• Prescribe drugs carefully to avoid adverse drug-drug interactions.</td>
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<tr>
<td>• Assess pill-swallowing capacity and offer pill-swallowing training.</td>
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<th>Follow-up Intervention Strategies</th>
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<tr>
<td>• Monitor adherence at each visit and in between visits by telephone or letter, as needed.</td>
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<tr>
<td>• Provide ongoing support, encouragement, and understanding of the difficulties associated with demands to attain 95% adherence with medication doses.</td>
</tr>
<tr>
<td>• Use patient education aids including pictures, calendars, and stickers.</td>
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<tr>
<td>• Encourage use of pill boxes, reminders, alarms, pagers, and timers.</td>
</tr>
<tr>
<td>• Provide follow-up clinic visits, telephone calls, and SMS text messages to support and assess adherence.</td>
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<tr>
<td>• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.</td>
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<tr>
<td>• Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.</td>
</tr>
<tr>
<td>• Consider directly observed therapy at home, in the clinic, or in selected circumstances, during a brief inpatient hospitalization.</td>
</tr>
<tr>
<td>• Consider gastrostomy tube use in selected circumstances.</td>
</tr>
</tbody>
</table>
References


69. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral...


Management of Medication Toxicity or Intolerance  (Last updated February 12, 2014; last reviewed February 12, 2014)

Overview

<table>
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<th>Panel’s Recommendations</th>
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<tr>
<td>• In children who have severe or life-threatening toxicity, all antiretroviral (ARV) drugs should be stopped immediately (AII). Once symptoms of toxicity have resolved, ARV therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) (AII*).</td>
</tr>
<tr>
<td>• When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen (AII*).</td>
</tr>
<tr>
<td>• The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity (AIII).</td>
</tr>
<tr>
<td>• Dose reduction is not a recommended option for management of ARV toxicity, except when therapeutic drug monitoring indicates a drug concentration above the normal therapeutic range (AII*).</td>
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| Rating of Recommendations: A = Strong; B = Moderate; C = Optional |
| Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion |
| † Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents |

Medication Toxicity or Intolerance

The goals of combination antiretroviral therapy (cART) include achieving and maintaining viral suppression and improving immune function, with a regimen that is not only effective but also as tolerable and safe as possible. This requires consideration of the toxicity potential of a cART regimen, as well as the individual child’s underlying conditions, concomitant medications, and prior history of drug intolerances or viral resistance.

Adverse effects have been reported with use of all antiretroviral (ARV) drugs, and are among the most common reasons for switching or discontinuing therapy, and for medication nonadherence. However, rates of treatment-limiting adverse events in ARV-naive patients enrolled in randomized trials or large observational cohorts appear to be declining with increased availability of better-tolerated and less toxic cART regimens and are generally less than 10%. In general, the overall benefits of cART outweigh its risks, and the risk of some abnormal laboratory findings (e.g., anemia, renal impairment) may be lower with cART than in its absence.

ARV drug-related adverse events can vary in severity from mild to severe and life-threatening. Drug-related toxicity can be acute (occurring soon after a drug has been administered), subacute (occurring within 1 to 2 days of administration), or late (occurring after prolonged drug administration). For some ARV medications, pharmacogenetic markers associated with risk of early toxicity have been identified, but the only such screen in routine clinical use is HLA B*5701 as a marker for abacavir hypersensitivity. For selected children aged <3 years who require treatment with efavirenz, an additional pharmacogenetic marker, CYP2B6 genotype, should be assessed (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

The most common acute and chronic adverse effects associated with ARV drugs or drug classes are presented in the Management of Medication Toxicity or Intolerance tables. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provide selected references regarding these toxicities in pediatric patients.

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/2/2014
Management of medication-related toxicity should take into account its severity, the relative need for viral suppression, and the available ARV options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution. However, even mild adverse effects may have a negative impact on medication adherence and should be discussed before therapy is initiated, at regular provider visits, and at onset of any adverse effects. Common, self-limited adverse effects should be anticipated, and reassurance provided that many adverse effects will resolve after the first few weeks of cART. For example, when initiating therapy with boosted protease inhibitors (PIs) many patients experience gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these side effects. Some patients may require antiemetics and antidiarrheal agents for symptom management. Central nervous system (CNS) adverse effects are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime to help minimize these adverse effects and be advised that these side effects should diminish or disappear within 2 to 4 weeks of initiating therapy in most people. In addition, mild rash can be ameliorated with drugs such as antihistamines. For some moderate toxicities, using a drug in the same class as the one causing toxicity but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required.

In patients who experience an unacceptable adverse effect from cART, every attempt should be made to identify the offending agent and replace the drug with another effective agent as soon as possible. Although many experts will stagger a planned interruption of a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART regimen, stopping the NNRTI first and the dual nucleoside analogue reverse transcriptase backbone 7-14 days later because of the long half-life of NNRTI drugs, in patients who have a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the adverse event has been determined, planning can begin for resumption of therapy with a new ARV regimen that does not contain the offending drug or with the original regimen, if the event is attributable to another cause. All drugs in the ARV regimen should then be started simultaneously, rather than one at a time with observation for adverse effects.

When therapy is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible. Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is permissible for patients whose viral loads are undetectable. However, substitution of a single active agent for a single drug in a failing multidrug regimen (e.g., a patient with virologic failure) is generally not recommended because of concern for development of resistance (see Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy).

Therapeutic drug monitoring (TDM) may be used in the management of the child with mild or moderate toxicity if the toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range (see Role of Therapeutic Drug Monitoring). This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then, it should be used with caution; an expert in the management of pediatric HIV infection should be consulted.

To summarize, management strategies for drug intolerance include:
- Symptomatic treatment of mild-to-moderate transient side effects.
- If necessary, change from one drug to another drug to which a patient’s virus is sensitive (such as changing to abacavir for zidovudine-related anemia or to nevirapine for efavirenz-related CNS symptoms).
- Change drug class, if necessary (such as from a PI to a non-nucleoside reverse transcriptase inhibitor or vice versa) and if a patient’s virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.
References


Table 11a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 1 of 3)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global CNS Depression</td>
<td>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</td>
<td>Onset:</td>
<td>Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates.</td>
<td>Prematurity</td>
<td>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.</td>
<td>Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period.</td>
</tr>
<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td>Onset: 1–2 days after initiating treatment</td>
<td>Variable, depending on age, symptom, assessment method</td>
<td>Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL</td>
<td>Administer EFV on an empty stomach, preferably at bedtime.</td>
<td>Provide reassurance about the likely time-limited nature of symptoms. Consider EFV trough level if symptoms excessive or persistent. If EFV trough level ≥4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug substitution.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most symptoms subside or diminish by 2–4 weeks, but may persist in a minority of patients.</td>
<td></td>
<td>Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype)</td>
<td>TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).</td>
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<td></td>
<td></td>
<td>Presentation</td>
<td></td>
<td>Prior history of psychiatric illness or use of psychoactive drugs</td>
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<td></td>
<td></td>
<td>May Include One or More of the Following:</td>
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<td></td>
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<td>Dizziness</td>
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<td></td>
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<td>Somnolence</td>
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<td></td>
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<td>Insomnia</td>
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<td></td>
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<td>Abnormal dreams</td>
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<td></td>
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<td>Impaired concentration</td>
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<td>Psychosis</td>
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<td></td>
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<td>Suicidal ideation</td>
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<td>Seizures (including absence seizures) or decreased seizure threshold.</td>
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<td>Note: Some CNS side effects (e.g.,</td>
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<td>impaired concentration, abnormal</td>
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<td>dreams, or sleep disturbances) may</td>
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<tr>
<td>be more difficult to assess in children.</td>
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</tbody>
</table>
Table 11a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 2 of 3)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | RAL | Presentation:  
- Increased psychomotor activity  
- Headaches  
- Insomnia  
- Depression | Children:  
- Increased psychomotor activity reported in one child | Elevated RAL concentrations | Pre-screen for psychiatric symptoms. | Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms. |
| | | | Adults:  
- Headache  
- Insomnia (<5% in adult trials) | Co-treatment with TDF or PPI | Monitor carefully for CNS symptoms. |
| | | | | Prior history of insomnia or depression | Use with caution in the presence of drugs that increase RAL concentration. |
| | RPV | Presentation:  
- Dizziness  
- Abnormal dreams/nighmare  
- Insomnia | In Adults:  
- 43% all grade neuropsychiatric AE at 96 weeks (mostly Grade 1, causing RPV discontinuation in only one case, significantly lower than EFV) | Prior history of neuropsychiatric illness | Monitor carefully for CNS symptoms. | Consider drug substitution in case of severe symptoms. |
| Intracranial Hemorrhage | TPV | Onset:  
- 7–513 days after starting TPV | Children:  
- No cases of ICH reported in children. | Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported. | Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery. | Discontinue TPV if ICH is suspected or confirmed. |
| | | | Adults:  
- In premarket approval data in adults, 0.23/100 patient-years or 0.04–0.22/100 patient years in a retrospective review of 2 large patient databases. | | | |
### Table 11a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity  
(Last updated February 12, 2014; last reviewed February 12, 2014)  
(page 3 of 3)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
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<th>Estimated Frequency</th>
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<th>Management</th>
</tr>
</thead>
</table>
| Cerebellar Ataxia | RAL | Onset:  
• As early as 3 days after starting RAL  
Presentation:  
• Tremor  
• Dysmetria  
• Ataxia | Two cases reported in adults during post-marketing period. | Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration. | Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme. | Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (e.g., drug-drug interaction) identified and removed. |

**Key to Acronyms:**  
AE = adverse effect; ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxyl fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucurononyl transferase

**References**


Table 11b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia
(Last updated February 12, 2014; last reviewed February 12, 2014)  (page 1 of 2)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|-----------------|----------------|
| Dyslipidemia    | PIs:           |
|                 | • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without ritonavir |
|                 | NRTIs:         |
|                 | • Especially d4T |
|                 | • EFV > NVP, RPV and ETR |
|                 | Onset:         |
|                 | • As early as 2 weeks to months after beginning therapy |
|                 | Presentation   |
|                 | PIs:          |
|                 | • ↑ LDL-C, TC, and TG |
|                 | NRTIs:        |
|                 | • ↑ LDL-C, TC, and HDL-C |
|                 | NRTIs:        |
|                 | • ↑ LDL-C, TC, and TG |
|                 | Risk Factors  |
|                 | • Advanced-stage HIV disease |
|                 | • High-fat, high-cholesterol diet |
|                 | • Lack of exercise |
|                 | • Obesity |
|                 | • Hypertension |
|                 | • Smoking |
|                 | • Family history of dyslipidemia or premature CVD |
|                 | • Metabolic syndrome |
|                 | • Fat maldistribution |
|                 | Prevention:    |
|                 | • Low-fat diet |
|                 | • Exercise |
|                 | • No smoking |
|                 | Monitoring:    |
|                 | Adolescents and Adults: |
|                 | • Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (>2 weeks—but ≤3 months—apart, average results) before initiating or changing lipid-lowering therapy. |
|                 | Children (Aged ≥2 Years) Without Lipid Abnormalities or Additional Risk Factors: |
|                 | • Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests. |
|                 | Children with Lipid Abnormalities and/or Additional Risk Factors: |
|                 | • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). |
|                 | Assessment of additional CVD risk factors should be done in all patients. HIV-infected patients are considered to be at moderate risk of CVD.a |
|                 | Counsel lifestyle modification, dietary interventions (e.g., low-fat diet; low simple carbohydrate diet in case of ↑ TG; exercise, smoking cessation) for adequate trial period (3–6 months). |
|                 | Pharmacologic Management: |
|                 | • Dyslipidemic children aged ≥10 years with LDL-C ≥250 mg/dL or TG levels ≥500 mg/dL and all children aged <10 years who require lipid-lowering treatment should be managed by a lipid specialist. |
|                 | • Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with antiretroviral treatment. b |
|                 | • Risks must be weighed against potential benefits |
|                 | • Consider switching to a new ART regimen less likely to cause lipid abnormalities. |
|                 | • Consider lipid-lowering therapy in consultation with a lipid specialist if 6-month trial of lifestyle modification fails. |
|                 | • No consensus exists as to what |

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### Table 11b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia
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<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:</td>
<td></td>
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<tr>
<td>• Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy.</td>
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<tr>
<td>• If minimal alterations in AST, ALT, and CK, monitor every 3–4 months in the first year and every 6 month thereafter (or as clinically indicated).</td>
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<tr>
<td>• Repeat FLPS 4 weeks after increasing doses of antihyperlipidemic agents.</td>
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</table>

**LDL-C should prompt treatment in children receiving ARV drugs. Drug therapy cut points recommended by NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years:** LDL–C ≥190 mg/dL, regardless of additional risks factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.

**The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL.**

**Initiate Drug Therapy Promptly in Patients with TG ≥500 mg/dL:**

- Statins such as pravastatin, atorvastatin, or rosuvastatin.
- Ezetimibe can be considered in addition to statins.

- Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children.

**The long-term risks of lipid abnormalities in children receiving cART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.**

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The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosuvastatin (Crestor®), fluvastatin, and ezetimibe (Zetia®) are approved for use in children aged ≥10 years

**Key to Acronyms:**

- ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; cART = combination antiretroviral therapy; CK = creatine kinase; CVD = cardiovascular disease; DRV/r = darunavir/ritonavir; d4T = stavudine; EFV = efavirenz; FLP = Fasting Lipid Profile; HDL-C = high-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; LFT = liver function test; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; TC = total cholesterol; TG = triglyceride; RTV = ritonavir; ETR = etravirine

**References**


Table 11c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects  (Last updated February 12, 2014; last reviewed February 12, 2014)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Nausea/Vomiting | Principally ZDV and PIs (such as LPV/r, RTV) but can occur with all ARVs | Onset:  
  • Early  
  Presentation:  
  • Nausea, emesis—may be associated with anorexia and/or abdominal pain. | Varies with ARV agent; 10%–30% in some series. | Unknown | Instruct patient to take PIs with food.  
  Generally improves with time; monitor for weight loss, ARV adherence. | Reassure patient/caretaker that nausea and vomiting will likely decrease over time.  
  Provide supportive care including instruction on dietary modification.  
  Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases. |
| Diarrhea        | PIs (NFV, LPV/r, FPV/r), buffered ddl | Onset:  
  • Early  
  Presentation:  
  • Generally soft, more frequent stools | Varies with ARV agent; 10%–30% in some series. | Unknown | Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration. | Exclude infectious causes of diarrhea.  
  Although data in children on treatment for ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate, bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful.  
  While there are few published data on its use, crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults but not in children. |
| Pancreatitis    | ddl, d4T (especially concurrently or with TDF), boosted PIs.  
  Reported, albeit rarely, with most ARVs | Onset:  
  • Any time, usually after months of therapy  
  Presentation:  
  • Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis). | <1%–2% in recent series.  
  Frequency was higher in the past with higher dosing of ddl. | Concomitant treatment with other medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin).  
  Hypertriglyceridemia.  
  Advanced disease.  
  Previous episode of pancreatitis. | Avoid use of ddl in patients with a history of pancreatitis. | Discontinue offending agent—avoid reintroduction.  
  Manage symptoms of acute episode.  
  If associated with hypertriglyceridemia, consider interventions to lower TG levels. |

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; d4T = stavudine; ddl = didanosine; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine
References


### Table 11d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 1 of 2)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Anemia**      | Principally ZDV | Onset: • Variable, weeks to months  
Presentation: Most Commonly:  
• Asymptomatic or mild fatigue  
• Pallor  
• Tachypnea  
Rarely:  
• Congestive heart failure | HIV-Exposed Newborns:  
• Severe anemia uncommon, but may be seen coincident with physiologic Hgb nadir  
HIV-Infected Children on ARVs:  
• 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV | HIV-Exposed Newborns:  
• Premature birth  
• In utero exposure to ARVs  
• Advanced maternal HIV  
• Neonatal blood loss  
• Concurrent ZDV plus 3TC neonatal prophylaxis  
HIV-Infected Children on ARVs:  
• Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency)  
• Myelosuppressive drugs (e.g., TMP-SMX, rifabutin)  
• Iron deficiency  
• Advanced or poorly controlled HIV disease | HIV-Exposed Newborns:  
• Obtain CBC at birth.  
• Consider repeat CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or known to have low birth Hgb).  
HIV-Infected Children on ARVs:  
• Avoid ZDV in children with moderate to severe anemia when alternative agents are available.  
• Obtain CBC as part of routine care. | HIV-Exposed Newborns:  
• Rarely require intervention unless Hgb is <7.0 g/dL or anemia is associated with symptoms.  
• Consider discontinuing ZDV if 4 weeks or more of a 6-week ZDV prophylaxis regimen are already completed (see the Perinatal Guidelinesb).  
HIV-Infected Children on ARVs:  
• Discontinue non-ARV, marrow-toxic drugs, if feasible.  
• Treat coexisting iron deficiency, OIs, malignancies.  
• For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin if essential to continue ZDV. |

| **Macrocytosis** | Principally ZDV; also d4T | Onset: • Within days to weeks of starting therapy  
• MCV often >100 fL  
Presentation:  
• Most often asymptomatic  
• Sometimes associated with anemia (occurs more often with ZDV than with d4T) | >90-95%, all ages | None | Obtain CBC as part of routine care | None required unless associated with anemia |

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Table 11d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 2 of 2)

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<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Principally ZDV</td>
<td>Onset:</td>
<td>HIV-Exposed Newborns:</td>
<td>HIV-Exposed Newborns:</td>
<td>HIV-Infected Children on ARVs:</td>
<td>HIV-Exposed Newborns:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variable</td>
<td>Rare</td>
<td>• In utero exposure to ARVs</td>
<td>• Obtain CBC as part of routine care.</td>
<td>• No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC &lt;500 cells/mm³, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see Perinatal Guidelines³).</td>
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<td></td>
<td>Presentation:</td>
<td>HIV-Infected Children on ARVs:</td>
<td>• Concurrent ZDV plus 3TC neonatal prophylaxis</td>
<td>HIV-Infected Children on ARVs:</td>
<td>HIV-Infected Children on ARVs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most commonly asymptomatic.</td>
<td>• 9.9%–26.8% of children on ARVs, depending upon the ARV regimen</td>
<td>• Advanced or poorly controlled HIV infection</td>
<td>• Discontinue non-ARV marrow-toxic drugs, if feasible.</td>
<td>• Discontinue non-ARV marrow-toxic drugs, if feasible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complications appear to be less than with neutropenias associated with cancer chemotherapy.</td>
<td>• Highest rates with ZDV-containing regimens</td>
<td>• Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)</td>
<td>• Treat co-existing OIs and malignancies.</td>
<td>• Treat co-existing OIs and malignancies.</td>
</tr>
<tr>
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<td></td>
<td>For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of G-CSF if essential to continue ZDV.</td>
<td>For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of G-CSF if essential to continue ZDV.</td>
</tr>
</tbody>
</table>

a HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

b Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Key to Acronyms: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; fl = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine
References


Table 11e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events  
(Last updated February 12, 2014; last reviewed February 12, 2014)  (page 1 of 2)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Hepatic Toxicity        | All ARVs may be associated with hepatitis. NVP and TPV are of particular concern. NVP, EFV, ABC, RAL, and MVC have been associated with hypersensitivity reactions. NRTIs (especially ZDV, ddl, and d4T) are associated with lactic acidosis and hepatic steatosis. | Onset:  
  • Hepatitis generally occurs within first few months of therapy, but can occur later.  
  • Steatosis presents after months to years of therapy.  
  • HBV-coinfected patients may develop severe hepatic flare with the initiation, withdrawal, or development of resistance to 3TC, FTC, or TDF (especially in patients receiving only one anti-HBV agent).  
  • Hepatitis may also represent IRIS early in therapy, especially in HBV- and HCV-infected patients.  
  Presentation:  
  • Asymptomatic elevation of AST and ALT.  
  • Symptomatic hepatitis with nausea, fatigue, and jaundice.  
  • Hepatitis may be component of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis. | Uncommon in children. Frequency varies with different agents and drug combinations. | HBV or HCV coinfection Elevated baseline ALT and AST Other hepatotoxic medications (including herbal preparations such as St. John’s wort [Hypericum perforatum], Chaparral [Larrea tridentate], Germander [Teudrium chamaedrys]) Alcohol use Underlying liver disease Pregnancy  
For NVP-Associated Hepatic Events in Adults:  
  • Female with pre-NVP CD4 count >250 cells/mm³  
  • Male with pre-NVP CD4 count >400 cells/mm³  
  • Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.¹  
  Higher drug concentrations for PIs, particularly TPV | Prevention:  
  • Avoid concomitant use of hepatotoxic medications.  
  • If hepatic enzymes are elevated >5 to 10 times ULN, some would consider discontinuing ARVs.  
  Monitoring:  
  For ARVs Other than NVP:  
  • Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., as HBV- or HCV-coinfected or elevated baseline AST and ALT).  
  For NVP:  
  • Obtain AST and ALT at baseline, at 2 and 4 weeks, then every 3 months. | Asymptomatic patients with elevated ALT or AST should be evaluated for other causes and monitored closely. If ALT or AST >5 to 10 times ULN, some would consider discontinuing ARVs. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restarting the offending agent. If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP Hypersensitivity). When clinical hepatitis is associated with lactic acidosis, avoid restarting the most likely agent, and ZDV, d4T, and ddl in particular (see also Lactic Acidosis). Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV. |
### Table 11e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated February 12, 2014; last reviewed February 12, 2014)  

#### Indirect Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Hyperbilirubinemia</td>
<td>IDV, ATV</td>
<td>Onset: • First months of therapy • Jaundice; otherwise asymptomatic elevation of indirect bilirubin levels with normal direct bilirubin, AST, and ALT.</td>
<td>HIV-Infected Children Receiving ATV: • 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.</td>
<td>N/A</td>
<td>Monitoring: • No specific monitoring.</td>
<td>Not necessary to discontinue the offending agent except for cosmetic reasons. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time.</td>
</tr>
</tbody>
</table>

#### Non-Cirrhotic Portal Hypertension

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset: • Generally after years of therapy • GI bleeding, esophageal varices, hypersplenism. • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism). • Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis.</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Cirrhotic Portal Hypertension</td>
<td>ARVs, especially ddl, d4T, and combination of ddl and d4T</td>
<td>Rare: • Probably less than 1%</td>
<td>Prolonged exposure to ARV therapy, especially ddl and the combination of ddl and d4T</td>
<td>N/A</td>
<td>Monitoring: • No specific monitoring.</td>
<td>Manage complications of GI bleeding and esophageal varices. Discontinue/replace d4T or ddl, if patient is receiving either.</td>
</tr>
</tbody>
</table>

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**Key to Acronyms:**

- 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; ddI = didanosine; d4T = stavudine; ddi = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; IDV = Indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

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**Key to Acronyms:**

- E.g. HLA-DRB1*0101 in Caucasians, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and Caucasians
References


Table 11f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus  
( Last updated February 12, 2014; last reviewed February 12, 2014 )

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Insulin Resistance, Asymptomatic Hyperglycemia, DM \(^a\) | Thymidine analogue NRTIs (i.e., d4T, ddI, ZDV)  
Several PIs (i.e., IDV, LPV/r; less often ATV, ATV/r, TPV/r) | Onset:  
• Weeks to months after beginning therapy; median of 60 days (adult data)  
Presentation:  
Most Commonly:  
• Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay  
Also Possible:  
• Frank DM (i.e., polyuria, polydipsia, polyphagia, fatigue, hyperglycemia) | Insulin Resistance:  
ARV-Treated Children:  
• 6%–33%  
Impaired Fasting Glucose:  
ARV-Treated Adults:  
• 3%–25%  
ARV-Treated Children:  
• 0%–7%  
Impaired Glucose Tolerance:  
ARV-Treated Adults:  
• 16%–35%  
ARV-Treated Children:  
• 3%–4%  
DM ARV-Treated Adults:  
• 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults)  
ARV-Treated Children:  
• Very rare in HIV-infected children | Risk Factors For Type 2 DM:  
• Lipodystrophy  
• Metabolic syndrome  
• Family history of DM  
• High BMI  
• Obesity | Prevention:  
• Lifestyle modification  
• Although uncertain, avoiding the use of d4T, IDV may reduce risk.  
Monitoring:  
• Monitor for polydipsia, polyuria, polyphagia, change in body habitus, and acanthosis nigricans.  
Obtain RPG levels at:  
• Initiation of ARV therapy, and  
• 3–6 months after therapy initiation, and  
• Once a year thereafter.  
For Either RPG ≥200 mg/dL Plus Symptoms of DM or FPG ≥126 mg/dL:  
• Patient meets diagnostic criteria for DM; consult endocrinologist.  
FPG 100–125 mg/dL:  
• Impaired FPG is suggestive of insulin resistance; consult endocrinologist.  
FPG <100 mg/dL:  
• Normal FPG, but Does Not Exclude Insulin Resistance:  
• Recheck FPG in 6–12 months. | Counsel on lifestyle modification (i.e., low-fat diet, exercise, no smoking).  
Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen.  
For Either RPG ≥200 mg/dL Plus Symptoms of DM or FPG ≥126 mg/dL:  
• Patient meets diagnostic criteria for DM; consult endocrinologist.  
FPG 100–125 mg/dL:  
• Impaired FPG is suggestive of insulin resistance; consult endocrinologist.  
FPG <100 mg/dL:  
• Normal FPG, but Does Not Exclude Insulin Resistance:  
• Recheck FPG in 6–12 months. |

\(^a\) Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. Insulin resistance is often defined as elevated insulin levels for the level of glucose observed; impaired FPG as an FPG of 100–125 mg/dL; impaired glucose tolerance as an elevated 2-hour PG of 140–199 mg/dL in a standard OGTT; and diabetes mellitus as either an FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, HgbA1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; d4T = stavudine; ddI = didanosine; DM = diabetes mellitus; DRV/r = ritonavir-boosted darunavir; FPG = fasting plasma glucose; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine
References


<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic Acidosis</td>
<td>NRTIs, in particular, d4T and ddl (highest risk in combination)</td>
<td>Onset: &lt;br&gt;1–20 months after starting therapy &lt;br&gt;(median onset 4 months in 1 case series).</td>
<td>Chronic, Asymptomatic Mild Hyperlactatemia &lt;br&gt;(2.1–5.0 mmol/L)</td>
<td>Adults: &lt;br&gt;- Female gender &lt;br&gt;- High BMI &lt;br&gt;- Chronic HCV infection &lt;br&gt;- African-American race &lt;br&gt;- Prolonged NRTI use &lt;br&gt;(particularly d4T and ddl) &lt;br&gt;- Co-administration of ddl with other agents &lt;br&gt;(e.g., d4T, TDF, RBV, tetracycline) &lt;br&gt;- Co-administration of TDF with metformin &lt;br&gt;- Overdose of propylene glycol &lt;br&gt;- CD4 count &lt;350 cells/mm³ &lt;br&gt;- Acquired riboflavin or thiamine deficiency &lt;br&gt;- Possibly pregnancy</td>
<td>Prevention: &lt;br&gt;- Avoid d4T and ddl individually and especially in combination in an ARV regimen. &lt;br&gt;- Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.</td>
<td>Lactate 2.1–5.0 mmol/L (Confirmed with Second Test): &lt;br&gt;- Consider replacing ddl and d4T with other ARVs. &lt;br&gt;- As alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. Lactate &gt;5.0 mmol/L (Confirmed with Second Test) or &gt;10.0 mmol/L (Any 1 Test): &lt;br&gt;- Discontinue all ARVs. &lt;br&gt;- Provide supportive therapy (IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). Anecdotal (Unproven) Supportive Therapies: &lt;br&gt;- Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C). Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and monthly monitoring of lactate for at least 3 months.</td>
</tr>
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<td></td>
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<td>Presentation &lt;br&gt;Usually Insidious &lt;br&gt;Onset of a Combination of Signs and Symptoms: &lt;br&gt;- Generalized fatigue, weakness, and myalgias &lt;br&gt;- Vague abdominal pain, weight loss, unexplained nausea or vomiting &lt;br&gt;- Dyspnea &lt;br&gt;- Peripheral neuropathy</td>
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<td>Note: Patients may present with acute multi-organ failure (such as fulminant hepatic, pancreatic, and respiratory failure).</td>
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</table>

**Key to Acronyms:**<br>3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddl = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; TDF = tenofovir disoproxil fumarate; THAM = tris(hydroxymethyl)aminomethane
References

General Reviews


Risk Factors


**Monitoring and Management**


### Table 11h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy  
(Last updated February 12, 2014; last reviewed February 12, 2014)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodystrophy (Fat Maldistribution)</td>
<td>See below for specific associations.</td>
<td>Onset: • Trunk and limb fat initially increase within a few months of start of cART; peripheral fat wasting may not begin to appear for 12 to 24 months after cART initiation.</td>
<td>Highly Variable</td>
<td>Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of cART Body habitus</td>
<td>See below.</td>
<td>See below.</td>
</tr>
<tr>
<td>General Information</td>
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<tr>
<td>Central Lipohypertrophy or Lipoaccumulation</td>
<td>Can occur in the absence of cART, but most associated with PIs and EFV; EFV also associated with gynecomastia and breast hypertrophy</td>
<td>Presentation: • Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).</td>
<td>Children: • Up to 27% Adults: • 6 to 93%</td>
<td>Obesity before initiation of therapy Sedentary lifestyle</td>
<td>Prevention: • Calorically appropriate low-fat diet and exercise, especially strength training. Smoking cessation (if applicable) to decrease future CVD risk.</td>
<td>Calorically appropriate low-fat diet and exercise, especially strength training.</td>
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<tr>
<td>Facial/Peripheral Lipoatrophy</td>
<td>Most associated with thymidine analogues NRTI (d4T &gt; ZDV)</td>
<td>Presentation: • Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.</td>
<td>Children: • Up to 47% (particularly in patients on d4T-containing regimens) Adults: • (up to 15%) in patients not treated with d4T or ZDV Adults: • 13% to 59% (particularly in patients on d4T-containing regimens)</td>
<td>d4T and ZDV Underweight before cART</td>
<td>Prevention: • Avoid use of d4T and ZDV. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.</td>
<td>Switch from d4T or ZDV to other NRTIs if possible without loss of virologic control. Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Injections of poly-L-lactic acid • Recombinant human growth hormone, growth hormone-releasing hormone, metformin, thiazolidinediones, anabolic steroids, or liposuction.</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** ARV = antiretroviral; BMI = body mass index; cART = combination antiretroviral therapy; CVD = cardiovascular disease; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*
References
See the archived version of Supplement III, February 23, 2009 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, (http://www.aidsinfo.nih.gov) for a more complete discussion and reference list.

General Reviews

Associated ARVs/Etiology

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/2/2014


### Management


Table 11i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects
(Last updated February 12, 2014; last reviewed February 12, 2014) (page 1 of 2)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urolithiasis/ Nephrolithiasis</td>
<td>IDV, ATV</td>
<td>Onset: • Weeks to months after starting therapy</td>
<td>IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%).</td>
<td>In adults, high serum IDV concentrations and elevated urine pH (&gt;5.7) associated with persistent pyuria. Unknown in children.</td>
<td>Prevention: • Maintain adequate hydration. Monitoring: • Obtain urinalysis at least every 6–12 months.</td>
<td>Provide adequate hydration and pain control; consider using alternative ARV.</td>
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<td></td>
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<td>Clinical findings: • Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine</td>
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<td></td>
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<td></td>
<td>IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%).</td>
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<td></td>
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<td>ATV nephrolithiasis is rare.</td>
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<td></td>
<td>Unknown in children.</td>
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<td></td>
<td>IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%).</td>
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<td>ATV nephrolithiasis is rare.</td>
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<td></td>
<td></td>
<td></td>
<td>Unknown in children.</td>
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<td></td>
<td>IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%).</td>
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<td></td>
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<td></td>
<td>ATV nephrolithiasis is rare.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Unknown in children.</td>
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<tr>
<td>Renal Dysfunction</td>
<td>TDF</td>
<td>Onset: • Variable; in adults, weeks to months after initiation of therapy.</td>
<td>Adults: • ~2% with increased serum creatinine • ~0.5% with severe renal complications</td>
<td>Risk May Be Increased in Children: • aged &gt;6 years • of Black race, Hispanic/Latino ethnicity • with advanced HIV infection • with concurrent use of ddl or PIs (especially LPV/r), and pre-existing renal dysfunction</td>
<td>Monitor urine protein and glucose or urinalysis, and serum creatinine at intervals of every 3–6 months. For patients taking TDF, some panelists add serum phosphate to the list of routine labs to monitor. In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also monitor serum phosphate. Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time. While unproven, routine monitoring intervals of every 3–6 months might be considered. Abnormal values should be confirmed by repeat testing, and frequency of monitoring can be increased if abnormalities are found and TDF is continued.</td>
<td>If TDF is the likely cause, consider using alternative ARV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypophosphatemia appears at a median of 18 months.</td>
<td>Children: • ~4% with hypophosphatemia or proximal tubulopathy; higher in advanced HIV infection or concomitant use of ddl</td>
<td>Risk May Be Increased in Children: • aged &gt;6 years • of Black race, Hispanic/Latino ethnicity • with advanced HIV infection • with concurrent use of ddl or PIs (especially LPV/r), and pre-existing renal dysfunction</td>
<td>Monitor urine protein and glucose or urinalysis, and serum creatinine at intervals of every 3–6 months. For patients taking TDF, some panelists add serum phosphate to the list of routine labs to monitor. In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also monitor serum phosphate. Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time. While unproven, routine monitoring intervals of every 3–6 months might be considered. Abnormal values should be confirmed by repeat testing, and frequency of monitoring can be increased if abnormalities are found and TDF is continued.</td>
<td>If TDF is the likely cause, consider using alternative ARV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation More Common: • Increased serum creatinine, proteinuria. Hypophosphatemia, usually asymptomatic, may present with bone and muscle pain, weakness.</td>
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<tr>
<td></td>
<td></td>
<td>Less Common: • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria</td>
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</tbody>
</table>
### Table 11i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects
(Last updated February 12, 2014; last reviewed February 12, 2014)  (page 2 of 2)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Dysfunction, continued</td>
<td>IDV</td>
<td>Renal cortical atrophy, acute renal failure</td>
<td>Rare</td>
<td>Unknown</td>
<td>Unknown</td>
<td>If IDV is likely cause, consider using alternative ARV.</td>
</tr>
</tbody>
</table>

**Note:** IDV not FDA-approved for use in children.

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ddI = didanosine; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

### References


### Table 11j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis  (Last updated February 12, 2014; last reviewed February 12, 2014)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia and Osteoporosis</td>
<td>cART, especially following initiation and regardless of regimen</td>
<td>Onset:  • Any age; greatest risk in months after initiation of associated ARV</td>
<td>Low BMD:  • 7% of a U.S. cohort had a BMD z score of ≤−2.0 (87% treated with cART).  • 24% to 32% of Thai and Brazilian adolescents had a BMD z score of ≤−2.0 (92% to 100% treated with cART).</td>
<td>Longer duration of HIV infection  • Greater severity of HIV disease  • Growth delay, pubertal delay  • Low BMI</td>
<td>Prevention:  • Ensure sufficient calcium and vitamin D intake.  • Encourage weight-bearing exercise.  • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids, medroxyprogesterone).</td>
<td>Ensure sufficient calcium and vitamin D intake. Encourage weight-bearing exercise. Reduce modifiable risk factors (e.g., smoking, low BMI, use of steroids, medroxyprogesterone). Role of bisphosphonates not established in children. Consider change in ARV regimen.</td>
</tr>
<tr>
<td></td>
<td>Specific Agents of Possible Concern: • TDF  • d4T  • PIs, especially LPV/r</td>
<td>Presentation:  • Most commonly asymptomatic; fracture (rare)</td>
<td></td>
<td></td>
<td>Monitoring:  • Assess nutritional intake (calcium, vitamin D, and total calories).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Osteoporosis diagnosis in children requires clinical evidence of bone fragility (e.g., fracture with minimal trauma) and cannot rely solely on measured low BMD.</td>
<td></td>
<td></td>
<td>Obtain serum 25-OH-vitamin D.</td>
<td>Observe DXA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Role of bisphosphonates not established in children.</td>
<td></td>
</tr>
</tbody>
</table>

*Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth because, in this population, the prevalence of vitamin D insufficiency is high.*

*Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for prepubertal children and children in early puberty who are initiating treatment with TDF. DXA should also be obtained in children with indications not uniquely related to HIV infection (such as cerebral palsy).*

**Key to Acronyms:** ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; cART = combination antiretroviral therapy; d4T = stavudine; DXA = dual energy x-ray absorptiometry; LPV/r = lopinavir / ritonavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

**References**

**Osteopenia and Osteoporosis**

3. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric


### Table 11k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity  (Last updated February 12, 2014; last reviewed February 12, 2014)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| ARV Toxic Neuropathy<sup>b</sup> | d4T, ddI | Onset:  
• Variable, weeks to months following NRTI initiation  
Presentation:  
• Decreased sensation  
• Aching, burning, painful numbness  
• Hyperalgesia (lowered pain threshold)  
• Alloodynia (non-noxious stimuli cause pain)  
• Decreased or absent ankle reflexes  
Distribution:  
• Bilateral soles of feet, ascending to legs and fingertips | HIV-Infected Children:  
• 1.13% prevalence (baseline 2001);  
• Incidence 0.23 per 100 person-years (2001–2006) in a U.S. cohort.  
• ≤1% discontinued d4T because of neuropathy in 3 large African cohorts (aged 1 month–18 years; median follow-up 1.8–3.2 years). | HIV-Infected Adults:  
• Pre-existing neuropathy (e.g., diabetes, alcohol abuse, vitamin B12 deficiency)  
• Elevated triglyceride levels  
• Older age  
• Poor nutrition  
• More advanced HIV disease  
• Concomitant use of other neurotoxic agents (e.g., INH)  
• Some mitochondrial DNA haplogroups may have increased risk | Limit use of d4T and ddI, if possible.  
As part of routine care, monitor for symptoms and signs of peripheral neuropathy. | Discontinue offending agent.  
Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful.  
Data are Insufficient to Allow the Panel to Recommend Use of any of the Following Modalities in Children:  
• tricyclic antidepressants  
• gabapentin  
• pregabalin  
• mexilitine  
• lamotrigine  
Consider referral to neurologist. |

<sup>a</sup> Peripheral neuropathy may be under-reported in children because symptoms are difficult to evaluate in young children.

<sup>b</sup> HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

**Key to Acronyms:** ARV = antiretroviral; d4T = stavudine; ddI = didanosine; INH = isoniazid; NRTI = nucleoside reverse transcriptase inhibitor

### References


### Table 11l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 1 of 4)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Rash            | Any ARV can cause rash. | Onset:  
• First few days to weeks after starting therapy  
Presentation:  
• Most rashes are mild-to-moderate, diffuse maculopapular eruptions.  
Note: Some rashes are the initial manifestation of systemic hypersensitivity (see HSR, SJS/TEN/EM major). | Common (>10% Adults and/or Children):  
• NVP, EFV, ETR, FPV, ATV, FTC  
Less Common (5%–10%):  
• ABC, DRV, TPV, TDF  
Unusual (2%–4%):  
• LPV/r, RAL, MVC, RPV | • Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV).  
• Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP. | When Starting NVP or Restarting After Interruptions >14 Days:  
• Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.a  
• Avoid the use of corticosteroids during NVP dose escalation.  
• Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction.  
• Consider concomitant medications and illnesses that cause rash. | Mild-To-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:  
• Most will resolve without intervention; ARVs can be continued while monitoring.a  
• Antihistamines may provide some relief.  
Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgias, Edema) and/or Rash Accompanied By Mucus Membrane Involvement (e.g., Conjunctivitis):  
• Manage as SJS/TEN/EM major (see below).  
Rash in Patients Receiving NVP:  
• Given elevated risk of HSR, measure hepatic transaminases.  
• If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).  
• Continue the agent as tolerated by the patient.  
• Adjust injection technique.  
• Rotate injection sites. |
| ENF             | Onset:  
• First few days to weeks after starting therapy  
Presentation:  
• Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time. | Adults and Children:  
• >90% | Unknown | | | |
**Table 11l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions**  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 2 of 4)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| **SJS/TEN/EM Major** | Many ARVs, especially NNRTIs (see frequency column) | Onset:  
• First few days to weeks after initiating therapy  
Presentation:  
• Initial rash may be mild, but often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia. | Infrequent:  
• NVP (0.3%), EFV (0.1%), ETR (<0.1%)  
Case Reports:  
• FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL | Adults:  
• Female gender  
• Race/ethnicity (black, Asian, Hispanic) | When Starting NVP or Restarting After Interruptions >14 Days:  
• Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to twice-daily dosing is associated with fewer rashes.  
• Counsel families to report symptoms as soon as they appear.  
• Discontinue all ARVs and other possible causative agents such as cotrimoxazole.  
• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.  
• Corticosteroids and/or IVIG are sometimes used but use of each is controversial.  
• Do not reintroduce the offending medication.  
• In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs. | • Discontinue all ARVs and other possible causative agents such as cotrimoxazole.  
• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.  
• Corticosteroids and/or IVIG are sometimes used but use of each is controversial.  
• Do not reintroduce the offending medication.  
• In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs. |
| **Systemic HSR** | ABC | Onset  
*With First Use*:  
• Within first 6 weeks.  
*With Re-introduction*:  
• Within hours.  
Presentation:  
• Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea). Symptoms worsen to include hypotension and vascular collapse with continuation. With re-challenge, symptoms can mimic anaphylaxis. | 2.3%–9% (varies by racial/ethnic group).  
• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701 negative); also HLA-DR7, HLA-DQ3.  
• HSR risk is higher in those of White race compared to those of Black or East Asian race.  
• Screening for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is positive.**  
• When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions. | | • Discontinue all ARVs and other possible causative agents such as cotrimoxazole.  
• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.  
• Corticosteroids and/or IVIG are sometimes used but use of each is controversial.  
• Do not reintroduce the offending medication.  
• In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs. | • Discontinue all ARVs and other possible causative agents such as cotrimoxazole.  
• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.  
• Corticosteroids and/or IVIG are sometimes used but use of each is controversial.  
• Do not reintroduce the offending medication.  
• In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs. |

*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*
Table 11. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  (Last updated February 12, 2014; last reviewed February 12, 2014) (page 3 of 4)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic HSR</td>
<td>NVP</td>
<td>Onset:</td>
<td>4% (2.5%–11%)</td>
<td>Adults:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most frequent in the first few weeks of therapy but can occur through 18 weeks.</td>
<td></td>
<td>• Treatment-naive with higher CD4 count (&gt;250 cells/mm^3 in women; &gt;400 cells/mm^3 in men).</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days:</td>
<td>• Discontinue ARVs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td>• Female gender (risk is 3-fold higher in females compared with males).</td>
<td>• 2-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce risk of reaction.</td>
<td>• Consider other causes for hepatitis and discontinue all hepatotoxic medications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy.</td>
<td></td>
<td>Children:</td>
<td></td>
<td>• Provide supportive care as indicated and monitor patient closely.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRESS syndrome has also been described.</td>
<td></td>
<td>• NVP hepatotoxicity and HSR are less common in prepubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 &lt;15%.</td>
<td>• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.</td>
<td>• Do not reintroduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP; and many experts would avoid the NNRTI drug class when restarting treatment.</td>
</tr>
<tr>
<td></td>
<td>ENF, ETR</td>
<td>Onset:</td>
<td>Rare</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Any time during therapy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discontinue ARVs. 
Rechallenge with ENF or ETR is not recommended.
Table 11l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  (Last updated February 12, 2014; last reviewed February 12, 2014)  (page 4 of 4)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic HSR</td>
<td>RAL</td>
<td>DRESS syndrome</td>
<td>Case report</td>
<td>Unknown</td>
<td>Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td>Discontinue all ARVs. Rechallenge with RAL is not recommended.</td>
</tr>
<tr>
<td>With or without skin involvement and excluding SJS/TEN</td>
<td>MVC</td>
<td>Rash preceding hepatotoxicity</td>
<td>Rare</td>
<td>Unknown</td>
<td>Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</td>
<td>Discontinue all ARVs. Rechallenge with MVC is not recommended.</td>
</tr>
</tbody>
</table>

"a The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. NVP should be stopped and not restarted if the rash is severe or is worsening or progressing.

Key to Acronyms: ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte cell; ddl = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; HSR = hypersensitivity reaction; IDV = indinavir; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PEP = post-exposure prophylaxis; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

References


Overview

In the United States, the vast majority of HIV-infected children are receiving combination antiretroviral therapy (cART), making treatment-experienced children the norm. Changes in the antiretroviral (ARV) regimen and other aspects of the management of treatment-experienced children can be organized into the following categories: (1) modifying ARV regimens in children on effective cART for simplification or improved adverse effect profile; (2) recognizing and managing ARV drug toxicity or intolerance (see Management of Medication Toxicity or Intolerance); (3) recognizing and managing treatment failure; and (4) considerations about interruptions in therapy.

Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy

Panel's Recommendation

• For children who have sustained virologic suppression on their current regimen, changing to a new antiretroviral regimen with improved pill burden or tolerance should be considered in order to facilitate continued adherence and increase safety (BII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Initial ARV regimens are chosen based on safety, pharmacokinetic and efficacy data for drugs available in formulations suitable for the age of the child at initiation of cART. New ARV options may become available as children grow and learn to swallow pills and as new drugs, drug formulations and data become available. For children who have sustained virologic suppression on their current regimen, changing to a new ARV regimen may be considered in order to permit use of pills instead of liquids, reduce pill burden, allow use of once-daily medications, reduce risk of adverse effects, and align their regimens with widely used, efficacious adult regimens.

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. Based on the NEVEREST study, young children (aged ≤3 years) with virologic suppression who switch from ritonavir-boosted lopinavir to nevirapine can maintain virologic suppression as well as those who continue ritonavir-boosted lopinavir, provided there is good adherence and no baseline resistance to nevirapine.1,2 By extrapolation, replacement of ritonavir-boosted lopinavir with efavirenz, another non-nucleoside reverse transcriptase inhibitor (NNRTI), another protease inhibitor, raltegravir, or another integrase inhibitor would likely be effective, but this has not been directly studied. Several small studies have demonstrated sustained virologic suppression and reassuring safety outcomes when drugs that have greater long-term toxicity risk are replaced with drugs that are thought to have less toxicity risk (e.g., replacing stavudine with tenofovir or zidovudine; replacing protease inhibitor with NNRTI), including improved lipid profiles, in small cohorts of children.3,7 Small studies have shown that children with virologic suppression on twice-daily regimens maintain virologic suppression if abacavir dosing is changed from twice daily to once daily (see Abacavir drug section) but show mixed results when switching ritonavir-boosted lopinavir dosing from twice daily to once daily.8,9
Table 12 displays examples of changes in ARV regimen components that are made for reasons of simplification, convenience and safety profile in children who have sustained virologic suppression on their current regimen. When considering such a change, it is important to ensure that a child does not have virologic treatment failure. It is also critical to consider past episodes of ARV treatment failure and all prior drug resistance testing results in order to avoid choosing new ARV drugs for which archived drug resistance would limit activity. The evidence supporting many of these ARV changes is indirect, extrapolated from data about drug performance in initial therapy or follow-on therapy after treatment failure. When such changes are made, careful monitoring is important to ensure that virologic suppression is maintained.

<table>
<thead>
<tr>
<th>ARV Drug(s)</th>
<th>Current Age</th>
<th>Body Size Attained</th>
<th>Potential ARV Regimen Change</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV or ddI (or d4T*)</td>
<td>≥1 year</td>
<td>N/A</td>
<td>ABC</td>
<td>Once-daily dosing (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Less long-term mitochondrial toxicity.</td>
</tr>
<tr>
<td>ABC Twice Daily</td>
<td>≥1 year</td>
<td>Any</td>
<td>ABC once daily</td>
<td>See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for full discussion.</td>
</tr>
<tr>
<td>LPV/r</td>
<td>≥1 year</td>
<td>≥3 kg</td>
<td>RAL</td>
<td>Better palatability. Less adverse lipid effect.</td>
</tr>
<tr>
<td>LPV/r Twice Daily</td>
<td>≥3 years</td>
<td>N/A</td>
<td>EFV</td>
<td>Once-daily dosing. Better palatability. Less adverse lipid effect. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children &lt; 3 years old.</td>
</tr>
<tr>
<td>LPV/r Twice Daily</td>
<td>≥6 years</td>
<td>15 kg</td>
<td>ATV/r</td>
<td>Once-daily dosing. Lower pill burden. Less adverse lipid effect.</td>
</tr>
<tr>
<td>ZDV or ddI</td>
<td>Adolescence</td>
<td>Pubertal maturity (Tanner IV or V)</td>
<td>TDF or ABC</td>
<td>Once-daily dosing. Less long-term mitochondrial toxicity. Coformulation with other ARVs can further reduce pill burden.</td>
</tr>
<tr>
<td>LPV/r Twice Daily</td>
<td>≥12 years</td>
<td>40 kg</td>
<td>DRV/r</td>
<td>Once-daily dosing possible. Lower pill burden.</td>
</tr>
</tbody>
</table>

* Because of concerns about long-term adverse effects, d4T may be replaced by a safer drug even before sustained virologic suppression is achieved (see Stavudine in Appendix A: Pediatric Antiretroviral Drug Information).

Key to Acronyms: ABC = abacavir; ATV/r = ritonavir-boosted atazanavir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = ritonavir-boosted darunavi; EFV = etavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References


Recognizing and Managing Antiretroviral Treatment Failure  (Last updated February 12, 2014, last reviewed February 12, 2014)

Panel’s Recommendations

- The causes of virologic treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions—should be assessed and addressed (AII).
- Perform antiretroviral (ARV) drug-resistance testing when virologic failure occurs, while a patient is still taking the failing regimen and before changing to a new regimen (AI*).
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of quantification using the most sensitive assay (AI*).
- ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results (AI*).
- The new regimen should include at least two, but preferably three, fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results (AII*).
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future ARV options (AII).
- Children who require evaluation and management of treatment failure should be managed in collaboration with a pediatric HIV specialist (AI*).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Definitions of Treatment Failure

Treatment failure can be categorized as virologic failure, immunologic failure, or clinical failure (or some combination of the three). Laboratory results must be confirmed with repeat testing before a final assessment of virologic or immunologic treatment failure is made.

Virologic Failure

Virologic failure occurs as an incomplete initial response to therapy or as a viral rebound after virologic suppression is achieved. Virologic suppression is defined as having plasma HIV RNA below the level of quantification using the most sensitive assay (<20 to 75 copies/mL). Older assays with lower limits of 200 or 400 copies/mL are not recommended. Virologic failure is defined for all children as a plasma HIV RNA >200 copies/mL after 6 months of therapy or repeated plasma HIV RNA greater than the level of quantification using the most sensitive assay after 12 months of therapy. Occasionally, infants with high plasma HIV RNA levels at initiation of therapy have HIV RNA levels that are declining but remain >200 copies/mL after 6 months of therapy. Among many of those receiving ritonavir-boosted lopinavir, suppression can be achieved without regimen change if efforts are made to improve adherence.1 However, ongoing non-suppression—especially with non-nucleoside reverse transcription inhibitor (NNRTI)-based regimens—increases risk of drug resistance.2 HIV-infected adults with detectable HIV RNA and a quantified result <200 copies/mL after 6 months of combination antiretroviral therapy (cART) often ultimately achieve virologic suppression without regimen change.3 “Blips,” defined as isolated episodes of plasma HIV RNA <500 copies/mL followed by return to viral suppression, are common and not generally reflective of virologic failure.46 Repeated or persistent plasma HIV
RNA detection above the level of quantification (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.6-8

Immunologic Failure
Immunologic failure is defined as an incomplete immunologic response to therapy or an immunologic decline while on therapy. While there is no standardized definition, many experts would consider as incomplete immunologic response to therapy the failure to maintain or achieve a CD4 T lymphocyte (CD4) cell count/percentage that is at least above the age-specific range for severe immunodeficiency. Evaluation of immune response in children is complicated by the normal age-related changes in CD4 cell count discussed previously (see Immunologic Monitoring in Children: General Considerations in Clinical and Laboratory Monitoring). Thus, the normal decline in CD4 values with age needs to be considered when evaluating declines in CD4 parameters. CD4 percentage tends to vary less with age. At about age 5 years, absolute CD4 count values in children approach those of adults; consequently, changes in absolute count can be used in children aged ≥5 years.

Clinical Failure
Clinical failure is defined as the occurrence of new opportunistic infections (OIs) and/or other clinical evidence of HIV disease progression during therapy. Clinical failure represents the most urgent and concerning type of treatment failure and should prompt an immediate evaluation. Clinical findings should be viewed in the context of virologic and immunologic response to therapy; in patients with stable virologic and immunologic parameters, development of clinical symptoms may not represent treatment failure. Clinical events occurring in the first several months after cART initiation often do not represent cART failure. For example, the development or worsening of an OI in a patient who recently initiated cART may reflect a degree of persistent immune dysfunction in the context of early recovery, or conversely, be a result of immune reconstitution inflammatory syndrome (IRIS). However, the occurrence of significant clinical disease progression should prompt strong consideration that the current treatment regimen is failing.

Discordance Between Virologic, Immunologic, and Clinical Responses
In general, cART that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of HIV-related illnesses. The converse is also generally true: ineffective cART that fails to suppress viremia is commonly accompanied by immunologic and clinical failure. However, patients may also present with failure in one domain (e.g., immunologic failure) but with a good response in the other domains (e.g., virologic and clinical response). In fact, the discordance in responses to cART can occur in any of these three domains in relation to the other two. It is essential to consider potential alternative causes of discordant responses before concluding that cART failure has truly occurred.

Incomplete Virologic Response Despite Adequate Clinical and Immunologic Responses
Some patients who are maintained on cART may sustain immunologic and clinical benefit for up to 3 years despite persistent low-level viremia. This observation is the rationale for continuing non-suppressive cART for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practical. The proposed mechanisms for immunologic and clinical benefit without complete virologic suppression are maintenance of a lower viral load or selection for strains harboring drug-resistance mutations that impair viral replicative capacity or fitness. Another potential explanation for this discordance is that some of these children may have host genetic and/or virologic characteristics that would have allowed them to be either “slow-progressors” or “long-term non-progressors” without therapy.

Poor Immunologic Response Despite Virologic Suppression Regardless of Clinical Response
Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. The first considerations in cases of poor immunologic response despite virologic suppression are to exclude laboratory error in CD4 or viral load measurements and to ensure that CD4 values
have been interpreted correctly in relation to the natural decline in CD4 count over the first 5 to 6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (such as HIV-1 non-M groups or non-B subtypes, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection and Clinical and Laboratory Monitoring). Once lab results are confirmed, evaluation for adverse drug effects, medical conditions, and other factors that can result in lower CD4 values is necessary (see Table 13).

In addition, it is common for patients with baseline severe immunosuppression to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in a transient early treatment period of persistent immunosuppression during which additional clinical disease progression can occur. Patients who have very low baseline CD4 values before initiating cART are at higher risk of an impaired CD4 response to cART and, based on adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.20-24

Certain antiretroviral (ARV) agents or combinations may be associated with a blunted CD4 response. For example, treatment with a regimen containing tenofovir disoproxil fumarate (tenofovir) and didanosine can blunt the CD4 response, especially if the didanosine dose is not reduced,25 and this combination is not recommended as part of initial therapy. Dosing of didanosine should be reduced when co-administered with tenofovir. In adults, ARV regimens containing zidovudine may also impair rise in CD4 cell count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine.26 Fortunately, this ARV drug-related suboptimal CD4 cell count response to therapy does not seem to confer an increased risk of clinical events. It is not clear whether this scenario warrants substitution of zidovudine with another drug.

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C, tuberculosis, malnutrition, Sjogren’s syndrome, sarcoidosis, syphilis) are independently associated with low CD4 values.

**Poor Clinical Response Despite Adequate Virologic and Immunologic Responses**

Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunological and virological responses to cART. Not all cases represent cART failure. One of the most important reasons for new or recurrent opportunistic conditions despite achieving virologic suppression and immunologic restoration/preservation within the first months of cART is IRIS, which does not represent cART failure and does not generally require discontinuation of cART.27,28 Children who have suffered irreversible damage to their lungs, brain, or other organs—especially during prolonged and profound pretreatment immunosuppression—may continue to have recurrent infections or symptoms in the damaged organs because the immunologic improvement may not reverse damage to the organs.29 Such cases do not represent cART failure and, in these instances, children would not benefit from a change in ARV regimen. Before reaching a definitive conclusion of cART clinical failure, a child should also be evaluated to rule out (and, if indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary tuberculosis, malnutrition, and malignancy. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason. Although such cases are rare, they may represent cART clinical failure and suggest that improvement in CD4 values may not necessarily represent the return of complete immunologic function.
Management of Virologic Treatment Failure

Each patient with incomplete virologic suppression on cART should be assessed to determine the cause of virologic treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. Treatment failure is generally the result of non-adherence but is often multifactorial. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, issues related to pharmacokinetics (PK) that could result in low drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance (See Antiretroviral Drug-Resistance Testing). The main barrier to long-term maintenance of sustained virologic suppression in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the ARV regimen. Table 14 outlines a comprehensive approach to evaluating causes of virologic treatment failure in children, with particular attention to adherence.
<table>
<thead>
<tr>
<th>Cause of Virologic Treatment Failure</th>
<th>Assessment Method</th>
<th>Intervention</th>
</tr>
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| **Non-Adherence**                   | 1. Interview child and caretaker  
   • Take 24-hour or 7-day recall  
   • Obtain description of:  
     • **WHO** gives medications  
     • **WHEN** medications are taken/given  
     • **WHAT** medications are taken/given (names, doses)  
     • **WHERE** medications are kept/administered  
   • **HOW medications make child feel**  
     • Have open-ended discussion of experiences taking/giving medications and barriers/challenges  
   2. Review pharmacy records  
   • Assess timeliness of refills  
   3. Observe medication administration  
   • Observe dosing/administration in clinic  
   • Conduct home-based observation by visiting health professional  
   • Admit to hospital for trial of therapy  
     • Observe administration/tolerance.  
     • Monitor treatment response |
|                                    | 4. Conduct psychosocial assessment  
   • Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes:  
     • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child’s achievement level  
     • Substance abuse (child, caretaker, family members)  
     • Mental health and behavior  
     • Child/youth and caretaker beliefs about cART  
     • Disclosure status (to child and others)  
   • **Peer pressure**  
   • Identify or re-engage family members to support/supervise adherence  
   • Establish fixed daily times and routines for medication administration  
   • To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are co-formulated under a third or fourth name  
   • Explore opportunities for facility or home-based DOT |
| Pharmacokinetics and Dosing Issues  | 1. Recalculate doses for individual medications using weight or body surface area  
   2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions  
   3. Consider drug levels for specific ARV drugs (see Role of Therapeutic Drug Monitoring) |  • Adjust drug doses  
   • Discontinue or substitute competing medications  
   • Reinforce applicable food restrictions |

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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Virologic Treatment Failure with No Viral Drug Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications suggests that the virus is not being exposed to the ARV agents. This lack of ARV drug exposure is usually a result of non-adherence, but it is important to exclude other factors such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be ensured, then adherence to the current regimen should result in virologic suppression. Resistance testing should take place while a child is on therapy. After discontinuation of therapy, predominant plasma viral strains may quickly revert to wild-type and re-emerge as the predominant viral population, in which case resistance testing may fail to reveal drug-resistant virus (see Antiretroviral Drug-Resistance Testing). An approach to identifying resistance in this situation is to restart the prior medications while emphasizing adherence and repeat resistance testing in 4 weeks if plasma virus remains detectable. If plasma virus is undetectable with the most sensitive assays, the virus is likely to be susceptible to the current therapy.

In some cases, the availability of a new regimen for which the convenience (e.g., single fixed-dose tablet once daily) is anticipated to address the main barrier to adherence may make it reasonable to change to this new regimen with close adherence and viral load monitoring. In most cases, however, when there is evidence of poor adherence to the current regimen and an assessment that good adherence to a new regimen is unlikely, emphasis and effort should be placed on improving adherence before initiating a new regimen (see Adherence). When efforts to improve adherence will require several weeks or months, some clinicians may choose to continue the current non-suppressive regimen or use a simplified, nucleoside reverse transcriptase inhibitor (NRTI)-only, non-suppressive regimen that may provide some clinical and immunologic benefit while preserving future ARV drug choices (see Therapeutic Options When Two Fully Active Agents Cannot Be Identified or Administered). Treatment with non-suppressive regimens in such situations should be regarded as an acceptable but not ideal interim strategy to prevent immunologic and clinical deterioration while working on adherence. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ARV drug regimen should be reassessed at every opportunity. Complete treatment interruption for a persistently non-adherent patient should prevent accumulation of additional drug resistance but has been associated with immunologic declines and poor clinical outcomes.

Virologic Treatment Failure with Viral Drug Resistance Identified

After reaching a decision that a change in therapy is needed, a clinician should attempt to identify at least two, but preferably three, fully active ARV agents from at least two different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence. This often requires using agents from one or more drug classes that are new to the patient. Substitution or addition of a single drug to a failing regimen should not be done because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency because of the presence of drug-resistance mutations that confer cross-resistance within a drug class. In children who are changing therapy owing to the occurrence or progression of abnormal neurodevelopment, many experts strive to include in the new treatment regimen agents (e.g.,

<table>
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<tr>
<th>Cause of Virologic Treatment Failure</th>
<th>Assessment Method</th>
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| ARV Drug Resistance                 | 1. Perform resistance testing, as appropriate (see Antiretroviral Drug-Resistance Testing). | • If no resistance to current drugs is detected, focus on improving adherence  
  • If resistance to current regimen detected, optimize adherence and evaluate potential for new regimen (see Management of Virologic Treatment Failure) |

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, DOT = directly observed therapy
A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with a patient in an age- and development-appropriate manner and with a patient’s caregivers. Clinicians must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate administration of a regimen. Timing of medication administration is particularly important to ensure adequate ARV drug exposures throughout the day. Palatability, size and number of pills, and dosing frequency all need to be considered when choosing a new regimen.

**Choice of Therapy with Goal of Complete Virologic Suppression**

Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made in collaboration with a pediatric HIV specialist. ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug potency in the new regimen. A general strategy for regimen change is shown in Table 15, although as additional agents are licensed and studied for use in children, newer strategies that are better tailored to the needs of each patient may be constructed.

If a child has received initial therapy with a NNRTI-based regimen, a change to a protease inhibitor (PI)-based regimen is recommended. Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. However, the NNRTI etravirine can retain activity against nevirapine- or efavirenz-resistant virus in the absence of certain key NNRTI mutations (see below). If a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is generally recommended. Ritonavir-boosted-lopinavir-based regimens have also been shown to have durable ARV activity in some PI-experienced children.

The availability of new drugs in existing classes (e.g., the NNRTI etravirine) and newer classes of drugs (e.g., integrase inhibitors) increases the likelihood of finding three active drugs, even for children with extensive drug resistance (Table 15). Etravirine in combination with ritonavir-boosted darunavir, as part of a new cART regimen, has been shown to be a safe and effective option for children in whom first-line cART fails. Etravirine is approved for use in children aged ≥6 years and darunavir in children aged ≥3 years. Raltegravir, an integrase inhibitor, is approved for children aged 4 weeks or older by the Food and Drug Administration (FDA). Use of newer agents in novel combinations is becoming more common in aging perinatally infected youth in the United States. It is important to review individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance. Appendix A: Pediatric Antiretroviral Drug Information provides more detailed information on drug formulation, pediatric and adult dosing, and toxicity, as well as discussion of available pediatric data for the approved ARV drugs.

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if ARV resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching from a liquid to a pill formulation or to a new formulation [e.g., ritonavir tablet]). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir. The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified, and ideally would be done in the framework of a clinical trial. Expanded access programs or clinical trials may be available (see www.clinicaltrials.gov). New drugs should be used in combination with at least one, and ideally two, additional active agents.

Safety, dosing, and efficacy of enfuvirtide have been established in treatment-experienced children aged ≥6 years, and enfuvirtide has been FDA-approved for this population. Enfuvirtide must be administered by subcutaneous injection twice daily, a disadvantage that presents a greater challenge to adherence in adolescents than in younger children. Enfuvirtide can be considered an option when designing a new regimen.
for children in whom multiple classes of ARV medications have failed, but newer and better tolerated agents have largely supplants use of enfuvirtide.

PK studies of certain dual-boosted PI regimens (ritonavir-boosted lopinavir with saquinavir and ritonavir-
boosted lopinavir with atazanavir/ritonavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in children.\(^{57-59}\) PK studies of other dual-boosted PI combinations, on the other hand, are limited but suggest inadequate drug levels of one or both PIs.\(^{60,61}\) The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series;\(^{62}\) however, multidrug regimens should be used cautiously because of their complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity because of the presence of drug-resistance mutations (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). Availability of newer potent PIs and new classes of ARV drugs (integrase and CCR5 inhibitors) may lessen the need for dual-PI regimens and for regimens of four or more drugs.

When searching for at least two fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability and future use of newer therapeutic agents that may not be studied or approved in children or may be in clinical development. Information concerning potential clinical trials can be found at [http://aidsinfo.nih.gov/clinical_trials](http://aidsinfo.nih.gov/clinical_trials) and through collaboration with a pediatric HIV specialist.

Pediatric dosing for off-label use of ARV drugs is problematic because absorption, hepatic metabolism, and excretion change with age.\(^{63}\) In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child’s body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.\(^{64}\)

Use of ARV agents without a pediatric indication is an absolute necessity for treatment of some HIV-infected children, but such off-label use must be done with care. It is essential that a provider consult with a pediatric HIV specialist to identify any particular concerns with each agent, to access any available data from clinical trials or other limited off-label pediatric use, and to investigate the availability of suitable clinical trials.

**Therapeutic Options When Two Fully Active Agents Cannot Be Identified or Administered**

It may be impossible to provide an effective and sustainable therapeutic regimen because no combination of currently available agents is active against extensively drug-resistant virus in a patient or because a patient is unable to adhere to or tolerate cART.

In such cases, non-suppressive regimens (or holding regimens) are sometimes used pending availability of additional active, tolerable drugs or improvement in ability to adhere. This interim strategy allows for the overall objective of preventing clinical and immunological deterioration until new agents are available to design a regimen that can be expected to achieve sustained virologic suppression. This approach should be regarded as acceptable but not ideal. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive cART regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, patients can derive immunologic and clinical benefit despite persistent viremia from treatment with lamivudine monotherapy or with lamivudine or emtricitabine in combination with one or more other NRTIs.\(^{31,32}\)

The newer NNRTI etravirine retains activity against many nevirapine- or efavirenz-resistant viruses with a limited number of NNRTI resistance-associated mutations. Ongoing use of efavirenz or nevirapine as part of a failing regimen should be avoided because it may lead to accumulation of additional NNRTI resistance mutations that will reduce etravirine activity and preclude its use in a future, suppressive regimen,\(^{65}\) and it may allow for accumulation of additional NRTI resistance.\(^{66}\)
Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low.\textsuperscript{2,67-69} However, continued PI use in the presence of resistance may limit viral replication and be beneficial to some patients.

When clinical or immunologic deterioration occurs while patients are receiving such holding regimens, it is important to reassess patient readiness and regimen availability. It may be appropriate to use investigational agents or agents approved for older age groups as second fully active drugs in the new regimen. In general, a single, new, fully active agent should not be added to non-suppressive holding regimens because resistance is likely to develop quickly.

**Table 15. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients with Failed Antiretroviral Therapy and Evidence of Viral Resistance\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Prior Regimen</th>
<th>Recommended Change (In Order of Relative Preference)\textsuperscript{a}</th>
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| 2 NRTIs + NNRTI | • 2 NRTIs + PI  
• 2 NRTIs + integrase inhibitor |
| 2 NRTIs + PI | • 2 NRTIs + NNRTI  
• 2 NRTIs + different RTV-boosted PI  
• 2 NRTIs + integrase inhibitor  
• NRTI(s) + integrase inhibitor + (NNRTI or different RTV-boosted PI) |
| 3 NRTIs | • 2 NRTIs + (NNRTI or PI)  
• 2 NRTIs + integrase inhibitor  
• Integrase inhibitor + 2 other active agents (chosen from NNRTI, PI, NRTI[s]) |
| Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s) | • 1 NRTI + RTV-boosted PI  
• NRTI(s) + RTV-boosted PI + integrase inhibitor (consider adding T-20 and/or MVC,\textsuperscript{b} if additional active drug[s] needed)  
• NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC,\textsuperscript{b} T-20, or integrase inhibitor, if additional active drug[s] needed)  
• > 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor if additional active drug[s] needed) |

\textsuperscript{a} ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression. Please see individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance. Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are listed in relative order of preference and are provided as examples but the list is not exhaustive.

\textsuperscript{b} No current FDA-approved pediatric indication for maraviroc.

**Key to Acronyms:**  
ATV = atazanavir, DRV = darunavir, ETR = etravirine, LPV = lopinavir, LPV/r = ritonavir-boosted lopinavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide

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Considerations About Interruptions in Antiretroviral Therapy  (Last updated February 12, 2014, last reviewed February 12, 2014)

Panel's Recommendations

- Outside the context of clinical trials, structured interruptions of combination antiretroviral therapy are not recommended for children (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Unplanned Interruptions:

Temporary discontinuation of combination antiretroviral therapy (cART) may be indicated in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient or parent request. Observational studies of children and youth with unplanned or non-prescribed treatment interruptions suggest that interruptions are common, most patients will experience immunologic decline during the treatment interruption, and most restart therapy.1-3

Structured Treatment Interruptions

Planned discontinuation of therapy, or structured treatment interruptions, was considered as a potential strategy to reduce toxicity, costs, and drug-related failure associated with cART.

Adult trials have demonstrated significantly higher morbidity and mortality in adults randomized to structured treatment interruptions compared with continuous cART.4 Current Department of Health and Human Services guidelines for adults recommend against planned long-term structured treatment interruptions in adults (see the Adult and Adolescent Antiretroviral Guidelines).

In children, there have been fewer studies of long-term structured treatment interruption. In one study, children with controlled viral load (HIV RNA <400 copies/mL for >12 months) were subjected to increasing intervals of treatment interruption. Of 14 children studied, 4 maintained undetectable viral loads with interruptions of up to 27 days. It has been hypothesized that enhanced HIV-specific immune responses may play a role in the viral suppression.3 However, new drug-resistance mutations were detected in 3 of 14 children in the structured treatment interruption study. In the European (PENTA) trial, 109 children with virologic suppression on cART were randomized to continuous therapy (CT) versus treatment interruption with CD4 T lymphocyte (CD4)-guided re-initiation of cART. On average, CD4 values decreased sharply in the first 10 weeks after structured treatment interruption. However, most children in the structured treatment interruption arm (almost 60%) did not reach CD4 criteria to restart therapy over 48 weeks. Children in the structured treatment interruption arm spent significantly less time on cART than children in the CT arm.6 None of the children in the trial experienced serious clinical illnesses or events, and the appearance of new drug-resistance mutations did not differ between the two arms.6

In some populations of children, structured treatment interruption has been more specifically considered. One trial was designed to answer whether infants who initiated ART early could safely discontinue therapy at some point and reinitiate treatment based on CD4 cell decline. The CHER study in South Africa assessed outcomes in infants randomized to deferred cART (initiation driven by CDC stage and CD4 status),
immediate cART with interruption after 40 weeks, or immediate cART with interruption after 96 weeks. While the 2 arms of interrupted therapy led to better outcomes compared to the deferred arms, up to 80% of infants had to restart therapy by the end of follow-up. The long-term outcomes in children after this interruption remain unknown and it is unclear if the short period of time on cART saved by most children merits the potential risks associated with cessation.

Given the increased availability of medications with less toxicity, the potential benefits of long-term structured treatment interruption may be decreasing. Current data do not support use of long-term structured treatment interruption in clinical care of HIV-infected children; additional studies of structured treatment interruption in children may be warranted.

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Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection  (Last updated February 12, 2014; last reviewed February 12, 2014)

Panel’s Recommendations

- Evaluation of plasma concentrations of antiretroviral drugs are not required in the management of most pediatric patients with HIV, but should be considered in children on combination antiretroviral therapy in the following scenarios: (BII)
  - Use of antiretroviral drugs with limited pharmacokinetic data and therapeutic experience in children (e.g., for use of efavirenz in children aged <3 years and darunavir with once-daily dosing in children aged <12 years);
  - Significant drug-drug interactions and food-drug interactions;
  - Unexpected suboptimal treatment response (e.g., lack of virologic suppression with history of medical adherence and lack of resistance mutations);
  - Suspected suboptimal absorption of the drug; or
  - Suspected dose-dependent toxicity.

- Evaluation of the genetic G516T polymorphism of drug metabolizing enzyme cytochrome P450 (CYP450) 2B6 in combination with the evaluation of plasma efavirenz concentrations is recommended for children aged <3 years receiving efavirenz due to significant association of this polymorphism with efavirenz concentrations (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents but not studies limited to postpubertal adolescents

The goal of therapeutic drug monitoring (TDM) of antiretroviral (ARV) drugs is to optimize treatment responses and tolerability, and to minimize drug-associated toxicity. A limited number of adult studies suggest that modified doses and regimen choices based on TDM result in achievement of targeted ARV drug concentrations and are associated with improved clinical response and/or tolerability.6,7,10-17 In children, the usefulness of TDM to guide dosing of ARV drugs has been demonstrated in a limited number of non-randomized clinical trials and case reports.6,7,10-17

Dosing of ARV drugs in HIV-infected children and adolescents depends on chronological age and/or body parameters (e.g., height, weight). Ongoing growth requires continuous reassessment of dosing of ARV drugs in order to avoid low drug exposure and development of viral resistance and virologic failure. Developmental differences in drug absorption, distribution, metabolism, and elimination contribute to high variability and a greater frequency of suboptimal exposure to multiple therapeutic agents in children and adolescents compared to adults.18 Suboptimal exposure to selected ARV agents with recommended dosing has been demonstrated in pediatric patients, especially in young children.14,15,19-21

Because of the diverse developmental challenges in palatability and acceptability of combination antiretroviral therapy (cART), children and adolescents are frequently faced with the use of altered dosing regimens and ARV combinations for which safety and efficacy have not been established in large clinical trials. Furthermore, dosing recommendations for ARV drugs at the time of licensing for pediatric use are frequently derived from a limited number of patients and pharmacokinetic (PK) modeling and may be revised as newer PK data become available.14,15,19,21 The Panel recommends considering TDM for certain ARV agents when the newly approved pediatric formulation and/or dosing are used based on limited PK and efficacy data in small populations (see specific drug information sections). TDM can also be considered in management of treatment failure for children on cART to increase efficacy and to decrease toxicity.
Use of TDM to Improve Efficacy

The relationship between ARV drug concentrations and ARV efficacy must be clearly defined for TDM to be useful.\textsuperscript{22-25} This association has been shown to be the strongest for protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) as well as for the CCR5 receptor antagonist maraviroc.\textsuperscript{26-28} For nucleoside reverse transcriptase inhibitors (NRTIs), intracellular concentrations of their triphosphate metabolites have been shown to be most important in determining therapeutic response. Obtaining intracellular NRTI metabolite concentrations is expensive, labor-intensive, requires large blood volumes, and is limited to research settings. Limited data have demonstrated that serum concentrations of NRTIs are also correlated with virologic suppression; however, no efficacy plasma concentrations have been derived for NRTIs.\textsuperscript{29}

Based on data from adult studies, consensus target efficacy plasma trough concentrations for treatment-naive and treatment-experienced patients have been developed by clinical pharmacology experts from the United States and Europe for the many PIs and NNRTIs, as well as the CCR5 receptor antagonist maraviroc (see Table 16). Efficacy trough concentrations for maraviroc and tipranavir have been derived in patients with multiple drug-resistant HIV strains only. Although exposure-response data for the PI darunavir, the NNRTI etravirine, and the integrase inhibitor raltegravir are accumulating, they have been considered insufficient to define target efficacy concentrations at this time.\textsuperscript{30-33} Table 16 includes data on the plasma trough concentrations derived from clinical trials of these drugs.

Table 16. Target Trough Concentrations of Antiretroviral Drugs\textsuperscript{a}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Established Efficacy Plasma Trough Concentrations</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>150</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>400\textsuperscript{b}</td>
</tr>
<tr>
<td>Indinavir</td>
<td>100</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>1,000</td>
</tr>
<tr>
<td>Nelfinavir\textsuperscript{c}</td>
<td>800</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>100–250</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1,000</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>3,000</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>&gt;50\textsuperscript{d}</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>20,500\textsuperscript{d}</td>
</tr>
<tr>
<td><strong>Plasma Trough Concentrations from Clinical Trials</strong></td>
<td></td>
</tr>
<tr>
<td>Darunavir\textsuperscript{e}</td>
<td>3300 (1,255–7,368)\textsuperscript{f}</td>
</tr>
<tr>
<td>Etravirine</td>
<td>275 (81–2,980)\textsuperscript{f}</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>72 (29–118)\textsuperscript{f}</td>
</tr>
</tbody>
</table>


\textsuperscript{b} Measurable amprenavir concentration

\textsuperscript{c} Measurable active (M8) metabolite

\textsuperscript{d} Plasma trough concentration in treatment-experienced patients with resistant HIV-1 strain only

\textsuperscript{e} Darunavir dose 600 mg twice daily

\textsuperscript{f} Median (range)
The suggested efficacy plasma trough concentrations are generally applicable to patients whose HIV is susceptible to the particular ARV drug. In treatment-experienced patients with virologic failure, a higher plasma trough concentration may be required to suppress viral replication when there is decreased susceptibility to the ARV drug.\textsuperscript{11,34-36} For the majority of PIs, viral resistance develops cumulatively with successive mutations, and higher drug exposure can potentially overcome lower levels of resistance. The concept of inhibitory quotient (IQ) has been developed and successfully applied to certain PIs, such as lopinavir/ritonavir.\textsuperscript{37} IQ is expressed as the ratio of patient plasma trough concentration ($C_{\text{min}}$) to specific viral susceptibility parameters (e.g., fold change in inhibitory concentration or the number of the drug specific resistance-associated mutations).\textsuperscript{1,34} This approach does not apply to drugs with low, single mutation thresholds for resistance (e.g., the NNRTIs nevirapine and efavirenz) because it is not possible to overcome such resistance by increasing the ARV drug exposure. Suboptimal plasma concentrations of efavirenz and nevirapine have been linked to virologic failure in children.\textsuperscript{10,21,38} Evaluation of efavirenz plasma concentrations in combination with pharmacogenetic evaluation for the polymorphism of the main drug metabolizing enzyme cytochrome P (CYP) 450 CYP2B6 is recommended if efavirenz is used in children aged <3 years to avoid suboptimal drug exposure (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

**Use of TDM to Decrease Toxicity**

The exposure-toxicity response relationship has been well defined for the PIs indinavir and atazanavir and the NNRTI efavirenz.\textsuperscript{24,39} Increased frequency of indinavir-associated nephrolithiasis has been reported to be associated with elevated peak and trough plasma concentrations of the drug in adults (indinavir is not recommended for use in pediatric patients).\textsuperscript{40} Increased plasma concentrations of atazanavir have been linked to elevated bilirubin concentrations in adolescents, and measurement of the atazanavir plasma concentrations has been suggested for management of the atazanavir-associated hyperbilirubinemia in adolescents.\textsuperscript{39} Adverse central nervous system (CNS) effects (e.g., CNS depression, dizziness, insomnia, hallucinations) associated with efavirenz have been shown to correlate with efavirenz plasma trough concentrations >4 mcg/mL in adult and pediatric studies.\textsuperscript{10,41,42} TDM-guided reduction in the efavirenz dose has been shown to successfully reduce neuropsychiatric side effects while allowing for continued virologic suppression in a prospective open-label multicenter adult study.\textsuperscript{43} A recent report on the PK of efavirenz in children aged <3 years demonstrated a significant relationship between high plasma efavirenz median concentrations and area under the curve versus time concentration (AUC) and drug-associated hematologic and CNS toxicity.\textsuperscript{12} Evaluation of the efavirenz plasma concentrations in combination with determination of polymorphism of the main drug-metabolizing enzyme CYP2B6 should be considered for preventing and decreasing efavirenz associated adverse events in children aged <3 years (see next section on pharmacogenetics).

**Pharmacogenetic Evaluation as Part of TDM**

The pharmacogenetics of HIV therapy investigate the interactions between human genetic polymorphisms and PK and the outcome of cART. Multiple metabolizing and drug transporter genes have been studied for their association with efficacy and toxicity of antiretroviral drugs. The most clinically significant relationship is demonstrated by the association between the CYP2B6 G to T polymorphism and the PK, toxicity and the clinical response to efavirenz. CYP2B6 T516T and G516T genotypes have been associated with elevated plasma efavirenz concentrations and CNS toxicity in children and adults, while CYP2B6 G516G genotype has been linked to the low plasma concentrations of efavirenz, decreased rates of virologic suppression and development of resistance.\textsuperscript{12,42,44,45} Adjustment of efavirenz dose based on a patient’s CYP2B6 G516T genotype has been shown to minimize risk of development of resistance and treatment failure and avoid or decrease drug-associated toxicity in adults and adolescents.\textsuperscript{11,46-48}

The effect of CYP2B6 G516T polymorphism on the PK of efavirenz appears to be most pronounced in younger children undergoing maturation of CYP450 enzymatic system.\textsuperscript{38} In ongoing PACTG P1070 study, efavirenz dosing of approximately 40 mg/kg in children aged <3 years produced therapeutic efavirenz plasma concentrations in 68% of children with GG/GT 516 rapid CYP2B6 genotypes, while the same dose...
led to significantly higher exposure with treatment-related toxicities ≥grade 3 in children with TT 516 CYP2B6 genotype.12 In this ongoing study, genotyping for CYP2B6 G516T polymorphism is incorporated in the pretreatment evaluation and will be used to determine the dosing regimen. While efavirenz is not recommended for initial therapy in children aged <3 years, should efavirenz use be considered in children aged <3 years, the Panel recommends obtaining CYP2B6 genotype as part of pretreatment evaluation and dose selection (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

Practical Considerations

The use of TDM in clinical practice poses multiple challenges, including availability of the ARV drug assays and certified laboratories; difficulties in collecting timed blood samples in children to obtain true plasma trough concentrations; prolonged time to obtain the results; limited availability of pharmacologic pediatric expertise; and cost and reimbursement considerations. More extended PK evaluation of the AUC in children involves higher volumes of blood samples, cost, and time commitment. Limited information on safety and effectiveness of dose adjustment strategies in children and adolescents may also limit the application of TDM in clinical practice.

When obtaining plasma concentrations in pediatric and adolescent patients, several important steps need to be taken. Crucially important for interpretation of the results is documentation of the following:

- Accurate information about the dose and formulation
- List of concomitant medications
- Food intake with the dose
- Timing of the dose and blood sample collection
- Adherence and resistance information

Additional practical suggestions on TDM of ARV drugs can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee22 and several pediatric review manuscripts.7,16,49 Most importantly, consultation with an expert in pediatric HIV pharmacology is required to obtain guidance on when to obtain samples for TDM, how to interpret the PK data, and how to evaluate the need for dose adjustment and repeat PK evaluation and follow up.

References


7. Rakhmanina NY, van den Anker JN, Soldin SJ, van Schaik RH, Mordwinkin N, Neely MN. Can therapeutic drug


Antiretroviral Drug-Resistance Testing  (Last updated February 12, 2014; last reviewed February 12, 2014)

HIV replication is a continuous process in most untreated patients, leading to the daily production of billions of virions. The goal of combination antiretroviral therapy (cART) is to suppress HIV replication as rapidly and fully as possible, as indicated by a reduction in plasma HIV RNA to below the limit of detection of the most sensitive assays available. Unfortunately, mutations in HIV RNA arise during viral replication because HIV reverse transcriptase (RT) is a highly error-prone enzyme. Consequently, ongoing replication in the presence of antiretroviral (ARV) drugs, as occurs in suboptimal adherence, readily and progressively selects for strains of HIV with mutations that confer drug resistance. Viruses harboring resistance-associated mutations can be transmitted in both perinatal and non-perinatal infection, underscoring the importance of resistance testing at the time of HIV diagnosis before cART initiation.¹²

Drug-resistance detection methods vary depending on the class of ARV agents. Viral coreceptor (tropism) assays are used to detect virus with tropism that will (CCR5 tropism) or will not (CXCR4 or dual/mixed [D/M] tropism) be blocked by CCR5 antagonists. Detection of virus with CXCR4 or D/M tropism indicates resistance to CCR5 antagonists. Both genotypic assays and phenotypic assays currently are used to detect the presence of virus that is resistant to inhibitors of the HIV reverse transcriptase (RT), integrase (IN), or protease (PR) enzymes. Clinical experience with testing for viral resistance to other agents is more limited, but genotypic assays that assess mutations in gp41 (envelope) genes also are commercially available.

Panel’s Recommendations

- Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment-naïve patients (AII). Genotypic resistance testing is preferred for this purpose (AIII).
- ARV drug resistance testing is recommended before changing therapy because of treatment failure (AI*).
- Resistance testing in patients with virological failure should be done while they are still on the failing regimen or within 4 weeks of discontinuation (AII*).
- Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ARV therapy regimens (BIII).
- The absence of detectable resistance to a drug does not ensure that use of the drug will be successful. Consequently, previously used ARV agents and previous resistance test results must be reviewed when making decisions regarding the choice of new agents for patients with virologic failure (AII).
- Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered (AI*). Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist (AI*).
- Consultation with a pediatric HIV specialist is recommended for interpretation of resistance assays when considering starting or changing an ARV regimen in pediatric patients (AI*).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

HIV Drug-Resistance and Resistance Assays
available. Experience is also limited with the use of commercially available genotypic and phenotypic assays in the evaluation of drug resistance in patients infected with non-B subtypes of HIV.3,4 Table 17 summarizes the indications for using available resistance testing.

**Genotypic Assays**

Genotypic assays for resistance to RT and PR inhibitors and IN strand transfer inhibitors are based on polymerase chain reaction (PCR) amplification and analysis of the RT, PR, and IN coding sequences present in HIV RNA extracted from plasma. Genotypic assays can detect resistance mutations in plasma samples containing approximately 1,000 copies/mL or more of HIV RNA and results generally are available within 1 to 2 weeks of sample collection.5 Not all available genotypic tests include IN resistance; it may need to be specifically requested. Interpretation of test results requires knowledge of the mutations selected by different ARV drugs and of the potential for cross resistance to other drugs conferred by certain mutations. For some drugs, the genetic barrier to the development of resistance is low and a single nucleotide mutation is enough to confer high-level resistance sufficient to remove any clinical utility of the drug. This is exemplified by resistance to nevirapine and efavirenz resulting from mutations in the HIV RT (e.g., K103N). Other mutations lead to drug resistance but simultaneously impair HIV replication. Clinically useful activity of the ARV agent may therefore remain, as demonstrated by evidence of continued clinical benefit from lamivudine in individuals with evidence of the high-level lamivudine resistance engendered by the M184V RT mutation.6 By contrast, HIV evolution to high-level resistance to some drugs is associated with the emergence of mutations that confer resistance as well as compensatory mutations that allow the virus to replicate more efficiently in the presence of the ARV agent. In addition, polymorphisms that occur naturally or in the presence of drug and are not significant alone may confer clinically significant drug resistance when present with other polymorphisms or major resistance mutations.7

The International AIDS Society-USA (IAS-USA) and the Stanford University HIV Drug Resistance Database maintain lists of resistance mutations that confer resistance to currently available ARV drugs (see http://www.iasusa.org/resistance_mutations, or http://hivdb.stanford.edu). A variety of online tools analyze the simultaneous effect of all mutations detected in a patient in order to assist the provider in interpreting genotypic test results. Although the response to cART in children and adolescents is not always predicted by the results of genotypic resistance assays, clinical trials in adults have demonstrated the benefit of resistance testing combined with consultation with specialists in HIV drug resistance in improving virologic outcomes.5,8-14 Given the potential complexity of interpretation of genotypic resistance, it is recommended that clinicians consult with a pediatric HIV specialist for assistance in the interpretation of genotypic results and design of an optimal new regimen.

**Phenotypic Assays**

Phenotypic resistance assays provide a more direct assessment of the impact on viral replication of mutations that are present in an individual’s HIV variants. As they are most often performed, phenotypic assays involve PCR amplification of the predominant RT, IN, PR, or gp41 envelope gene sequences from patient plasma and insertion of those amplified patient sequences into the backbone of a cloned strain of HIV that expresses a reporter gene. Replication of this recombinant virus in the presence of a range of drug concentrations is monitored by quantification of the reporter gene and is compared with replication of a reference drug susceptible HIV variant. The drug concentration that inhibits viral replication by 50% (i.e., the mean inhibitory concentration, or IC50) is calculated, and the ratio of the IC50 of test and reference viruses is reported as the fold increase in IC50 (i.e., fold resistance change). Automated, recombinant phenotypic assays that can produce results in 2 to 3 weeks are commercially available; however, they are more costly than genotypic assays.

Analytic techniques have also been developed to use the genotype to predict the likelihood of a drug-resistant phenotype. This bioinformatic approach, currently applicable for RT, IN, and PR inhibitor resistance only, matches the pattern of mutations obtained from the patient sample with a large database of samples for which
both genotype and phenotype are known. Therefore, the sample is assigned a predicted phenotype susceptibility (or virtual phenotype) based on the data from specimens matching the patient’s genotype.

**Tropism (Viral Coreceptor Usage) Assays**

HIV enters cells by a complex, multistep process that involves sequential interactions between the HIV envelope protein molecules and the CD4 T lymphocyte (CD4) receptor, and then with either the CCR5 or CXCR4 coreceptor molecules, culminating in the fusion of the viral and cellular membranes. Viruses initially are CCR5 tropic in the majority of untreated individuals, including infants and children perinatally infected with HIV. However, a shift in coreceptor tropism often occurs over time, from CCR5 usage to either CXCR4- or D/M-tropic. ARV-treated patients with extensive drug resistance are more likely to harbor detectable CXCR4- or D/M-tropic virus than untreated patients with comparable CD4 counts.\(^{15-17}\)

Resistance to CCR5 antagonists is detected using specialized phenotypic assays (Phenoscript [VIRalliance] and Trofile [Monogram Biosciences, Inc]). These assays involve the generation of recombinant viruses bearing patient-derived envelope proteins (gp120 and gp41). The relative capacity of these pseudoviruses to infect cells bearing the cell surface proteins CCR5 or CXCR4 is based on the expression of a reporter gene.

Detection of CXCR4 of D/M tropism is a contraindication to the use of the CCR5 antagonists as part of a therapeutic regimen. Coreceptor assays must be performed before a CCR5 inhibitor is used and should be considered in patients exhibiting virologic failure on a CCR5 inhibitor such as maraviroc.

The Trofile assay takes about 2 weeks to perform and requires a plasma viral load $\geq$1,000 copies/mL and at least 3 mL of plasma. The initial version of the Trofile assay used during the clinical trials that led to the licensure of maraviroc was able to detect CXCR4-tropic virus with 100% sensitivity when present at a frequency of 10% of the plasma virus population, but only 83% sensitivity when the variant was present at a frequency of 5%. In initial clinical trials of CCR5 antagonist drugs, this sensitivity threshold was not always sufficient to exclude the presence of clinically meaningful levels of CXCR4- or D/M-tropic virus in patients initiating a CCR5 inhibitor-based regimen. The current enhanced sensitivity version of the TrofileTM assay (Trofile-ESTM) is able to detect CXCR4- or D/M-tropic virus representing as little as 0.3% of the plasma virus.\(^{18,19}\)

One of the tropism assays can also be performed following amplification of HIV sequences from peripheral blood DNA (Trofile-DNA™ [Monogram Biosciences, Inc]) and may be most useful when a change to a regimen containing a CCR5 antagonist is being considered for individuals with plasma viral load below 1,000 copies/mL and can be used even when the viral load is undetectable (e.g., if single-drug substitution for toxicity).

**Limitations of Current Resistance and Tropism Assays**

Limitations of the genotypic, phenotypic, and phenotype-prediction assay approaches include lack of uniform quality assurance testing and high cost. In addition, drug-resistant variants are likely to exist at low levels in every HIV-infected patient. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population or are present in the reservoir of latently infected cells may not be detected by any of the currently available commercial resistance assays.\(^{20}\) A comprehensive review of the past use of ARV agents and the virologic responses to those agents, and all prior resistance mutations (i.e., cumulative genotype), even if not present on the current genotype, is important in making decisions regarding the choice of new agents for patients with virologic failure.\(^{21}\)

The primary limitations of phenotypic assays are that their predictive power depends upon the sensitivity of the genotypic methods used and the number of matches to the patient’s genotype. These tests also are more costly than genotypic testing, therefore, their use should be reserved for clinical settings in which the information they provide will add benefit (see Table 17).

Genotypic assays to assess tropism have been proposed as an alternative approach to determining the tropism of plasma HIV. However, they are not currently recommended because of the limited experience with this
approach indicates that the sensitivity may be lower than phenotypic tropism assays, particularly in the setting of CCR5 antagonist interruption where reversion to wild-type may occur.22,23

Although drug resistance may be detected in the circulating plasma of infants, children, and adults who are not receiving therapy at the time of the assay, loss of detectable resistance and reversion to predominantly wild-type virus often occur in the first 4 to 6 weeks after ARV drugs are stopped.24-26 As a result, resistance testing is of greatest value when performed prior to or within 4 weeks after drugs are discontinued, or as soon after diagnosis as possible.27 The absence of detectable resistance to a drug at the time of testing does not ensure that future use of the drug will be successful,1,28 especially if the agent shares cross resistance with drugs previously used. It may be prudent to repeat resistance testing if an incomplete virological response to a new treatment regimen is observed in an individual with prior treatment failure(s) (see Management of Children Receiving Antiretroviral Therapy).

**Use of Resistance Assays in Determining Initial Treatment**

Transmission of drug-resistant strains to newly infected individuals (via perinatal and non-perinatal transmission of HIV) has been well documented and is associated with suboptimal virologic response to initial cART if this resistance is not taken into account when designing the initial regimen.29-33 Drug-resistant variants of HIV may persist for months after birth in infected infants34 and impair the response to cART.35 Consequently, ARV drug-resistance testing is recommended for all treatment-naive children before therapy is initiated. Standard genotypic testing is preferred in this setting because it may reveal the presence of both RT and PR resistance mutations and polymorphisms that facilitate the replication of drug-resistant virus. Genotypic testing for integrase resistance mutations prior to initial treatment is only recommended in special circumstances (e.g., acquisition of HIV from an individual treated with an integrase inhibitor with concern for transmission of integrase resistance).

**Use of Resistance Assays in the Event of Virologic Failure**

Several studies in adults5,8-14 have indicated that early virologic responses to salvage regimens were improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Although not yet confirmed in children,36 resistance testing appears to be a useful tool in selecting active drugs when changing ARV regimens in cases of virologic failure. Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction because virologic failure in the setting of cART may be associated with resistance to only one component of the regimen.3 Poor adherence should be suspected when no evidence of resistance to a failing regimen is identified (see Management of Children Receiving Antiretroviral Therapy).

**Table 17: Recommendations for Use of Available Resistance Testing**

<table>
<thead>
<tr>
<th>Resistance Test</th>
<th>Initial Treatment</th>
<th>Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard genotype (RT, PR)</td>
<td>Resistance testing indicated</td>
<td>Resistance testing indicated</td>
</tr>
<tr>
<td>Integrase phenotype/genotype</td>
<td>Only if concern for acquisition of virus with resistance</td>
<td>If failure on integrase inhibitor</td>
</tr>
<tr>
<td>Trofile™</td>
<td>Only if considering CCR5 antagonist as part of initial treatment</td>
<td>Only if considering CCR5 antagonist for subsequent regimen</td>
</tr>
<tr>
<td>Phenotype (RT, PR)</td>
<td>Not recommended prior to initial treatment unless genotypic evidence that multi-drug resistance was acquired</td>
<td>In the setting of extensive drug resistance, may assist in determining most active cART regimen. Must be used in conjunction with cumulative genotypic resistance results and cART history and response</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** cART = combination antiretroviral therapy; PR = protease; RT = reverse transcriptase
References


Conclusion  (Last updated February 12, 2014; last reviewed February 12, 2014)

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral (ARV) drugs and newer classes of drugs are approved. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional ARV drugs become approved and optimal use of these drugs in children becomes better understood, the Panel will modify these guidelines. These guidelines are only a starting point for medical decision-making and are not meant to supersede the judgment of clinicians experienced in the care of HIV-infected children. Because of the complexity of caring for HIV-infected children, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist.

The Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association of the Infectious Disease Society of America, the Pediatric Infectious Disease Society, and the American Academy of Pediatrics jointly developed and published guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children; these guidelines are available at http://aidsinfo.nih.gov. Similar guidelines for adults are also available at the same website.

References


Appendix A: Pediatric Antiretroviral Drug Information

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)
Didanosine (ddI, Videx)
Emtricitabine (FTC, Emtriva)
Lamivudine (3TC/Epivir)
Stavudine (d4T, Zerit)
Tenofovir Disoproxil Fumarate (TDF, Viread)
Zidovudine (ZDV, AZT, Retrovir)
Abacavir (ABC, Ziagen)  (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric Oral Solution: 20 mg/mL
Tables: 300 mg (scored)
Fixed-Dose Combination (FDC) Tablets

With Lamivudine (3TC):
• ABC 600 mg + 3TC 300 mg (Epzicom)

With Zidovudine (ZDV) and 3TC:
• ABC 300 mg + ZDV 300 mg + 3TC 150 mg (Trizivir)

Dosing Recommendations

Neonate/Infant Dose:
• Not approved for infants aged <3 months.

Pediatric Dose:

Oral Solution (Aged ≥3 Months):
• 8 mg/kg (maximum 300 mg) twice daily.

Weight Band Dosing (Weight ≥14 kg)

Scored 300-mg tablet.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Twice-Daily Dosage Regimen</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM Dose</td>
<td>PM Dose</td>
</tr>
<tr>
<td>14 to 21 kg</td>
<td>½ tablet (150 mg)</td>
<td>½ tablet (150 mg)</td>
</tr>
<tr>
<td>&gt;21 to &lt;30 kg</td>
<td>½ tablet (150 mg)</td>
<td>1 tablet (300 mg)</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>1 tablet (300 mg)</td>
<td>1 tablet (300 mg)</td>
</tr>
</tbody>
</table>

In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte (CD4) counts for more than 24 weeks, changing from twice-daily to once-daily dosing at 16–20 mg/kg/day to a maximum of 600 mg once daily is recommended if part of a once-daily regimen (see text below).

Adolescent (Aged ≥16 Years)/Adult Dose:
• 300 mg twice daily or 600 mg once daily.

Trizivir

Adolescent (Weight ≥40 kg)/Adult Dose:
• One tablet twice daily.

Selected Adverse Events

• Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough and shortness of breath).

• Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; however, other studies have not substantiated this finding, and there are no data in children.

Special Instructions

• Test patients for the HLA-B*5701 allele before starting therapy to predict risk of HSR. Patients positive for the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.

• Warn patients and parents about risk of serious potentially fatal HSR. Occurrence of HSRs requires immediate and permanent discontinuation of ABC. Do not re-challenge.

• ABC can be given without regard to food. Oral solution does not require refrigeration.

Metabolism

• Systemically metabolized by alcohol dehydrogenase and glucuronyl transferase
**Epzicom**

*Adolescent (Aged ≥16 Years)/Adult Dose:*
- One tablet once daily.

- Intracellularly metabolized to carbovir triphosphate (CBV-TP).
- Active metabolite is 82% renally excreted.
- ABC requires dosage adjustment in hepatic insufficiency.
- Do not use fixed-dose combinations such as Trizivir and Epzicom in patients with impaired hepatic function because the dose of abacavir cannot be adjusted.
- Do not use Trizivir and Epzicom in patients with creatinine clearance (CrCl) <50 mL/min and patients on dialysis (because of the fixed dose of lamivudine).

**Drug Interactions** *(see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)*

- Abacavir does not inhibit, nor is it metabolized by hepatic cytochrome P (CYP) 450 enzymes. Therefore, it does not cause changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors *(see more information in Drug Interaction section below under Pediatric Use).*
- Through interference with alcohol dehydrogenase and glucuronyl transferase, alcohol increases abacavir levels by 41%.

**Major Toxicities**

- More common: Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- Less common (more severe): Serious and sometimes fatal hypersensitivity reactions (HSRs) observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. HSR to abacavir is a multi-organ clinical syndrome usually characterized by rash or signs or symptoms in two or more of the following groups:
  - Fever
  - Constitutional, including malaise, fatigue, or achiness
  - Gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain
  - Respiratory, including dyspnea, cough, or pharyngitis.
- Laboratory and radiologic abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have also been reported. Pancreatitits can occur. This reaction generally occurs in the first 6 weeks of therapy, but has also been reported after a single dose. If an HSR is suspected, abacavir should be stopped immediately and not restarted—hypotension and death may occur upon re-challenge. The risk of abacavir HSR is associated with the presence of HLA-B*5701 allele; it is greatly reduced by testing patients for HLA-B*5701 prior to the initiation of therapy and by not using abacavir in those who test positive for the HLA-B*5701.
- Rare: Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction (in observational studies in adults). Lactic acidosis and severe hepatomegaly.
with steatosis, including fatal cases, have been reported. Pancreatitis can occur.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/ABC.html](http://hivdb.stanford.edu/pages/GRIP/ABC.html)).

**Pediatric Use**

**Approval**

Abacavir is Food and Drug Administration (FDA)-approved for use in HIV-infected children as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy.

**Efficacy**

Abacavir used either twice daily or once daily has demonstrated durable antiviral effectiveness in pediatric trials.1-3

**Pharmacokinetics**

**Pharmacokinetics in Children**

Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that children have more rapid clearance of abacavir than adults and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure.4,5 Metabolic clearance of abacavir in adolescents and young adults (aged 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.6

**Exposure-Response Relationship**

Plasma area under the drug-concentration-by-time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak.7,8 Intracellular concentrations of NRTIs are most strongly associated with antiviral effectiveness, and the active form of abacavir is the intracellular metabolite carbovir triphosphate (CBV-TP).9,10 Measurement of intracellular CBV-TP is more difficult than measurement of plasma AUC, so the abacavir plasma AUC is frequently considered as a proxy measurement for intracellular concentrations. However, this relationship is not sufficiently strong that changes in plasma AUC can be assumed to reflect true changes in intracellular active drug.11 Intracellular CBV-TP concentrations are affected by gender and have been reported to be higher in females than in males.11-13 This effect of gender and the interactions with PIs (see Drug Interactions section below) on abacavir PK further complicate linking clinically available plasma abacavir concentrations with more difficult to obtain—but pharmacodynamically more important—intracellular CBV-TP concentrations.

**Drug Interactions**

Abacavir plasma AUC has been reported to be decreased by 17% and 32% with concurrent use of the boosted PIs atazanavir/ritonavir and lopinavir/ritonavir, respectively.14 In a study comparing PK parameters of abacavir in combination with either lopinavir/ritonavir or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of lopinavir/ritonavir; however, the CBV-TP concentrations appeared to be increased in the lopinavir/ritonavir cohort.15 The mechanism and the clinical significance of these drug interactions with the PIs are unclear. No dose adjustment for abacavir or PIs is recommended.

**Dosing**

**Frequency of Administration**

Abacavir 600 mg is administered once daily in adults; however, once-daily use in children remains controversial. The PENTA-13 crossover trial compared abacavir exposure at 16 mg/kg once daily with 8 mg/kg twice daily in 24 children aged 2 to 13 years who had undetectable or low, stable viral loads. This study showed equivalent AUC_{0-24} for both dosing regimens and improved acceptability of therapy in the
once-daily dosing arm.\textsuperscript{15,16} However, trough abacavir plasma concentrations were lower in younger children (aged 2–6 years) receiving the once-daily regimen.\textsuperscript{16} The PENTA-15 crossover trial studied 18 children aged 3 to 36 months, again comparing abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in children with viral loads <400 copies/mL or with stable viral loads on twice-daily abacavir at baseline. ABC AUC\textsubscript{0-24} and clearance were similar in children on the once- and twice-daily regimens. After the change from twice-daily to once-daily abacavir, viral load remained <400 copies/mL in 16 of 18 participants through 48 weeks of monitoring.\textsuperscript{17} A study of 41 children (aged 3 to 12 years in Uganda who were stable on twice-daily fixed-dose co-formulation of abacavir/lamivudine) also showed equivalent AUC\textsubscript{0-24} and stable clinical outcome (i.e., disease stage and CD4 T lymphocyte [CD4] cell count) after the switch to once-daily abacavir during a median follow-up of 1.15 years. Virologic outcome was not evaluated in this study.\textsuperscript{18}

**Abacavir Steady-State Pharmacokinetics with Once-Daily or Twice-Daily Dosing**

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Pediatric PENTA 15\textsuperscript{17}</th>
<th>Pediatric PENTA 13\textsuperscript{16}</th>
<th>Pediatric Arrow\textsuperscript{18}</th>
<th>Adult \textsuperscript{6}</th>
<th>Adult \textsuperscript{11}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Europe</td>
<td>Europe</td>
<td>Uganda</td>
<td>United States</td>
<td>United States</td>
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<tr>
<td>N of Subjects</td>
<td>18</td>
<td>14</td>
<td>36</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mean Age Years</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Sex % Male</td>
<td>56%</td>
<td>43%</td>
<td>42%</td>
<td>53%</td>
<td>53%</td>
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<tr>
<td>Body Weight kg</td>
<td>11</td>
<td>19</td>
<td>19</td>
<td>63\textsuperscript{a}</td>
<td>72\textsuperscript{a}</td>
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<tr>
<td>Subjects Using PI(s)</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Dosing Interval Hours</td>
<td>12</td>
<td>24</td>
<td>12</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Dose mg</td>
<td>8\textsuperscript{a}</td>
<td>16\textsuperscript{a}</td>
<td>8\textsuperscript{a}</td>
<td>16\textsuperscript{a}</td>
<td>19\textsuperscript{b}</td>
</tr>
<tr>
<td>Dose Range mg/kg</td>
<td>7.7–8.3\textsuperscript{c}</td>
<td>15.5–16.3\textsuperscript{c}</td>
<td>5.0–8.4</td>
<td>15.6–17.1</td>
<td>15.4–23.1\textsuperscript{c}</td>
</tr>
<tr>
<td>AUC\textsubscript{0-24} mg*hr/L</td>
<td>10.85\textsuperscript{d}</td>
<td>11.57\textsuperscript{d}</td>
<td>9.91\textsuperscript{d}</td>
<td>13.37\textsuperscript{b}</td>
<td>15.6\textsuperscript{b}</td>
</tr>
<tr>
<td>C\textsubscript{max} mg/L</td>
<td>1.38\textsuperscript{d}</td>
<td>4.68\textsuperscript{d}</td>
<td>2.14\textsuperscript{d}</td>
<td>4.80\textsuperscript{d}</td>
<td>4.18\textsuperscript{d}</td>
</tr>
<tr>
<td>C\textsubscript{min} mg/L</td>
<td>0.03\textsuperscript{d}</td>
<td>&lt;0.02\textsuperscript{d}</td>
<td>0.025\textsuperscript{d}</td>
<td>&lt;0.015\textsuperscript{d}</td>
<td>0.02\textsuperscript{d}</td>
</tr>
<tr>
<td>Cl/F/kg L/hr/kg</td>
<td>1.47\textsuperscript{d}</td>
<td>1.38\textsuperscript{d}</td>
<td>1.58\textsuperscript{d}</td>
<td>1.16\textsuperscript{d}</td>
<td>1.23\textsuperscript{d}</td>
</tr>
</tbody>
</table>

Data are medians except as noted.

\textsuperscript{a} mg/kg
\textsuperscript{b} total daily dose in mg/kg (divided doses were given but sometimes in unequal amounts morning and evening)
\textsuperscript{c} interquartile range
\textsuperscript{d} geometric mean
\textsuperscript{e} mL/min/kg

**Key to Acronyms:** AUC = area under the curve; C\textsubscript{max} = maximal (peak) concentration; C\textsubscript{min} = minimal (trough) concentration; PI = protease inhibitor
Most recently, a pediatric PK model was developed based on data from 69 children in the PENTA trials (13 and 15) and ARROW study. Irrespective of age, body weight was identified as the most significant factor influencing the oral clearance of abacavir in children. Predicted steady state peak (C\text{max}) and AUC\text{0-12} abacavir concentrations on standard twice-daily dosing were lower in toddlers and infants aged 0.4 to 2.8 years when compared with children aged 3.6 to 12.8 years. Model-based predictions showed that equivalent systemic plasma abacavir exposure was achieved after once- or twice-daily dosing regimens. The model did not include information on ethnicity and other potentially important demographic factors. No clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir. None of the pediatric clinical trials evaluated the pharmacodynamically most important intracellular CBV-TP concentrations. All three pediatric studies presented in the table above enrolled only patients who had low viral loads or were clinically stable on twice-daily abacavir before changing to once-daily dosing. Recent data from 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily (336 children) versus twice-daily abacavir (333 children) in combination with a once- or twice-daily lamivudine-based regimen. Therefore, as part of a once-daily regimen, the Panel suggests a switch from twice-daily to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose [maximum of 600 mg] once daily) for clinically stable patients with undetectable viral loads and stable CD4 cell counts for more than 6 months.

**Toxicity**

Abacavir has less of an effect on mitochondrial function than zidovudine, stavudine, or didanosine.  

**References**


Dosing Recommendations

**Neonate/Infant Dose (Aged 2 Weeks to <3 Months):**
- 50 mg/m² body surface area every 12 hours
- Manufacturer recommends 100 mg/m² body surface area every 12 hours in this age range. The Panel members interpret pharmacokinetic data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m² body surface area every 12 hours.

**Infant Dose (Aged ≥3 Months to 8 Months):**
- 100 mg/m² body surface area every 12 hours

**Pediatric Dose of Oral Solution (Age >8 Months):**
- 120 mg/m² body surface area every 12 hours
- Dose range: 90–150 mg/m² body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naive children aged 3–21 years, 240 mg/m² body surface area once daily (oral solution or capsules) has effectively resulted in viral suppression.

**Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Body Weight ≥20 kg)**

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 kg to &lt;25 kg</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>25 kg to &lt;60 kg</td>
<td>250 mg once daily</td>
</tr>
<tr>
<td>≥60 kg</td>
<td>400 mg once daily</td>
</tr>
</tbody>
</table>

**Selected Adverse Events**

- Peripheral neuropathy
- Electrolyte abnormalities
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (the risk is increased when didanosine is used in combination with stavudine).
- Pancreatitis (less common in children than in adults, more common in adults when didanosine is used in combination with tenofovir or stavudine)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

**Special Instructions**

- Because food decreases absorption of didanosine, administration of didanosine on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. To improve adherence, some practitioners administer didanosine without regard to timing of meals (see text below).
- Didanosine oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of didanosine than for the enteric-coated formulation.
Didanosine in Combination with Tenofovir Disoproxil Fumarate (Tenofovir):
- This combination should be avoided, if possible, because of enhanced didanosine toxicity.

Pediatric/Adolescent Dose of Didanosine when Combined with Tenofovir:
- No data on this combination in children or adolescents aged <18 years, but decrease in didanosine dose is recommended as in adults.

Adult Dose of Didanosine when Combined with Tenofovir

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 kg</td>
<td>250 mg once daily</td>
</tr>
<tr>
<td>≥60 kg</td>
<td>400 mg once daily</td>
</tr>
</tbody>
</table>

- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.

Metabolism
- Renal excretion 50%.
- Dosing of didanosine in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer’s prescribing information for adjustment of dosage in accordance with creatinine clearance.

**Drug Interactions** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Absorption:** The presence of antacids in didanosine oral solution has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by timing doses to avoid giving other medications concurrently with didanosine oral solution.
- **Mechanism unknown:** Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir and this combination should be avoided if possible.
- **Renal elimination:** Drugs that decrease renal function can decrease didanosine clearance.
- **Enhanced toxicity:** Didanosine mitochondrial toxicity is enhanced by ribavirin.
- **Overlapping toxicities:** The combination of stavudine with didanosine may result in enhanced toxicity. That combination should not be used unless the potential benefit clearly outweighs the potential risk (see below).

**Major Toxicities:**
- **More common:** Diarrhea, abdominal pain, nausea, and vomiting.
- **Less common (more severe):** Peripheral neuropathy, electrolyte abnormalities, and hyperuricemia. Lactic
Acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported, and are more common with didanosine in combination with stavudine. Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir or stavudine) can occur. Increased liver enzymes and retinal depigmentation and optic neuritis have been reported.

- **Rare:** Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/didanosine.html](http://hivdb.stanford.edu/pages/GRIP/didanosine.html)).

**Pediatric Use**

**Approval**

Didanosine is Food and Drug Administration (FDA)-approved for use in children as part of a dual-nucleoside reverse transcriptase inhibitor backbone in combination antiretroviral therapy.

**Dosing**

**Standard Dose in Children**

Recommended doses of didanosine oral solution in children have traditionally been 90 to 150 mg/m² body surface area per dose twice daily. Doses higher than 180 mg/m² body surface area twice daily are associated with increased toxicity.¹ The pharmacokinetic (PK) variable of greatest pharmacodynamic significance is the area under the curve (AUC), with virologic response best with didanosine AUC ≥0.60 mg*h/L.²,³ In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg/m² body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with adequate exposure predicted in 88% of patients at a dose of 120 mg/m² body surface area twice daily,³ so that is the currently recommended dose for children aged 8 months to 3 years.

**Special Considerations in Ages 2 Weeks to <3 Months**

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m² body surface area per dose twice daily, increasing to 120 mg/m² body surface area per dose twice daily at age 8 months. However, 2 small studies suggest that a higher AUC is seen in infants aged <6 weeks and that a dose of 100 mg/m² body surface area per day (either as 50 mg/m² body surface area per dose twice daily or 100 mg/m² body surface area once daily) in infants aged <6 weeks achieves AUCs consistent with those seen at higher doses when used in older children.⁴,⁵ Therefore, because these PK differences in younger infants (aged 2 weeks–3 months) compared with older children raise concern for increased toxicity in the younger age group, the Panel recommends a dose of 50 mg/m² of body surface area twice daily for infants aged younger than 3 months.

**Frequency of Administration (Once-Daily or Twice-Daily)**

A once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing. In a study of 10 children aged 4 to 10 years, EC didanosine (Videx EC) administered as a single dose of 240 mg/m² body surface area once daily was shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine.⁴ The resultant intracellular (active) drug concentrations are unknown. In 24 HIV-infected children, didanosine oral solution at a dose of 180 mg/m² body surface area once daily was compared with 90 mg/m² body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group.⁶ Long-term virologic suppression with a once-daily regimen of efavirenz, emtricitabine, and didanosine (oral solution or EC beadlet capsules) was reported in 37 treatment-naive children aged 3 to 21 years.⁷ The didanosine dose used in that study was 240 mg/m²/dose once daily, and PK analysis showed no
dose changes were needed to reach PK targets. A European trial of once-daily combination therapy in 36 children aged 3 to 11 years that included didanosine at a dose of 200 to 240 mg/m² body surface area demonstrated safety and efficacy with up to 96 weeks of follow up. In 53 children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg/m² body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was less in the children given once-daily therapy. In 51 children (median age 6.0 years, range 2.5 to 15.0 years) in Burkina Faso, the once-daily combination of didanosine-lamivudine-efavirenz resulted in Week-48 viral load <300 copies/mL in 81% of treated participants. That study used didanosine at a dose of 240 mg/m²/day, administered in the fasting state as tablets with a separate antacid (not enteric-coated capsules).

**Food Restrictions**

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and it may decrease medication adherence by increasing regimen complexity. A comparison showed that regardless of whether didanosine oral solution was given to children with or without food, systemic exposure measured by AUC was similar; absorption of didanosine administered with food was slower and elimination more prolonged. To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults suggest that didanosine can be given without regard to food. A European study dosed didanosine oral solution as part of a 4-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction and showed good virologic outcome with up to 96 weeks of follow-up.

**References**


**Emtricitabine (FTC, Emtriva)** (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

**Formulations**

**Pediatric Oral Solution:** 10 mg/mL

**Capsules:** 200 mg

**Combination Tablets:**

- With tenofovir disoproxil fumarate (tenofovir): 200 mg emtricitabine plus 300 mg tenofovir (Truvada)
- With tenofovir and efavirenz: 200 mg emtricitabine plus 300 mg tenofovir plus 600 mg efavirenz (Atripla)
- With tenofovir and rilpivirine: 200 mg emtricitabine plus 300 mg tenofovir plus 25 mg rilpivirine (Complera)
- With emtricitabine and elvitegravir and cobicistat: 200 mg emtricitabine plus 150 mg elvitegravir plus 150 mg cobicistat plus 300 mg tenofovir (Stribild)

**Dosing Recommendations**

**Neonate/Infant Dose (Aged 0 to <3 Months):**

**Oral Solution:**

- 3 mg/kg once daily.

**Pediatric Dose (Aged ≥3 Months to 17 Years):**

**Oral Solution:**

- 6 mg/kg (maximum dose 240 mg) once daily; higher maximum dose because the oral solution has 20% lower plasma exposure in pediatric pharmacokinetic analysis.

**Capsules (for Children who Weigh >33 kg):**

- 200 mg once daily.

**Adolescent (Aged ≥18 Years)/Adult Dose:**

**Oral Solution:**

- 240 mg (24 mL) once daily.

**Capsules:**

- 200 mg once daily.

**Combination Tablets**

- **Truvada**
  - Adolescent (Aged ≥12 Years And ≥35 Kg and Adult Dose):
    - 1 tablet once daily.

- **Atripla**
  - Adolescent (Aged ≥12 Years And ≥40 Kg and Adult Dose):
    - 1 tablet once daily.

**Selected Adverse Events**

- Minimal toxicity
- Severe acute exacerbation of hepatitis can occur in hepatitis B virus (HBV)-coinfected patients who discontinue emtricitabine
- Hyperpigmentation/skin discoloration on palms and/or soles

**Special Instructions**

- Emtricitabine can be given without regard to food; however, administer Atripla on an empty stomach because it also contains efavirenz.
- Emtricitabine oral solution can be kept at room temperature up to 77°F (25°C) if used within 3 months; refrigerate for longer-term storage.
- Before using emtricitabine, screen patients for HBV.

**Metabolism**

- **Limited metabolism:** No cytochrome P (CYP) 450 interactions.
- Renal excretion 86%: Competition with other compounds that undergo renal elimination.
- Do not use Atripla (fixed-dose combination) in...
Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- Other nucleoside reverse transcriptase inhibitors (NRTIs): Do not use emtricitabine in combination with lamivudine because the agents share similar resistance profiles and lack additive benefit. **Do not use separately with Combivir, Epzicom, or Trizivir because lamivudine is a component of these combinations. Do not use separately when prescribing Truvada, Atripla, Complera, or Stribild because emtricitabine is a component of these formulations.**

- Renal elimination: Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion). Drugs that decrease renal function could decrease clearance.

- **Use with Stribild:** If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Major Toxicities

- **More common:** Headache, insomnia, diarrhea, nausea, rash, and hyperpigmentation/skin discoloration (possibly more common in children).

- **Less common (more severe):** Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in HIV/hepatitis B virus-coinfected patients who changed from emtricitabine-containing to non-emtricitabine-containing regimens.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/FTC.html](http://hivdb.stanford.edu/pages/GRIP/FTC.html)).

Pediatric Use

Approval

Emtricitabine is Food and Drug Administration (FDA)-approved for once-daily administration in children starting at birth. Owing to its once-daily dosing, minimal toxicity, and pediatric pharmacokinetic (PK) data, emtricitabine is commonly used as part of a dual-NRTI backbone in combination antiretroviral therapy.
Efficacy and Pharmacokinetics

Pharmacokinetics

A single-dose PK study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children aged 2 to 17 years. Emtricitabine was found to be well absorbed following oral administration, with a mean elimination half-life of 11 hours (range 9.7 to 11.6 hours). Plasma concentrations in children receiving the 6 mg/kg emtricitabine once-daily dose were approximately equivalent to those in adults receiving the standard 200-mg dose.

A study in South Africa evaluated the PKs of emtricitabine in 20 HIV-exposed infants aged <3 months, given emtricitabine as 3 mg/kg once daily for two, 4-day courses, separated by an interval of ≥2 weeks. Emtricitabine exposure (area under the curve [AUC]) in neonates receiving 3 mg/kg emtricitabine once daily was in the range of pediatric patients aged >3 months receiving the recommended emtricitabine dose of 6 mg/kg once daily and adults receiving the once-daily recommended 200-mg emtricitabine dose (AUC approximately 10 hr*ug/mL). Over the first 3 months of life, emtricitabine AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (N = 6) receiving a single dose of emtricitabine 3 mg/kg after a single maternal dose of 600 mg during delivery, the AUC exceeded that seen in adults and older children, but the half-life (9.2 hours) was similar. Extensive safety data are lacking in this age range.

Efficacy

Based on the aforementioned dose-finding study, emtricitabine was studied at a dose of 6 mg/kg once daily in combination with other antiretroviral (ARV) drugs in 116 patients aged 3 months to 16 years. PK results were similar, and follow-up data extending to Week 96 indicated that 89% of the ARV-naive and 76% of the ARV-experienced children maintained suppression of plasma HIV RNA <400 copies/mL (75% of ARV-naive children and 67% of ARV-experienced children at <50 copies/mL). Minimal toxicity was observed in this trial. In PACTG P1021, emtricitabine at a dose of 6 mg/kg (maximum 240 mg/day as liquid or 200 mg/day as capsules) in combination with didanosine and efavirenz, all given once daily, was studied in 37 ARV-naive HIV-infected children aged 3 months to 21 years. Eighty-five percent of children achieved HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm³ at Week 96.

Both emtricitabine and lamivudine have antiviral activity and efficacy against hepatitis B. For a comprehensive review of this topic, hepatitis C, and tuberculosis during HIV co-infection, please see the Pediatric Opportunistic Infections Guidelines.

References

Dosing Recommendations

**Neonate/Infant Dose (Aged <4 Weeks) for Prevention of Transmission or Treatment:**
- 2 mg/kg twice daily

**Pediatric Dose (Aged ≥4 Weeks):**
- 4 mg/kg (up to 150 mg) twice daily

**Pediatric Dosing for Scored 150-mg Tablet (Weight ≥14 kg):**

<table>
<thead>
<tr>
<th>Weight</th>
<th>AM Dose</th>
<th>PM Dose</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 to 21 kg</td>
<td>½ tablet (75 mg)</td>
<td>½ tablet (75 mg)</td>
<td>150 mg</td>
</tr>
<tr>
<td>&gt;21 to &lt;30 kg</td>
<td>½ tablet (75 mg)</td>
<td>1 tablet (150 mg)</td>
<td>225 mg</td>
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<tr>
<td>≥30 kg</td>
<td>1 tablet (150 mg)</td>
<td>1 tablet (150 mg)</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

**Adolescent (Aged ≥16 Years)/Adult Dose:**
- **Body Weight <50 kg:**
  - 4 mg/kg (up to 150 mg) twice daily
- **Body Weight ≥50 kg:**
  - 150 mg twice daily or 300 mg once daily

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic HBV infection

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before administering 3TC.

Metabolism

- Renal excretion—dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with creatinine clearance (CrCl) <50 mL/min, on dialysis, or with impaired hepatic function.
### Combivir
**Adolescent (Weight ≥30 kg)/Adult Dose:**
- 1 tablet twice daily

### Trizivir
**Adolescent (Weight >40 kg)/Adult Dose:**
- 1 tablet twice daily

### Epzicom
**Adolescent (Aged >16 Years and Weight >50 kg)/Adult Dose:**
- 1 tablet once daily

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**Drug Interactions** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Renal elimination:** Drugs that decrease renal function could decrease clearance of lamivudine.
- **Other nucleoside reverse transcriptase inhibitors (NRTIs):** Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit.\(^1\) **Do not use separately** when prescribing Truvada, Atripla, Complera, or Stribild because emtricitabine is a component of these formulations. Do not use separately when prescribing Combivir, Epzicom, or Trizivir because lamivudine is already a component of these combinations.

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**Major Toxicities**

- **More common:** Headache, nausea.
- **Less common (more severe):** Peripheral neuropathy, pancreatitis, lipodystrophy/lipoatrophy.
- **Rare:** Increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/3TC.html](http://hivdb.stanford.edu/pages/GRIP/3TC.html)).

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**Pediatric Use**

**Approval**

Lamivudine is Food and Drug Administration (FDA)-approved for use in children aged ≥3 months, and it is a common component of most nucleoside backbone regimens.

**Efficacy**

Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral (ARV) drugs, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response.\(^2,10\) Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone.\(^3,5,7,9,10\) In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.\(^11\)
Pharmacokinetics in Infants

Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.7 A population pharmacokinetic (PK) analysis of infants receiving lamivudine affirms that adjusting the dose of lamivudine from 2 mg/kg to 4 mg/kg every 12 hours at age 4 weeks for infants with normal maturation of renal function provides optimal lamivudine exposure.12 For infants in early life, the higher WHO weight-band dosing (up to 5 times the FDA dose) results in increased plasma concentrations compared to the 2 mg/kg dosing.13 In HPTN 040, lamivudine was given for prophylaxis of perinatal transmission in the first 2 weeks of life along with nelfinavir and 6 weeks of zidovudine according to a lower weight band dosing scheme. All infants weighing >2,000 g received 6 mg twice daily and infants weighing ≤2,000 g received 4 mg twice daily for 2 weeks. These doses resulted in lamivudine exposure similar to that seen in infants who received the standard 2 mg/kg/dose twice-daily dosing schedule for neonates.14

Dosing Considerations—Once Daily versus Twice Daily Administration

The standard adult dosage for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. Population PK data indicate that once-daily dosing of 8 mg/kg leads to area under the curve (AUC)0-24 values similar to 4 mg/kg twice daily but Cmin values significantly lower and Cmax values significantly higher in children aged 1 to 18 years.15 Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children aged 2 to 13 years in the PENTA-13 trial,2 and in children 3 to 36 months of age in the PENTA 15 trial.16 Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC0-24 and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC0-24 and good clinical outcome (disease stage and CD4 T lymphocyte [CD4] cell count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years.17 All three studies enrolled only patients who had low viral load or were clinically stable on twice-daily lamivudine before changing to once-daily dosing. Nacro et al. studied a once-daily regimen in ARV-naive children in Burkina-Faso composed of non-enteric-coated didanosine (ddI), lamivudine, and efavirenz. Fifty-one children ranging in age from 30 months to 15 years were enrolled in this open-label, Phase II study lasting 12 months.18 The patients had advanced HIV infection with a mean CD4 percentage of 9 and median plasma RNA of 5.51 log10/copies/mL. At 12-month follow-up, 50% of patients had a plasma RNA <50 copies/mL and 80% were <300 copies/mL with marked improvements in CD4 percentage. Twenty-two percent of patients harbored multi-class-resistant viral strains. While PK values were similar to the PENTA and ARROW trials, the study was complicated by use of non-enteric-coated ddI, severe immunosuppression, and non-clade B virus. In addition, rates of virologic failure and resistance profiles were not separated by age. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged 3 years and older with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 cell count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily. More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of lamivudine can be used effectively to initiate ARV therapy in children.
Lamivudine undergoes intracellular metabolism to its active form, lamivudine triphosphate. In adolescents, the mean half-life of intracellular lamivudine triphosphate (17.7 hours) is considerably longer than that of unphosphorylated lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate have been shown to be equivalent with once- and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing in adolescents aged 16 and older who weigh 50 kg or more.19,20

WHO Dosing

Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150-mg scored tablets.21,22

Both emtricitabine and lamivudine have antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection the reader should access the Pediatric Opportunistic Infections guidelines.

References


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Table: Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine

<table>
<thead>
<tr>
<th>Study/(Reference)</th>
<th>PENTA 1524</th>
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<th>ARROW25</th>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>7</td>
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<td>Race (% Black or African American)</td>
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<td>Dosing Interval (hours)</td>
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<td>12</td>
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<td>Cmin (mg/L)</td>
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<tr>
<td>Cl/F/kg (L/hr/kg)</td>
<td>0.79a</td>
<td>0.86a</td>
<td>0.90a</td>
</tr>
</tbody>
</table>

* Geometric mean

Note: Data are medians except as noted.

Key to Acronyms: AUC = area under the curve; PI = protease inhibitor

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* Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*


Stavudine (d4T, Zerit) (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Powder for Oral Solution: 1 mg/mL
Capsules: 15 mg, 20 mg, 30 mg, 40 mg
Generic: Stavudine capsules and solution have been approved by the Food and Drug Administration for manufacture and distribution in the United States

Dosing Recommendations

Neonate/Infant Dose (Birth to 13 Days):
- 0.5 mg/kg twice daily

Pediatric Dose (Aged ≥14 Days And Weighing <30 kg):
- 1 mg/kg twice daily

Adolescent (≥30 kg)/Adult Dose:
- 30 mg twice daily

Selected Adverse Events

- Mitochondrial toxicity
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors). The risk is increased when used in combination with didanosine.
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- Stavudine can be given without regard to food.
- Shake stavudine oral solution well before use. Keep refrigerated; the solution is stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- Renal elimination: Drugs that decrease renal function could decrease stavudine clearance.
- Other Nucleoside Reverse Transcriptase Inhibitors (NRTIs): Stavudine should not be administered in combination with zidovudine because of virologic antagonism.
- Overlapping toxicities: The combination of stavudine and didanosine is not recommended for initial therapy because of overlapping toxicities. Reported toxicities are more often reported in adults and
include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

- **Ribavirin and interferon**: Hepatic decompensation (sometimes fatal) has occurred in HIV/hepatitis C virus-coinfected patients receiving combination antiretroviral therapy (cART), interferon, and ribavirin.
- **Doxorubicin**: Simultaneous use of doxorubicin and stavudine should be avoided. Doxorubicin may inhibit the phosphorylation of stavudine to its active form.

**Major Toxicities**

- **More common**: Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- **Less common (more severe)**: Peripheral sensory neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a history of peripheral neuropathy, and in those patients receiving other drugs associated with neuropathy. Pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis, pancreatitis, peripheral neuropathy, and hepatotoxicity), particularly in adults, including pregnant women. This combination should not be used for initial therapy. Risk factors found to be associated with lactic acidosis in adults include female gender, obesity, and prolonged nucleoside exposure.¹
- **Rare**: Increased liver enzymes and hepatic toxicity, which may be severe or fatal. Neurologic symptoms including rapidly progressive ascending neuromuscular weakness are most often seen in the setting of lactic acidosis.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html), and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/d4T.html).

**Pediatric Use**

**Approval**

Although stavudine is Food and Drug Administration (FDA)-approved for use in children, its use is limited because it carries a higher risk of side effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

**Efficacy**

Data from multiple pediatric studies of stavudine alone or in combination with other antiretroviral (ARV) agents demonstrate that stavudine appears safe and is associated with clinical and virologic response.²⁻⁸ In resource-limited countries, stavudine is frequently a component of initial cART with lamivudine and nevirapine in children, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 T lymphocyte (CD4) count and complete viral suppression in 50% to 80% of treatment-naïve children.⁹⁻¹² In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in patients receiving cotrimoxazole prophylaxis.¹³ Short-term use of stavudine in certain settings where access to other ARVs may be limited, remains an important strategy for treatment of young children.¹⁴

**Toxicity**

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving cART.¹⁵,¹⁶ In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest—but significantly higher—rate of clinical and laboratory toxicities than those containing zidovudine,
with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use. Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults. In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children.

**Lipodystrophy and Metabolic Abnormalities**

Lipodystrophy syndrome (LS), and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children. There are concerns that children with metabolic disorders and abnormalities in body fat distribution including subcutaneous fat loss and central fat accumulation are potentially at increased risk of cardiovascular disease in early adulthood. Stavudine use has consistently been associated with a higher risk of lipodystrophy and other metabolic abnormalities (e.g., insulin resistance) in multiple pediatric studies involving children from the United States, Europe, Tanzania, Uganda, and Thailand. Lipodystrophy developed in 27% to 66% of children, with lipoatrophy being the most common form of lipodystrophy. The wide range of reported rates of LS is influenced by lack of consensus about clinical definition, ability of clinical staff to identify fat abnormalities in children, measurements used to diagnose abnormalities, duration of follow-up, and population differences. Evaluation of LS in Tanzanian children found that anthropometric measurements predicted LS in well-nourished children, but generally failed to do so in children with lower weights. While ever- or current- stavudine use has consistently been associated with a higher risk of LS, additional factors include older age and duration on ARVs. Improvements in lipodystrophy have been observed among Thai children after discontinuation of stavudine in two separate studies. Improvement or resolution was reported in 22.9% to 73% of cases.

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine. In adults, female gender, higher body mass index (BMI), and lower initial CD4 cell count are risk factors for developing lactic acidosis and hyperlactatemia. The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available (for additional information on lactic acidosis see Table 11g in Management of Medication Toxicity or Intolerance).

**Mechanism**

Many of the above-mentioned adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA in fat, muscle, peripheral blood mononuclear cells, and other tissues. In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.

**World Health Organization Recommendations**

The World Health Organization recommends that stavudine be phased out of use because of unacceptable toxicity, with a strong recommendation that a maximum stavudine dose of 30 mg twice daily be used instead of the FDA-recommended 40 mg twice daily in patients weighing 60 kg or more. Several studies have compared the efficacy and toxicity of the 2 doses: similar efficacy with either the 30-mg or 40-mg dose but a significantly lower incidence of peripheral neuropathy in the 30-mg than in the 40-mg group, but the overall incidence was considered to be unacceptably high. Lipoatrophy and peripheral neuropathy are more likely to occur with higher doses but the risk of lactic acidosis is associated with female gender and a high BMI. When data from 48,785 adult patients from 23 HIV programs in resource-limited countries was evaluated, factors associated with higher toxicity rates included stavudine 40-mg dose, female gender, older age, advanced clinical stage, and low CD4 counts at the time of initiation of therapy. A recent South African study involving 3910 adult patients initiated on stavudine, confirmed higher rates of drug-related toxicity for peripheral neuropathy (OR 3.12), lipoatrophy (OR 11.8), and hyperlactatemia/lactic acidosis (OR 8.37) in patients receiving the 40 mg dose compared to the 30-mg dose and that patients receiving the higher dose were more likely to discontinue stavudine use (OR 1.71) during the first year on cART.
prospective analysis of this cohort has confirmed that treatment initiation with tenofovir disoproxil fumarate has lowered drug-related adverse effects and that stavudine use is declining in South Africa.44

Pharmacokinetics

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.45 These early studies were conducted at a time when treatment options were limited and many children had failure to thrive. The authors in this early PK study state that stavudine distributes in total body water and because total body weight correlates well with lean body mass (or weight) stavudine dosages in obese children should be based on lean body weight.45

Formulations

The pediatric formulation for stavudine oral solution requires refrigeration and has limited stability once reconstituted. As an alternative dosing method for children, capsules can be opened and dispersed in a small amount of water, the appropriate dose drawn up into an oral syringe, and administered immediately. Because plasma exposure is equivalent with stavudine administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.46

References


Tenofovir Disoproxil Fumarate (TDF, Viread)  
(Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

**Formulations**

**Oral Powder:** 40 mg per 1 g of oral powder (1 level scoop = 1 g oral powder; supplied with dosing scoop)

**Tablet:** 150 mg, 200 mg, 250 mg, and 300 mg

**Combination Tablets:**

- With emtricitabine:
  - 200 mg emtricitabine plus 300 mg tenofovir disoproxil fumarate (hereafter, tenofovir) (Truvada)

- With emtricitabine plus efavirenz:
  - 200 mg emtricitabine plus 600 mg efavirenz plus 300 mg tenofovir (Atripla)

- With emtricitabine plus rilpivirine:
  - 200 mg emtricitabine plus 25 mg rilpivirine plus 300 mg tenofovir (Complera)

- With emtricitabine plus elvitegravir plus cobicistat:
  - 200 mg emtricitabine plus 150 mg elvitegravir plus 150 mg cobicistat plus 300 mg tenofovir (Stribild)

**Dosing Recommendations**

**Neonate/Infant Dose:**
- Not Food and Drug Administration (FDA)-approved or recommended for use in neonates/infants aged <2 years.

**Pediatric Dose (Aged ≥2 Years to <12 Years)*:**
- 8 mg/kg/dose once daily

**Oral Powder Dosing Table**

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>Oral Powder Once Daily Scoops of Powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to &lt;12</td>
<td>2</td>
</tr>
<tr>
<td>12 to &lt;14</td>
<td>2.5</td>
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<td>14 to &lt;17</td>
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<td>7</td>
</tr>
<tr>
<td>≥35</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**Selected Adverse Events**

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density (BMD)

**Special Instructions**

- Oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg tenofovir.
  - Mix oral powder in 2 to 4 ounces of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
  - Do not try to mix the oral powder with liquid: the powder may float on the top even after vigorous stirring.
  - Tenofovir can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains efavirenz, the combination tablet should be administered on an empty stomach.
**Tablet Dosing Table**

**(Aged ≥2 Years and Weight ≥17 kg)**

<table>
<thead>
<tr>
<th>Body Weight kg</th>
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<tbody>
<tr>
<td>17 to &lt;22</td>
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<td>22 to &lt;28</td>
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<tr>
<td>28 to &lt;35</td>
<td>250 mg</td>
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<tr>
<td>≥35</td>
<td>300 mg</td>
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</table>

**Adolescent (Aged ≥12 Years and Weight ≥35 kg)* and Adult Dose:**
- 300 mg once daily

**Combination Tablets**

**Truvada (Tenofovir plus Emtricitabine):**
- Adolescent (aged ≥12 years and weight ≥35 kg) and adult dose: 1 tablet once daily.

**Atripla (Tenofovir plus Emtricitabine plus Efavirenz):**
- Adolescent (aged ≥12 years and weight ≥40 kg) and adult dose: 1 tablet once daily.

**Complera (Tenofovir plus Emtricitabine plus Rilpivirine):**
- Adult dose (aged ≥18 years): 1 tablet once daily in treatment-naive adults with baseline viral load <100,000 copies/mL. Administer with a meal.

**Stribild (Tenofovir plus Emtricitabine plus Elvitegravir plus Cobicistat):**
- Adult dose (aged ≥18 years): 1 tablet once daily in treatment-naive adults. Administer with food.

**Tenofovir In Combination With Didanosine:**
- Co-administration increases didanosine concentrations, so the combination of tenofovir and didanosine should be avoided if possible. If used, requires didanosine dose reduction (see section on didanosine).

**Tenofovir in Combination With Atazanavir:**
- Co-administration reduces atazanavir concentrations, so when atazanavir is used in combination with tenofovir; atazanavir should always be boosted with ritonavir. **Atazanavir co-administration increases tenofovir concentrations, so monitor for tenofovir toxicity.**

**Tenofovir in Combination with Ritonavir-Boosted Lopinavir/Ritonavir:**
- Co-administration increases tenofovir concentrations. Monitor for tenofovir toxicity.

**Metabolism**

- Renal excretion.
- Dosing of tenofovir in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function (creatinine clearance <50 mL/min). Consult manufacturer’s prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).

**Tenofovir in Combination with Ritonavir-Boosted Lopinavir/Ritonavir:**
- Co-administration increases tenofovir concentrations. Monitor for tenofovir toxicity.
- Measure serum creatinine and urine dipstick for protein and glucose before starting a tenofovir-containing regimen and monitor serum creatinine and urine dipstick for protein and glucose at intervals during continued therapy. Measure serum phosphate if clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before use of tenofovir. Severe acute exacerbation of HBV infection can occur when tenofovir is discontinued; therefore, monitor hepatic function for several months after therapy with tenofovir is stopped.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

*See text for concerns about decreased BMD, especially in pre-pubertal patients and those in early puberty (Tanner Stages 1 and 2).
**Drug Interactions** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Renal elimination:** Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (tenofovir).

- **Other nucleoside reverse transcriptase inhibitors (NRTIs):** Didanosine serum concentrations are increased when the drug is co-administered with tenofovir and this combination should be avoided if possible because of increase in didanosine toxicity.

- **Protease inhibitors (PIs):** Tenofovir decreases atazanavir plasma concentrations. Atazanavir without ritonavir should not be co-administered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.

- **Use of Stribild:** If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

**Major Toxicities**

- **More common:** Nausea, diarrhea, vomiting, and flatulence.

- **Less common (more severe):** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density (BMD) have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Renal toxicity, including increased serum creatinine, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Patients at increased risk of renal glomerular or tubular dysfunction should be closely monitored.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/tenofovir.html).

**Pediatric Use**

**Approval**

Tenofovir is Food and Drug Administration (FDA)-approved for use in children aged ≥2 years when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

**Efficacy in Clinical Trials in Adults Compared to Children and Adolescents**

The standard adult dose of tenofovir approved by the FDA for adults and children aged ≥12 years and weight ≥35 kg is 300 mg once daily; for children aged 2 to 12 years, the FDA-approved dose is 8 mg/kg/dose administered once daily, which closely approximates the dose of 208 mg/m²/dose used in early studies in children.¹

In adults, the recommended dose is highly effective.²,³

In children aged 12 to <18 years, no difference in viral load response was seen between 2 treatment groups in a randomized, placebo-controlled trial of tenofovir 300 mg once daily or placebo, plus an optimized background regimen, in 87 treatment-experienced adolescents in Brazil and Panama.⁴-⁶ Subgroup analyses suggest this lack of response was from imbalances in viral susceptibility to the optimized background regimens.

In children aged 2 to <12 years, tenofovir 8 mg/kg/dose once daily showed non-inferiority to zidovudine- or stavudine-containing cART over 48 weeks of randomized treatment using a snapshot analysis (product label). This was a switch study in children aged 2 to 12 years with viral load <400 copies/mL during...
treatment with zidovudine or stavudine as part of cART, randomized to continue their zidovudine or stavudine (N = 49) or switch to tenofovir (N = 48) while continuing other components of the regimen (Gilead study 352).4

Other pediatric studies have also shown that virologic success is related to prior treatment experience. In 115 pediatric patients treated with tenofovir, viral load decreased to <50 copies/mL at 12 months in 50% of patients on first-line therapy, 39% of patients on second-line therapy, and 13% of patients on third-line or subsequent therapy.7 This cohort used a target dose of 8 mg/kg, but 18% of patients were dosed at greater than 120% of the target dose and 37% were dosed at less than 80% of the target dose.

Pharmacokinetics

Relationship of Drug Exposure to Virologic Response and Toxicity

Virologic success is related to drug exposure. In a study using a median daily dose of 208 mg/m²,8 lower single-dose and steady-state area under the curve (AUC) were associated with inferior virologic outcome.

Pharmacokinetic (PK) studies in children receiving an investigational 75-mg tablet formulation of tenofovir showed that a median dose of 208 mg/m² of body surface area (range 161–256 mg/m² body surface area) resulted in a median single dose AUC and maximum plasma concentration (Cmax) that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg.1,9 Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure.1 This lower exposure occurred even though participants were concurrently treated with ritonavir, which boosts tenofovir exposure. Lower-than-anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir.10

Further studies are needed of tenofovir PK and clinical outcomes in children, especially when used in combinations that do not include lopinavir and/or ritonavir.

Formulations

Special Considerations

The taste-masked granules that make up the oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed in the vehicle, tenofovir should be administered promptly because, if allowed to sit too long, its taste becomes bitter.

Toxicity

Bone

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (i.e., Tanner Stages 1 and 2) may be at higher risk than children with more advanced development (i.e., Tanner Stage ≥3).1,11,12 In a Phase I/II study of an investigational 75-mg formulation of tenofovir in 18 heavily pretreated children and adolescents, a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DXA) scan was reported in 5 of 15 (33%) children evaluated at Week 48.1 Two of the 5 children who discontinued tenofovir at 48 weeks experienced partial or complete recovery of BMD by 96 weeks.13 Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years.8,13 In a second study of 6 patients who received the commercially available, 300 mg formulation of tenofovir, 2 pre-pubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her cART regimen with subsequent recovery of BMD.14 Loss of BMD at 48 weeks was associated with higher drug exposure.8

In the industry-sponsored study that led to FDA approval of tenofovir in adolescents aged ≥12 years and weight ≥35 kg, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm4,5 (see

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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In the Gilead switch study (352) in children aged 2 to 12 years over the 48 weeks of randomized treatment, total body BMD gain was less in the tenofovir group than in the zidovudine or stavudine group, but the mean rate of lumbar spine BMD gain was similar between groups. At 48 weeks all participants were offered tenofovir, and for the participants who were treated with the drug for 96 weeks, total body BMD \( z \) score declined by -0.338 and lumbar spine BMD \( z \) score declined by -0.012.4

Not all studies of tenofovir in children have identified a decline in BMD.15,16 No effect of tenofovir on BMD was found in a study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz.17 All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen.18

**Monitoring**

The Panel does not recommend routine DXA monitoring for children or adolescents treated with tenofovir. Given the potential for BMD loss in children treated with tenofovir, some experts recommend obtaining a DXA before initiation of tenofovir therapy and approximately 6 months after starting tenofovir, especially in pre-pubertal patients and those early in puberty (i.e., Tanner Stages 1 and 2). Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in early adolescence is concerning and favors judicious use of tenofovir in this age group.

**Renal**

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in those with higher tenofovir trough plasma concentrations.19 Possible tenofovir-associated nephrotoxicity manifests as Fanconi syndrome, reduced creatinine clearance (CrCl), and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including ritonavir-boosted lopinavir and didanosine for 1 year.20 Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine.21 Renal toxicity leading to discontinuation of tenofovir was reported in 3.7% (6 of 159) of HIV-1-infected children treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland.7 Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 27% (12 of 44) of children treated with tenofovir compared with 4% (2 of 48) of children not treated with tenofovir.22 An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing cART.23 Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovir-containing antiretroviral regimens from 5 Spanish hospitals. The patients ranged in age from 8 to 17 years (median age 12.5 years) and had received tenofovir for 16 to 143 months (median 77 months). The following observations were made: 18 patients had declines in CrCl after at least 6 months of therapy; 28 patients had decreases in tubular reabsorption of phosphate, which worsened with longer time on tenofovir; and 33 patients had proteinuria, including 10 patients with proteinuria in the nephrotic range.24 However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years.25 Of 89 participants who received tenofovir in Gilead study 352 (median drug exposure 104 weeks), 4 discontinued from the study for renal tubular dysfunction, 3 of whom had hypophosphatemia and decrease in total body or spine BMD \( z \) score.4

**Monitoring**

Because of the potential for tenofovir to decrease creatinine clearance and to cause renal tubular dysfunction, it is recommended to measure serum creatinine and urine dipstick for protein and glucose prior to drug initiation. In an asymptomatic person, the optimal frequency for routine monitoring of creatinine and renal tubular function (urinalysis or urine protein) is unclear. Many panel members monitor creatinine with other laboratory tests every 3 to 4 months, and urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and the absence of proteinuria.
Tenofovir has antiviral activity and efficacy against Hepatitis B. For a comprehensive review of this topic, and Hepatitis C and tuberculosis during HIV co-infection, please see the Pediatric Opportunistic Infections guidelines.

References


12. Thomas V, Purdy J, Reynolds J, Hadigan C, Hazra R. Bone mineral density in adolescents infected with HIV perinatally or childhod: Data from the NIH intramural program. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8–11, 2009; Montreal, Canada.


16. Giacomet V, Mora S, Martelli L, et al. A 12-month treatment with tenofovir does not impair bone mineral accrual in...


Zidovudine (ZDV, AZT, Retrovir)  (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg
Tablets: 300 mg
Syrup: 10 mg/mL

Concentrate for Injection or Intravenous (IV) Infusion: 10 mg/mL

Generic: Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

Combination Tablets:
With lamivudine:
• 300 mg zidovudine plus 150 mg lamivudine (Combivir, generic)

With lamivudine plus abacavir:
• 300 mg zidovudine plus 150 mg lamivudine plus 300 mg abacavir (Trizivir)

Dosing Recommendations

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Zidovudine Oral Dosing</th>
<th>Zidovudine Intravenous Dosing (If Unable to Tolerate Oral Agents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35 weeks</td>
<td>4 mg/kg body weight every 12 hours</td>
<td>3 mg/kg body weight IV every 12 hours</td>
</tr>
<tr>
<td>≥30 to &lt;35 weeks</td>
<td>2 mg/kg body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days</td>
<td>1.5 mg/kg body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days</td>
</tr>
<tr>
<td>&lt;30 weeks</td>
<td>2 mg/kg body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks</td>
<td>1.5 mg/kg body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks</td>
</tr>
</tbody>
</table>

Selected Adverse Events

• Bone marrow suppression: macrocytosis with or without anemia, neutropenia
• Nausea, vomiting, headache, insomnia, asthenia
• Lactic acidosis/severe hepatomegaly with hepatic steatosis
• Nail pigmentation
• Hyperlipidemia
• Insulin resistance/diabetes mellitus
• Lipoatrophy
• Myopathy

Special Instructions

• Give zidovudine without regard to food.
• If substantial granulocytopenia or anemia develops in patients receiving zidovudine, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells and platelets.
Pediatric Dose (Aged 6 Weeks to <18 Years)

**Body Surface Area Dosing:**
- Oral: 240 mg/m² body surface area every 12 hours*

**Weight-Based Dosing**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Twice-Daily Dosing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 kg to &lt;9 kg</td>
<td>12 mg/kg</td>
</tr>
<tr>
<td>9 kg to &lt;30 kg</td>
<td>9 mg/kg</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

**Adolescent (Aged ≥18 Years)/Adult Dose:**
- 300 mg twice daily

**Combivir**

**Adolescent (Weight ≥30 kg)/Adult Dose:**
- 1 tablet twice daily

**Trizivir**

**Adolescent (Weight ≥40 kg)/Adult Dose:**
- 1 tablet twice daily

* Three-times-daily dosing is approved but rarely used in clinical practice.

**Metabolism**
- Metabolized to zidovudine glucuronide, which is renally excreted.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal insufficiency.
- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

**Drug Interactions** (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)

- Other nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine should not be administered in combination with stavudine because of in vitro virologic antagonism.
- Bone marrow suppressive/cytotoxic agents including ganciclovir, valganciclovir, interferon alfa, and ribavirin: These agents may increase the hematologic toxicity of zidovudine.
- Nucleoside analogues affecting DNA replication: Nucleoside analogues such as ribavirin antagonize in vitro antiviral activity of zidovudine.
- Doxorubicin: Simultaneous use of doxorubicin and zidovudine should be avoided. Doxorubicin may inhibit the phosphorylation of zidovudine to its active form.

**Major Toxicities**

- More common: Hematologic toxicity, including granulocytopenia and anemia, particularly in patients with advanced HIV-1 disease. Headache, malaise, nausea, vomiting, and anorexia. Incidence of neutropenia may be increased in infants receiving lamivudine.¹
- Less common (more severe): Myopathy (associated with prolonged use), myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- Rare: Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study.²
Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/zidovudine.html).

Resistance mutations were shown to be present in 29% (5 of 17) of infants born to mothers who received zidovudine during pregnancy.3

Pediatric Use

Approval

Zidovudine is frequently included as a component of the NRTI backbone for combination antiretroviral therapy (cART).4-20 Pediatric experience with zidovudine both for treatment of HIV and for prevention of perinatal transmission is extensive.

Efficacy and Dosing (PMTCT or Treatment)

Perinatal trial PACTG 076 established that zidovudine prophylaxis given during pregnancy, labor, and delivery, and to the newborn reduced risk of perinatal transmission of HIV by nearly 70%21 (see the Perinatal Guidelines for further discussion on the use of zidovudine for PMTCT of HIV). Although the PACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice daily oral infant dosing for prophylaxis. Zidovudine 4 mg/kg body weight every 12 hours is now recommended for neonates/infants >35 weeks of gestation for prevention of transmission or treatment (see the Perinatal Guidelines).

Pharmacokinetics

Overall, zidovudine pharmacokinetics (PK) in pediatric patients aged >3 months are similar to those in adults. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing is not recommended because of low intracellular zidovudine triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.22 PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with term newborns of similar postnatal age.5 Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease.23

Toxicity

While the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since the routine use of cART, a regimen containing zidovudine may increase the risk.24 Recent analysis of data from a U.S.-based, multicenter prospective cohort study (PACTG 219/219C) found that ongoing zidovudine exposure was independently associated with a higher rate of cardiomyopathy.24

References


Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

- Efavirenz (EFV, Sustiva)
- Etravirine (ETR, Intelenz, TMC 125)
- Nevirapine (NVP, Viramune)
- Rilpivirine (RPV, Edurant, TMC 278)
Efavirenz (EFV, Sustiva) (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations
Capsules: 50 mg, 200 mg
Tablets: 600 mg
Combination Tablets:
With Emtricitabine and Tenofovir Disoproxil Fumarate (Tenofovir):
• Emtricitabine 200 mg + Tenofovir 300 mg + Efavirenz 600 mg (Atripla)

Dosing Recommendations

Neonatal Dose:
• Efavirenz is not approved for use in neonates.

Pediatric Dose:
Infants and Children Aged 3 Months to <3 Years and Weight ≥3 kg:
• The Panel recommends that efavirenz generally not be used in children aged 3 months to <3 years. If use of efavirenz is unavoidable due to the clinical situation, the Panel suggests the use of investigational doses of efavirenz in this age group. See text for investigational dosing tables; evaluation of CYP 2B6 genotype is required prior to use. Therapeutic drug monitoring is recommended with an efavirenz concentration measured 2 weeks after initiation and at age 3 years for possible dose adjustment. For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

Children Aged ≥3 years and Weight ≥10 kg:
Administer Efavirenz Once Daily

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Efavirenz Dose (mg)a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;15 kg</td>
<td>200 mg</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg</td>
<td>250 mg</td>
</tr>
<tr>
<td>20 kg to &lt;25 kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>25 kg to &lt;32.5 kg</td>
<td>350 mg</td>
</tr>
<tr>
<td>32.5 kg to &lt;40 kg</td>
<td>400 mg</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

a The dose in mg can be dispensed in any combination of capsule strengths.
b Some experts recommend a dose of 367 mg/m² body surface area (maximum dose 600 mg) because of concern for under-dosing, especially at the upper end of each weight band (see Pediatric Use for details).

Selected Adverse Events

• Rash
• Central nervous system (CNS) symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures
• Increased transaminases
• False-positive with some cannabinoid and benzodiazepine tests
• Potentially teratogenic
• Lipohypertrophy, although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors

Special Instructions

• Efavirenz can be swallowed as a whole capsule or tablet or administered by sprinkling the contents of an opened capsule on food as described below.
• Administer whole capsule or tablet of Atripla on an empty stomach. Avoid administration with a high-fat meal because of potential for increased absorption.
• Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
• Efavirenz should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Instructions for Use of Capsule as a Sprinkle Preparation with Food or Formula:
• Hold capsule horizontally over a small container and carefully twist to open to avoid spillage.
Adolescent (Body Weight ≥40 kg)/Adult Dose:
- 600 mg once daily

Atripla
- Atripla should not be used in pediatric patients <40 kg where the efavirenz dose would be excessive.

Adult Dose:
- One tablet once daily

• Gently mix capsule contents with 1–2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt), or reconstituted infant formula at room temperature.
• Administer infant formula mixture using a 10-mL syringe.
• After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred, and dispensed to the patient.
• Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

Metabolism
• Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor)
• CYP2B6, CYP3A4, and CYP2A6 substrate
• Dosing of efavirenz in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
• Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product and tenofovir and emtricitabine require dose adjustment based on renal function, Atripla should not be used in patients with creatinine clearance (CrCl) <50 mL/minute or in patients on dialysis.
• Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers at higher risk of toxicity (see text for information about therapeutic drug monitoring for management of mild or moderate toxicity).

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)

• Metabolism: Mixed inducer/inhibitor of CYP3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions. Importantly, dosage adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, or maraviroc.
• Before efavirenz is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions with efavirenz.

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Major Toxicities:

- **More common:** Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities, such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.

- **Rare:** Potential risk of teratogenicity. Classified as Food and Drug Administration (FDA) Pregnancy Class D, which means that there is positive evidence of human fetal risk based on studies in humans (see Pediatric Use section below; see also the Perinatal Guidelines.1

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/EFV.html).

Pediatric Use

**Approval**

Efavirenz is FDA-approved for use as part of combination antiretroviral therapy in children aged 3 months or older who weigh at least 3.5 kg.

**Pharmacokinetics (PK): Pharmacogenomics**

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large interpatient variability in drug exposure. CYP2B6 is the primary enzyme for efavirenz metabolism, and pediatric patients with the CYP 2B6 516 T/T genotype (which has an allele frequency of 20% in African Americans), have reduced metabolism resulting in higher efavirenz levels compared with those with the G/G or G/T genotype.2-4 IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/kg using opened capsules resulted in therapeutic efavirenz concentrations in 68% of children aged <3 years with G/G or G/T genotype but excessive exposure in those with T/T genotype.4 Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years.4 Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.5-8

**PK and Dosing: Infants and Children Aged <3 Years**

Limited PK data in children aged <3 years or who weigh <13 kg have shown that it is difficult to achieve target trough concentrations in this age group.4,8 Hepatic enzyme activity is known to change with age. CYP 2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP 2B6 when compared with the CYP 2B6-516-G/T or -T/T genotype.2 In children with CYP 2B6-516-G/G genotype, oral clearance rate has been shown to be higher in children younger than aged 5 years than in older children.2 Efficacy data in infants and young children are mostly limited to studies of liquid efavirenz formulations, such as in PACTG 382 and PACTG 1021, and showed poor virologic response due to variable PK properties and tolerability of the liquid formulations in this young age group. Liquid formulations are not approved for use or available in the United States. Efficacy data for opened capsules with contents used as sprinkles suggest better palatability and bioavailability for infants and children aged <3 years. IMPAACT study P1070, an ongoing study of HIV-infected and HIV/tuberculosis-coinfected children aged <3 years, using efavirenz dosed by weight band based on CYP2B6 GG/GT versus TT genotype (see Tables 1a and 1b below), showed HIV RNA <400 copies/mL in 61% by intent to treat analysis at 24 weeks.4 When used without regard to genotype, doses higher than the FDA-recommended ones resulted in therapeutic efavirenz concentrations in an increased proportion of study participants with GG/GT genotypes but excessive exposure in a high proportion of those with TT genotypes.4 Therefore, dosing tables have been modified so that infants and young children with TT genotype will receive a reduced dose. Additional subjects will be studied to confirm that this dose is appropriate for this subset of patients. The modified doses listed in Tables 1a and 1b are under investigation.
The FDA has approved efavirenz for use in infants and children aged 3 months to <3 years at doses derived from a population PK model based on data from adult subjects in PACTG 1021 and PACTG 382, and AI266-922, which is an ongoing study assessing the PK, safety, and efficacy of capsule sprinkles in children aged 3 months to 6 years (see Table 2).

Table 2: FDA-approved Dosing for Children Aged 3 Months to <3 years (Without Regard to CYP 2B6 Genotype)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Efavirenz Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 kg to &lt;5 kg</td>
<td>100 mg</td>
</tr>
<tr>
<td>5 kg to &lt;7.5 kg</td>
<td>150 mg</td>
</tr>
<tr>
<td>7.5 kg to &lt;15 kg</td>
<td>200 mg</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

The FDA-approved doses are lower than the CYP 2B6 extensive metabolizer doses and higher than the CYP 2B6 slow metabolizer doses currently under study in P1070. Further studies are needed to determine if the FDA dosing can achieve therapeutic levels for the group aged 3 months to 3 years. There is concern that FDA-approved doses may result in frequent under-dosing in CYP 2B6 extensive metabolizers. The Panel recommends that efavirenz generally not be used in children aged 3 months to <3 years. If the clinical situation demands use of efavirenz, Panel members recommend determining CYP2B6 genotype (search for laboratory performing this testing at [http://www.ncbi.nlm.nih.gov/gtr/labs](http://www.ncbi.nlm.nih.gov/gtr/labs)). Patients should be classified as extensive CYP 2B6 516 GG and GT genotypes versus slow CYP 2B6 516 TT genotype metabolizers to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Tables 1a and 1b). Whether the doses used are investigational or FDA-approved, efavirenz plasma concentrations should be measured 2 weeks post-initiation (see Role of Therapeutic Drug Monitoring). For dose adjustment, consultation with an expert is recommended. In addition, when dosing following the P1070 investigational dose recommendations, efavirenz concentrations should be measured at age 3 years to guide potential dose adjustments.

* Investigational doses are based on IMPAACT study P1070. Evaluation of CYP 2B6 genotype is required. Therapeutic drug level monitoring is recommended with a trough measured 2 weeks after initiation and at age 3 years for possible dose adjustment.

**PK: Children Aged ≥3 Years and Adolescents**

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations.
> 1 mcg/mL in adults. Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA levels ≤ 400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL). In a West African pediatric study, ANRS 12103, early reduction in viral load (by 12 weeks) was greater in children with efavirenz minimum plasma concentration (Cmin) levels > 1.1 mcg/mL or area under the curve (AUC) > 51 mcg h/mL.

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, efavirenz concentrations can be suboptimal. Therefore, some experts recommend therapeutic drug monitoring with efavirenz and possibly use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In one study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered efavirenz dose was 13 mg/kg (367 mg/m²) and the range was from 3 to 23 mg/kg (69–559 mg/m²). A PK study in 20 children aged 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/m² twice daily plus efavirenz 350 mg/m² once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough was lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together. Therapeutic drug monitoring can be considered when using efavirenz in combinations with potentially complex drug interactions.

**Dosing: Special Considerations**

For patients at least 3 months old who cannot swallow capsules or tablets, the efavirenz capsule contents can be administered with a small amount (1 to 2 teaspoons) of food. Use of 2 teaspoons of infant formula can be considered for infants who cannot reliably consume solid foods. The capsule should be held horizontally over a small container and carefully twisted open to avoid spillage and dispersion of capsule contents into the air. The capsule contents should be gently mixed with an age-appropriate soft food, such as applesauce, grape jelly, or yogurt, or reconstituted infant formula at room temperature, in a small container. The infant formula mixture should be administered using a 10-mL syringe. After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred and dispensed to the patient. The efavirenz mixture should be administered within 30 minutes of mixing and no additional food or formula should be consumed for 2 hours after administration.

**Toxicity: Children versus Adults**

The toxicity profile for efavirenz differs for adults and children. A side effect commonly seen in children is rash, which was reported in up to 40% of children compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment. Although severe rash and Stevens-Johnson syndrome have been reported, they are rare. In adults, CNS symptoms have been reported in more than 50% of patients. These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. For patients who can swallow capsules or tablets, ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric adverse effects. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies and in 30% of children with efavirenz concentrations greater than 4 mcg/mL. CNS adverse effects may be harder to detect in children because of the difficulty in assessing neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients.

**Toxicity: Potential Risk of Teratogenicity**

Prenatal efavirenz exposure has been associated with CNS congenital abnormalities in the offspring of cynomolgus monkeys. Based on these data and retrospective reports in humans of an unusual pattern of
severe CNS defects in five infants after first-trimester exposure to efavirenz-containing regimens (three reports of meningomyeloceles and two of Dandy-Walker malformations), efavirenz has been classified as FDA Pregnancy Class D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy. Alternate antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception (if such alternative regimens are acceptable to provider and patient and will not compromise a woman’s health). See the Perinatal Guidelines.

**Therapeutic Drug Monitoring**

**Note:** see Role of Therapeutic Drug Monitoring.

In the setting of potential toxicity, it is reasonable for a clinician to use therapeutic drug monitoring (TDM) to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range. This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then, it should be used with caution. Also, the Panel recommends TDM when dosing efavirenz in children aged 3 months to <3 years due to variable PK properties in this young age group. An efavirenz concentration, preferably a trough, measured 2 weeks after initiation, and consultation with an expert, is recommended for dose adjustment. Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations greater than 1000 ng/mL in adults. In addition, efavirenz concentrations should be measured at age 3 years for potential dose adjustment if dosing was initiated at age <3 years using investigational dose recommendations.

**References**


Etravirine (ETR, Intenence, TMC 125)  
(Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations
Tablets: 25 mg, 100 mg, and 200 mg

Dosing Recommendations

Neonate/Infant Dose:
- Not approved for use in neonates/infants.

Pediatric Dose:
- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are currently underway.

Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years (and Weighing at Least 16 kg)

<table>
<thead>
<tr>
<th>Body Weight Kilogram (kg)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 kg to &lt;20 kg</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>20 kg to &lt;25 kg</td>
<td>125 mg twice daily</td>
</tr>
<tr>
<td>25 kg to &lt;30 kg</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>200 mg twice daily</td>
</tr>
</tbody>
</table>

Adult Dose (Antiretroviral-Experienced Patients):
- 200 mg twice daily following a meal

Selected Adverse Events

- Nausea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

Special Instructions

- Always administer etravirine following a meal. Area under the curve (AUC) of etravirine is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to etravirine.
- Etravirine tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow etravirine tablets may disperse the tablets in liquid, as follows: Place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication and stir well until the water looks milky. If desired, add more water or alternatively orange juice or milk (Note: Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm [>40°C] drinks, or carbonated beverages should be avoided.) Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Dosing of etravirine in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
Drug Interactions (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- Etravirine is associated with multiple drug interactions. Before administration, the patient’s medication profile should be carefully reviewed for potential drug interactions with etravirine.
- Etravirine should not be co-administered with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, and unboosted protease inhibitors. It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., nevirapine, efavirenz, or rilpivirine). Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir, but no dose adjustment is currently recommended when etravirine and raltegravir are used together.

Major Toxicities

- More common: Nausea, diarrhea, and mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- Less common (more severe): Peripheral neuropathy, severe rash including Stevens-Johnson syndrome, hypersensitivity reactions (HSRs) (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ETR.html).

Pediatric Use

Approval

Etravirine is Food and Drug Administration (FDA)-approved for use in ARV-experienced children and adolescents aged 6 to 18 years.
Efficacy in Clinical Trials

The PIANO study (TMC125-C213), was a single-arm, Phase II trial involving 101 ARV treatment-experienced, HIV-1 infected pediatric subjects aged 6 to <18 years and weighing ≥16 kg. Subjects eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA of at least 500 copies/mL and viral susceptibility to etravirine at screening. All patients received etravirine with an investigator-selected, optimized background regimen of a ritonavir-boosted protease inhibitor plus nucleoside analogue reverse transcriptase inhibitors and optional enfuvirtide and/or raltegravir. At week 24, 56% of these pediatric subjects had plasma HIV-1 RNA concentrations <400 copies/mL and 52% had <50 copies/mL. At week 48, 56% of the subjects had <50 copies/mL, with a mean CD4 T lymphocyte cell increase of 156 x106/mm3. A greater fraction of children aged 6 to <12 years had plasma HIV RNA-1 <50 copies/mL than adolescents aged 12 to <18 years (68% versus 48%), which the investigators attributed to less advanced disease, less prior NNRTI experience at baseline, and better adherence among the children. However, the population PK data from this Phase II trial (101 treatment-experienced children aged 6–17 years) revealed slightly lower etravirine exposures in adolescents (aged 12–17 years) compared with children aged 6 to 11 years and with adults (see below).

The safety, efficacy, and tolerability of etravirine in treatment-experienced patients was also evaluated in a multicenter retrospective study of 23 multidrug-resistant pediatric patients with a median age of 14.2 years (interquartile range 12.5 to 15.8 years). The backbone regimen included at least 2 fully active drugs in 91% of patients. During a median of 48.4 weeks of follow-up, 20 patients (87%) achieved HIV-1 RNA <400 copies/mL and 18 of 23 (78%) achieved HIV-1 RNA <50 copies/mL. No patients showed complete resistance to etravirine after follow up but 3 of the 21 patients who interrupted etravirine treatment because of virological or immunological failure had single resistance mutations at baseline.

The efficacy of etravirine-containing regimens in children who have previously been treated with an NNRTI is unclear. However, in a multi-center retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit, et al. found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥4, which would be predicted to compromise its effectiveness.

Pharmacokinetics

In a Phase I dose-finding study involving children aged 6 to 17 years, 17 children were given 4 mg/kg twice daily. The PK parameters AUC12h and Cmin were below preset statistical targets based on prior studies involving adults. Based on acceptable PK parameters, the higher dose (5.2 mg/kg twice daily; maximum 200 mg per dose) was chosen for evaluation in the Phase II PIANO study. Exposures remained lower in older adolescents than adults and younger children.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Mean AUC12 (ng*h/mL)</th>
<th>Mean C0h (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged 6–11 Years (N = 41)</td>
<td>5764</td>
<td>381</td>
</tr>
<tr>
<td>Adolescents Aged 12–17 Years (N = 60)</td>
<td>4834</td>
<td>323</td>
</tr>
<tr>
<td>All Pediatric Participants</td>
<td>5236</td>
<td>347</td>
</tr>
<tr>
<td>Adults</td>
<td>5506</td>
<td>393</td>
</tr>
</tbody>
</table>

AUC12 = Area under the curve for 12 h post-dose; C0h = pre-dose concentration during chronic administration.

Etravirine is often combined with ritonavir-boosted darunavir for treatment of HIV-infected adults with prior virologic failure. King et al. examined PK data from 37 pediatric patients receiving this combination, all receiving the maximum 200 mg etravirine dose. For both drugs, the estimated 90% confidence intervals for AUC and Cmin fell below targeted lower limits defined using data from studies in adults. While this
combination has been effective in a small cohort of HIV-infected adolescents,\(^8\) these data suggest a need for continued study of PK interactions involving etravirine and other ARV agents in pediatric patients.

**Toxicity**

The frequency, type, and severity of adverse drug reactions in pediatric subjects enrolled in the PIANO trial were comparable to those reported in adult subjects, except for rash, which was observed more frequently in pediatric subjects. The most common adverse drug reactions (in at least 2% of pediatric subjects) were rash and diarrhea. Rash (≥Grade 2) occurred in 15% of pediatric subjects. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The discontinuation rate for rash was 4%. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared with male subjects.

**References**

**Nevirapine (NVP, Viramune)**  (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

### Formulations

**Tablets:** immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg  
**Suspension:** 10 mg/mL

### Dosing Recommendations

#### Neonate/Infant Dose (≤14 Days):
- When used for prevention of perinatal transmission of HIV see [Perinatal Guidelines](#).
- Treatment dose is undetermined for infants aged ≤14 days (see Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants).

#### Pediatric Dose Immediate Release Formulation (>15 Days):
- See note below about initiation of therapy.
- **<8 Years:**
  - 200 mg/m² of body surface area (BSA)/dose (maximum dose of immediate release tablets is 200 mg twice daily).
- **≥8 Years:**
  - 120–150 mg/m² BSA/dose (maximum dose of immediate release tablets is 200 mg twice daily or extended release tablets 400 mg once daily).
  - When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m² dosage as the child grows, as long as there are no untoward effects.

**Note:** Nevirapine is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate dose administered twice daily. **However, in children ≤2 years of age some experts initiate nevirapine without a lead-in**

### Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

### Special Instructions

- Can be given without regard to food.
- Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14 day lead-in period, do not increase dose until rash resolves (see Major Toxicities section).
- Nevirapine XR tablets must be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for >14 days, nevirapine dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement).
- Most cases of nevirapine-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests (LFTs), is important during this period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of LFTs is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have LFTs performed. Nevirapine should be permanently
Pediatric Dose Extended Release Formulation (>6 Years)

- Patients >6 years who are already taking immediate release nevirapine twice daily can be switched to nevirapine XR without lead-in dosing as long as plasma RNA is undetectable.

Note: Nevirapine is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate dose administered once daily for the XR preparation. The total daily dose should not exceed 400 mg.

<table>
<thead>
<tr>
<th>BSA Range (m²)</th>
<th>NVP XR (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.58–0.83</td>
<td>200 mg once daily (2 x 100 mg)</td>
</tr>
<tr>
<td>0.84–1.16</td>
<td>300 mg once daily (3 x 100 mg)</td>
</tr>
<tr>
<td>≥1.17</td>
<td>400 mg once daily (1 x 400 mg)</td>
</tr>
</tbody>
</table>

Adolescent/Adult Dose:

- 200 mg twice daily or 400 mg XR once daily.

Note: For 200-mg regimen, initiate therapy with 200 mg once daily for the first 14 days and increase to 200 mg twice daily if there is no rash or other untoward effects. For 400-mg XR regimen, initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release nevirapine, XR tablets can be used without the 200-mg lead-in period. Patients must swallow nevirapine XR tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of nevirapine at the same time.

Nevirapine In Combination with Ritonavir-Boosted Lopinavir:

- A higher dose of ritonavir-boosted lopinavir may be needed. See Ritonavir-Boosted Lopinavir section.

discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.

- Shake suspension well and store at room temperature.

Metabolism

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).

- Dosing of nevirapine in patients with renal failure receiving hemodialysis: An additional dose of nevirapine should be given following dialysis.

- Dosing of nevirapine in patients with hepatic impairment: Nevirapine should not be administered to patients with moderate or severe hepatic impairment.
Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- Metabolism: Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; auto-induction of metabolism occurs in 2 to 4 weeks, with a 1.5- to 2-fold increase in clearance. There is potential for multiple drug interactions. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner but to a lesser extent than efavirenz. Altered adverse effect profiles related to elevated nevirapine levels have not been documented probably because there are alternative CYP metabolic pathways for nevirapine.\(^1\) Please see efavirenz section for further details.

- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions. Nevirapine should not be co-administered to patients receiving atazanavir (with or without ritonavir).

Major Toxicities

Note: These are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis.

- More common: Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated hepatic transaminases. Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. However, the risk of developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against a patient’s overall ability to tolerate the regimen and the current antiviral response.

- Less common (more severe): Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C infection, female gender, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 cell count \(\geq 250\) cells/mm\(^3\) in adult females and \(\geq 400\) cells/mm\(^3\) in adult males). In children, recent results indicate that there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage \(\geq 15\%\).\(^2\) Hypersensitivity reactions have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NVP.html).

Pediatric Use

Approval

Nevirapine is Food and Drug Administration (FDA) approved for treatment of HIV in children from infancy (aged \(\geq 15\) days) onward and remains a mainstay of therapy especially in resource-limited settings. It has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI)\(^3\)-\(^11\) In November 2012 the extended release tablet formulation was FDA-approved for use in children aged \(\geq 6\) years.
**Efficacy**

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission; nevirapine-based, combination antiretroviral therapy (cART) is less likely than ritonavir-boosted lopinavir-based cART to control virus load. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus ritonavir-boosted lopinavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure defined as <1 log decrease in HIV RNA in Weeks 12–24 or HIV RNA >400 copies/mL at Week 24) compared with 7% in the zidovudine/lamivudine/ritonavir-boosted lopinavir, $P = 0.0009$. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the ritonavir-boosted lopinavir arm, $P = 0.027$. Enrollment into the comparison study of nevirapine versus LPV/r in children aged 6 to 36 months not previously exposed to nevirapine has reported similar results, suggesting that ritonavir-boosted lopinavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients based on two trials: VERxVE and TRANxITION. VERxVE enrolled treatment-naive adults who received 200 mg of immediate-release nevirapine for 14 days before commencing daily dosing of nevirapine extended release or standard twice-daily dosing of immediate-release tablets. A backbone of tenofovir and emtricitabine was used. TRANxITION enrolled patients already receiving full-dose immediate-release nevirapine and randomized them to receive the extended-release tablets or remain on their current nevirapine regimen. Both studies have shown equivalent efficacy, adverse effect, and CD4 profiles through 144 weeks. Trial 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial performed in 85 HIV-1 infected pediatric subjects aged 3 years to <18 years who had received at least 18 weeks of immediate-release nevirapine and had plasma HIV-1 RNA <50 copies per mL prior to trial enrollment. Subjects were stratified according to age (3 to <6 years, 6 to <12 years, and 12 <18 years). Following a 10-day period with immediate-release nevirapine, subjects were treated with nevirapine XR tablets once daily in combination with other antiretrovirals (ARVs) for 10 days, after which steady-state pharmacokinetics were determined. Forty subjects who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of nevirapine XR through a minimum of 24 weeks of treatment. Of the 40 subjects who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with nevirapine XR, all 39 subjects continued to have plasma HIV-1 RNA less than 50 copies per mL. This dosage form was approved for use in children aged ≥6 years in November 2012.

**General Dosing Considerations**

Body surface area (BSA) has traditionally been used to guide nevirapine dosing for infants and young children. It is important to avoid under-dosing of nevirapine because a single point mutation in the HIV genome may confer non-nucleoside reverse transcriptase inhibitor resistance to both nevirapine and efavirenz. Younger children (≤8 years of age) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children aged >8 years.8,9 Because of this, it is recommended that dosing for children younger than age 8 years be 200 mg/m² of BSA per dose when given twice daily (immediate release tablet maximum dose 200 mg twice daily) or 400 mg/m² of body surface area per dose when administered once daily as the extended release preparation (maximum dose of the extended release preparation 400 mg/dose once daily). For children aged 8 years and older, the recommended dose is 120 mg/m² of BSA per dose (maximum dose 200 mg) administered twice daily to a maximum of 400 mg once daily when the extended release preparation is used in children aged ≥6 years. When adjusting the dose in a growing child, the milligram dose need not be decreased (from 200 mg/m² to 120 mg/m²) as the child reaches 8 years; rather, the milligram dose is left static as long as there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m² dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m² of BSA every 12 hours or 300 mg/m² per dose once daily if using the extended release preparation (maximum of 200 mg per dose twice daily of the immediate release tablets or 400 mg per dose once daily of the extended release tablets) regardless.
of age, as recommended in the FDA-approved product label.

**Dosing Considerations: Lead-In Requirement**

One explanation for the poorer performance of nevirapine in the P1060 trial was the potential for under-dosing during the lead-in period. This potential for under-dosing with an increased risk of resistance has led to the re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditional dosing of nevirapine is initiated with an age-appropriate dose once daily (200 mg/m² in infants ≥15 days of age and children <8 years using the immediate release preparations) during the first 2 weeks of treatment to allow for the auto-induction of the liver enzymes CYP3A and CYP2B6, which are involved in nevirapine metabolism. Studies, largely in adult cohorts, previously indicated the potential for greater drug toxicity without this lead-in. The CHAPAS-1 Trial randomized 211 children to initiate cART with nevirapine without a lead-in (age-appropriate dose twice daily of the immediate release preparation) or with a lead-in (age-appropriate dose once daily of the immediate release preparation) for 2 weeks followed by standard twice-daily dosing of the immediate release preparation. Children were followed for a median of 92 weeks (68–116), and there was no difference in grade 3 or 4 adverse events between the two groups. The group initiating nevirapine without a lead-in had a statistically significant increase in grade 2 rash, but the majority of subjects were able to continue nevirapine therapy after a brief interruption. CD4 and virologic endpoints were no different through 96 weeks. In a sub-study of this trial, the investigators looked at nevirapine levels 3 to 4 hours after a morning dose of nevirapine after 2 weeks of therapy. For children <2 years of age, 13% (3/23) initiating at full dose versus 32% (7/22) initiating at half dose had subtherapeutic NVP levels (<3 mg/L) at 2 weeks (p = 0.16). There were no rash events in the substudy group aged <2 years and in the parent CHAPAS study there was a strong age effect on rash occurrence (increased risk with increasing age), suggesting that a lead-in dose may not be necessary in young patients.

Additional trials are in development or are underway to further evaluate the potential of initiating nevirapine therapy without the lead-in dose in treatment-naive children. Reinitiating half-dose nevirapine for another 2 weeks in those children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes, and the results of CHAPAS-1, the panel recommends restarting full-dose nevirapine in children who interrupt therapy for 14 days or less.

**Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants**

For infants aged ≤14 days and for premature infants (until 42 weeks corrected gestational age), pharmacokinetic (PK) data are currently inadequate to formulate an effective complete cART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of cART. Reports of cardiovascular, renal, and central nervous system toxicity associated with ritonavir-boosted lopinavir in young infants preclude the administration of this agent in the first 2 weeks of life. Currently, a study of early treatment is being developed in the International Maternal Pediatric Adolescent AIDS Clinical Trials network; based on PK modeling, an investigational dose of 6 mg/kg administered twice daily for nevirapine in full-term infants will be tested. Providers considering treatment of infants aged <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will involve weighing the risks and benefits of using unapproved cART dosing, and incorporate case-specific factors such as exposure to ARV prophylaxis.

**References**


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*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*
Rilpivirine (RPV, Edurant, TMC 278) (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

**Formulations**

- **Tablet:** 25 mg

- **Combination Tablet:**

  *With Emtricitabine and Tenofovir Disoproxil Fumarate (Tenofovir):*
  - Rilpivirine 25 mg + Emtricitabine 200 mg + Tenofovir 300 mg (Complera)

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**Dosing Recommendations**

- **Neonate/Infant Dose:**
  - Not approved for use in neonates/infants.

- **Pediatric Dose:**
  - Not approved for use in children. A clinical trial in treatment-naive adolescents (aged 12–18 years) is under way using a 25-mg dose.

- **Adolescent (>18 years)/Adult Dose (Antiretroviral-Naive Patients Only):**
  - 25 mg once daily

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**Selected Adverse Events**

- Depression, mood changes
- Insomnia
- Headache
- Rash

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**Special Instructions**

- Instruct patients to take rilpivirine with a meal of at least 500 calories (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Antacids should only be taken either at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug with a known risk of torsades de pointes (http://www.qtdrugs.org/).
- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

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**Metabolism**

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal
disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.

**Drug Interactions**

- **Metabolism:** Rilpivirine is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before rilpivirine is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions.

**Major Toxicities**

- **More common:** Insomnia, headache, and rash
- **Less common (more severe):** Depression or mood changes

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)).

**Pediatric Use**

Rilpivirine is approved in combination with other ARV agents for treatment-naive, HIV-infected adults with viral load ≤100,000 copies/mL. The pharmacokinetics, safety, and efficacy of rilpivirine in pediatric patients have not been established. An international trial currently under way is investigating a 25-mg dose of rilpivirine in combination with two nucleoside reverse transcriptase inhibitors in antiretroviral-naive children aged 12 to 18 years who weigh ≥32 kg and have a viral load ≤100,000 copies/mL.

**Reference**

Protease Inhibitors (PIs)

- Atazanavir (ATV, Reyataz)
- Darunavir (DRV, Prezista)
- Fosamprenavir (FPV, Lexiva)
- Indinavir (IDV, Crixivan)
- Lopinavir/Ritonavir (LPV/r, Kaletra)
- Nelfinavir (NFV, Viracept)
- Ritonavir (RTV, Norvir)
- Saquinavir (SQV, Invirase)
- Tipranavir (TPV, Aptivus)
Dosing Recommendations

Neonate/Infant Dose:
- Not approved for use in neonates/infants. ATV should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric Dose:
- Data are insufficient to recommend dosing in children aged <6 years.

For Children Aged ≥6 to <18 Years

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Once-Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to &lt;20 kg</td>
<td>ATV 150 mg plus RTV 100 mg, both once daily with food</td>
</tr>
<tr>
<td>20 to &lt;40 kg</td>
<td>ATV 200 mg plus RTV 100 mg, both once daily with food*</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>ATV 300 mg plus RTV 100 mg, both once daily with food</td>
</tr>
</tbody>
</table>

* Some experts would increase ATV to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with tenofovir (see text for discussion).

For Treatment-Naive Pediatric Patients who do not Tolerate Ritonavir (RTV):
- ATV boosted with RTV (ATV/r) is preferred for children and adolescents. Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children aged <13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see Pediatric Use).
- Only RTV-boosted ATV should be used in combination with tenofovir disoproxil fumarate (TDF) because TDF decreases ATV exposure.

Adolescent (Aged ≥18 to 21 Years)/Adult Dose Antiretroviral-Naive Patients:
- ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food (if unboosted ATV is

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram (ECG) PR interval, first-degree symptomatic atrioventricular (AV) block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with RTV boosting)

Special Instructions

- Administer ATV with food to enhance absorption.
- Because ATV can prolong the ECG PR interval, use ATV with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions for recommendations on dosing ATV when the drug is co-administered with H2 receptor antagonists). When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is co-administered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients receiving PPIs should receive no more than a 20-mg dose equivalent of
Drug Interactions (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Metabolism:** Atazanavir is both a substrate and an inhibitor of the cytochrome P (CYP) 3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.

- A patient’s medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug is administered.

- **Nucleoside reverse transcriptase inhibitors (NRTIs):** Tenofovir disoproxil fumarate (tenofovir) decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.

- **Non-nucleoside reverse transcriptase inhibitors:** Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be co-administered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be co-administered with atazanavir in treatment-experienced patients, but may be used in combination with atazanavir 400 mg omeprazole, which should be taken approximately 12 hours before boosted ATV. Co-administration of ATV with PPIs is not recommended in treatment-experienced patients.

- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

- **Metabolism**
  - ATV is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).
  - Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer’s prescribing information for dosage adjustment in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
  - Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.
plus ritonavir boosting in treatment-naive adults.

- **Integrase Inhibitors:** Atazanavir is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir. This interaction may not be clinically significant.

- **Absorption:** Atazanavir absorption is dependent on low gastric pH. When atazanavir is administered with medications that alter gastric pH, dosage adjustment is indicated. No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors (PPIs) in adults are as follows:

- **Antacids:** Atazanavir concentrations are decreased when the drug is co-administered with antacids and buffered medications (including buffered didanosine formulations); therefore, atazanavir should be administered 2 hours before or 1 hour after these medications.

- **H2-receptor antagonists (unboosted atazanavir in treatment-naive patients):** H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the antiretroviral (ARV) agent. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2 receptor antagonist (a single dose of an H2 receptor antagonist should not exceed a dose comparable to famotidine 20 mg; a total daily dose should not exceed a dose comparable to famotidine 40 mg).

- **H2-receptor antagonists (boosted atazanavir in treatment-naive or -experienced patients):** H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV. Dose recommendations for H2 receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily for treatment-naive patients or a ≤20-mg dose equivalent of famotidine twice daily for treatment-experienced patients. Boosted atazanavir (atazanavir 300 mg plus ritonavir 100 mg) should be administered simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist.

- **H2-receptor antagonists (boosted atazanavir with tenofovir):** Treatment-experienced patients using both tenofovir and H2-receptor antagonists should be given an increased dose of atazanavir (atazanavir 400 mg plus ritonavir 100 mg plus tenofovir 300 mg).

- **PPIs:** Co-administration of PPIs with atazanavir is expected to substantially decrease atazanavir plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naive patients are ≤20-mg dose equivalent of omeprazole taken approximately 12 hours before boosted atazanavir (atazanavir 300 mg + ritonavir 100 mg). Co-administration of atazanavir with PPIs is not recommended in treatment-experienced patients.

**Major Toxicities**

- **More common:** Indirect hyperbilirubinemia that can result in jaundice or icterus, but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesia.

- **Less common:** Prolongation of PR interval of electrocardiogram. Abnormalities in atrioventricular (AV) conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild to moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other protease inhibitors (PIs). However, the addition of ritonavir to atazanavir is associated with lipid abnormalities but to a lesser extent than with other boosted PIs.

- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or hepatitis C are at increased risk).
**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/ATV.html](http://hivdb.stanford.edu/pages/GRIP/ATV.html)).

**Pediatric Use**

**Approval**

Atazanavir is FDA-approved for use in children and adolescents. Ritonavir-boosted atazanavir is generally preferred over unboosted atazanavir and is used in combination with NRTIs for treatment in children aged ≥6 years.

**Pharmacokinetics and Dosing**

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of ritonavir boosting, atazanavir can achieve protocol-defined pharmacokinetic (PK) targets, but only when used at higher doses of atazanavir (on a mg/kg body weight or mg/m² body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children older than 6 but younger than 13 years of age required atazanavir dosing of 520 mg/m² per day of atazanavir capsule formulation to achieve PK targets. Doses required for older adolescents were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents aged >13 years required atazanavir dosing of 620 mg/m² per day.¹ In this study, the areas under the curve (AUCs) for the unboosted arms were similar to the ritonavir-boosted atazanavir groups but the maximum plasma concentration (C_max) was higher and minimum plasma concentration (C_min) lower for the unboosted arms. Median doses of atazanavir in mg/m² both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring (TDM) is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.² Higher target trough concentrations may be required in PI-experienced patients.

**Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A¹**

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Was ATV Given with RTV Boosting?</th>
<th>ATV Median Dose (mg/m²*)</th>
<th>ATV Median Dose (mg*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–13 years</td>
<td>No</td>
<td>509</td>
<td>475</td>
</tr>
<tr>
<td>&gt;13 years</td>
<td>Yes</td>
<td>208</td>
<td>200</td>
</tr>
<tr>
<td>&gt;13 years</td>
<td>No</td>
<td>620</td>
<td>900</td>
</tr>
<tr>
<td>&gt;13 years</td>
<td>Yes</td>
<td>195</td>
<td>350</td>
</tr>
</tbody>
</table>

* Dose satisfied protocol-defined AUC/PK parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. TDM was used to determine patient-specific dosing in this trial.

In the report of the P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m² in pediatric subjects when dosed with ritonavir.¹ However, given the available atazanavir capsule dose strengths, it is not possible to administer the exact mg dose equivalent to the body surface area-based dose. A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A) supports the use of the following weight-based atazanavir/ritonavir doses that are listed in the current FDA-approved product label for children aged ≥6 to <18 years:

- 150/100 mg (15 to <20 kg)
- 200/100 mg (20 to <40 kg)
- 300/100 mg (≥40 kg)³
The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling. The authors acknowledge that atazanavir/ritonavir at 250/100 mg appeared to be a more appropriate dose than atazanavir/ritonavir at 200/100 mg for the 35 to <40 kg weight group; however, this dose is not achievable with current capsule dose strengths (150, 200, and 300 mg). Some experts would increase ATV to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with tenofovir.

A third pediatric study of atazanavir, a population PK study of 51 children with mean age 14.3 years and weight 51 kg that targeted mean adult exposure for a 300/100 mg atazanavir/ritonavir dosage, showed that the following atazanavir/ritonavir doses might be an appropriate alternative to the FDA recommendations: 200/100 (25–39 kg), 250/100 mg (39–50 kg) and 300/100 (>50 kg). In addition, simulations suggested that the following doses should be used in children when combined with 300 mg tenofovir: 250/100 mg for children weighing 35 to 39 kg, then 300/100 mg for children weighing over 39 kg. The authors conclude that these recommendations should be prospectively confirmed. Again, the 250-mg dose is not achievable with current capsule dose strengths and some experts would increase ATV to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with tenofovir.

**Toxicity**

8.5% (11 of 129) of patients enrolled in the IMPAACT/PACTG 1020A trial had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram abnormalities were observed in a small number of patients: Grade 3 QTc prolongation in 1 patient, Grade 2 PR or HR changes in 9 patients, and Grade 3 PR prolongations in 3 patients. No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs.

**References**


Darunavir (DRV, Prezista)  (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 75 mg, 150 mg, 400 mg, 600 mg, 800 mg
Oral suspension: 100 mg/mL

Dosing Recommendations

Note: DRV should not be used without low-dose boosting ritonavir (RTV).

Neonate/Infant Dose:
- Not approved for use in neonates/infants.

Pediatric Dose: Aged <3 years:
- Do not use DRV in children aged <3 years or weighing <10 kg because of concerns related to seizures and death in infant rats due to immaturity of the blood-brain barrier and liver metabolic pathways.
- The dosing for antiretroviral treatment-naive and treatment-experienced pediatric patients aged ≥3 years (includes patients with or without one or more DRV resistance-associated mutations)

Aged 3 to <18 Years and Weight >10 kg

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose (twice daily with food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to &lt;11 kg*</td>
<td>DRV 200 mg (2.0 mL) plus RTV 32 mg (0.4 mL)</td>
</tr>
<tr>
<td>11 to &lt;12 kg*</td>
<td>DRV 220 mg (2.2 mL) plus RTV 32 mg (0.4 mL)</td>
</tr>
<tr>
<td>12 to &lt;13 kg*</td>
<td>DRV 240 mg (2.4 mL) plus RTV 40 mg (0.5 mL)</td>
</tr>
<tr>
<td>13 to &lt;14 kg*</td>
<td>DRV 260 mg (2.6 mL) plus RTV 40 mg (0.5 mL)</td>
</tr>
<tr>
<td>14 to &lt;15 kg</td>
<td>DRV 280 mg (2.8 mL) plus RTV 48 mg (0.6 mL)</td>
</tr>
<tr>
<td>15 to &lt;30 kg</td>
<td>DRV 375 mg (combination of tablets or 3.8 mL) plus RTV 48 mg (0.6 mL)</td>
</tr>
<tr>
<td>30 to &lt;40 kg</td>
<td>DRV 450 mg (combination of tablets or 4.6 mL) plus RTV 100 mg (tablet or 1.25 mL)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>DRV 600 mg (tablet or 6 mL) plus RTV 100 mg (tablet or 1.25 mL)</td>
</tr>
</tbody>
</table>

Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- In patients with one or more DRV-associated mutation(s), DRV should be used only twice daily. DRV resistance-associated mutations are: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- DRV must be administered with food, which increases area under the curve (AUC) and maximum plasma concentration (C_max) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- DRV contains a sulfonamide moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires co-administration of tablets with different strengths to achieve the recommended doses depending on weight band. Careful instructions to caregivers when recommending a combination of different-strength tablets is very important. Store DRV tablets and oral suspension at room temperature (25°C or 77°F). Oral suspension should be stored in the original container and shaken well before dosing.
**Adolescent (Aged ≥12 Years)/Adult Dose**
(Treatment-Naive or Antiretroviral Therapy-Experienced with no DRV Resistance-Associated Mutations)

30 to <40 kg:
- DRV 675 mg (combination of tablets or 6.8 mL) plus RTV 100 mg (tablet or 1.25 mL) once daily

≥40 kg:
- DRV 800 mg (tablet or combination of tablets or 8 mL) plus RTV 100 mg (tablet or 1.25 mL) once daily

- The 675 mg DRV dose is rounded for convenience.
- RTV 80 mg/mL oral solution.

**Adolescent (Aged ≥18 Years)/Adult Dose**
(Treatment Experienced with at Least One DRV Resistance-Associated Mutation):
- DRV 600 mg plus RTV 100 mg, both twice daily with food.

**Drug Interactions**
(see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. Potential exists for multiple drug interactions.
  - Co-administration of darunavir/ritonavir is contraindicated with drugs that are highly dependent on the CYP3A clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - When darunavir plus ritonavir twice daily was used in combination with etravirine in 40 HIV-infected patients aged 11 to 20 years, both darunavir and etravirine exposure were lower than that found in adults. When darunavir plus ritonavir twice daily was used in combination with tenofovir in 13 HIV-infected patients aged 13 to 16 years, both tenofovir and darunavir exposures were lower than those found in adults treated with the same combination. No dose adjustment is currently recommended for the combination of darunavir/ritonavir with either of these drugs, but caution is advised and therapeutic drug monitoring may be potentially useful.

- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions.

**Metabolism**
- Cytochrome (CYP) P450 3A4 inhibitor and substrate.

**Dosing in Patients with Hepatic Impairment:**
- DRV is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV is not recommended in patients with severe hepatic impairment.

**Dosing in Patients with Renal Impairment:**
- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.
Major Toxicities

- **More common:** Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- **Less common:** Skin rash, including erythema multiforme and Stevens-Johnson syndrome. Fever and elevated hepatic transaminases. Lipid abnormalities.
- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (such as hepatitis B or hepatitis C virus coinfection, or those with baseline elevation in transaminases).

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/DRV.html](http://hivdb.stanford.edu/pages/GRIP/DRV.html)).

Pediatric Use

Approval

Darunavir co-administered with ritonavir is approved by the Food and Drug Administration (FDA) as a component of combination antiretroviral therapy in treatment-naive and treatment-experienced children aged 3 years and older.

Efficacy

Data from the randomized, open-label, multicenter pediatric trial, which evaluated darunavir with ritonavir twice daily among 80 treatment-experienced children aged 6 to <18 years, demonstrated that 66% of patients had week 24 plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL. In another clinical trial (TMC114-C228) involving 27 children (3 to <6 years of age) from Argentina, Brazil, India, Kenya, and South Africa, 59% of children (out of 27) and 71% (out of 20) had viral load <50 copies/mL at week 24 and at week 48, respectively.

Pharmacokinetics

Pharmacokinetics in Younger Children

Administration of twice-daily ritonavir-boosted darunavir oral suspension in children aged 3 to <6 years and weighing 10 to <20 kg was conducted in 27 children (see above) who experienced failure of their previous antiretroviral therapy regimen and had fewer than 3 darunavir resistance mutations on genotypic testing. The darunavir AUC(0–12h), measured as a percent of the adult AUC value, was 128% overall: 140% in subjects weighing 10 to <15 kg and 122% in subjects weighing 15 to <20 kg.

Pharmacokinetics in Older Children

Using darunavir tablets and ritonavir liquid or tablets, initial pediatric pharmacokinetic (PK) evaluation was based upon a Phase II randomized, open-label, multi-center study that enrolled 80 treatment-experienced children and adolescents aged 6 to <18 years and weighing ≥20 kg. In Part I of the trial, a weight-adjusted dose of darunavir 9 to 15 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with 24-hour area under the curve (AUC)24h of 81% and pre-dose concentration (C0h) of 91% of the corresponding adult PK parameters. A pediatric dose 20% to 33% higher than the directly scaled adult dose was needed to achieve drug exposure similar to that found in adults and was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 to 19 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily. This resulted in darunavir AUC24h of 123276 ng*h/mL (range 71850–201520) and C0h of 3693 ng/mL (range 1842–7191), 102% and 114% of the respective PK values in
Doses were given twice daily and were stratified by body weight bands of 20 to <30 kg and 30 to <40 kg. Based on the findings in the safety and efficacy portion of the study, current weight-band doses of twice-daily ritonavir-boosted darunavir for treatment-experienced pediatric patients with weight >20 to <40 kg were selected (see Table A).

**Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Backbone (Children Aged 3–18 Years and Adults Aged >18 Years).**

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Dose of DRV/RTV</th>
<th>AUC\textsubscript{12h} (mcg*h/mL) Median\textsuperscript{a}</th>
<th>C\textsubscript{0h} (ng/mL) Median\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to &lt;15 kg\textsuperscript{a}</td>
<td>13</td>
<td>20/3 mg/kg</td>
<td>66.0</td>
<td>3,533</td>
</tr>
<tr>
<td>10 to &lt;15 kg\textsuperscript{a}</td>
<td>4</td>
<td>25/3 mg/kg</td>
<td>116.0</td>
<td>8,522</td>
</tr>
<tr>
<td>15 to &lt;20 kg\textsuperscript{a}</td>
<td>11</td>
<td>20/3 mg/kg</td>
<td>54.2</td>
<td>3,387</td>
</tr>
<tr>
<td>15 to &lt;20 kg\textsuperscript{a}</td>
<td>14</td>
<td>25/3 mg/kg</td>
<td>68.6</td>
<td>4,365</td>
</tr>
<tr>
<td>Aged 6 to &lt;12 years\textsuperscript{b}</td>
<td>24</td>
<td>Weight bands\textsuperscript{b}</td>
<td>56.4</td>
<td>3,354</td>
</tr>
<tr>
<td>Aged 12 to &lt;18 years\textsuperscript{b}</td>
<td>50</td>
<td>Weight bands\textsuperscript{b}</td>
<td>66.4</td>
<td>4,059</td>
</tr>
<tr>
<td>Adults aged &gt;18 years, (3 studies)\textsuperscript{c}</td>
<td>285/278/119</td>
<td>600/100 mg</td>
<td>54.7–61.7</td>
<td>3,197–3,539</td>
</tr>
</tbody>
</table>

\textsuperscript{a} FDA pharmacokinetics review 2011

\textsuperscript{b} Weight band dosing was with darunavir/ritonavir at doses of 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for \geq 40 kg. Data from FDA pharmacokinetics review 2008

\textsuperscript{c} Product label

**Dosing**

**Dosing of Ritonavir with Darunavir**

A separate study in 19 Thai children used ritonavir 100 mg capsule twice daily as the boosting dose with twice-daily darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30–40 kg), and 600 mg twice daily (body weight \geq 40 kg).\textsuperscript{8} The darunavir exposures with 100-mg ritonavir twice daily were similar to those obtained in the studies with lower (<100 mg) liquid preparation based ritonavir doses.\textsuperscript{7,8} The tolerability and PK data from this small study support the higher doses of ritonavir boosting with 100-mg capsule or tablet in children with body weight \geq 20 kg, particularly when lower dose formulations are unavailable or if a child does not tolerate the liquid ritonavir formulation. Data are not available to evaluate the safety and tolerability of using ritonavir 100 mg tablet/capsule formulations in children who weigh less than 20 kg.

**Frequency of Administration**

In February 2013, FDA approved the use of darunavir once daily for treatment-naive children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). To derive once-daily pediatric dosing recommendations for younger pediatric subjects aged 3 to <12 years weighing 10 to <40 kg, population PK modeling and simulation was used.\textsuperscript{6} A dedicated pediatric trial evaluating once-daily darunavir with ritonavir dosing in children aged 6 to <12 years was not conducted. No efficacy data have been obtained regarding use of once-daily darunavir with ritonavir in treatment-naive or treatment-
experienced children aged <12 years. Therefore, the Panel recommends dosing darunavir with ritonavir only twice daily in children aged >3 years and <12 years. The Panel recommends that once-daily darunavir with ritonavir be used only in treatment-naive and treatment-experienced adolescents aged ≥12 years and without darunavir resistance-associated mutations. If darunavir and ritonavir are used once daily in children aged <12 years, the Panel recommends conducting PK (measurement of plasma concentrations and inhibitory quotient) evaluation (see Therapeutic Drug Monitoring) and close monitoring of viral load.

FDA approval was based on the results from two small pediatric trials: TMC114-C230 evaluating once-daily dosing in treatment-naive adolescents aged 12 to 18 years and weighing ≥40 kg (see below) and the TMC114-C228 sub-trial evaluating once-daily dosing in treatment-experienced children aged 3 to <6 years (see below).

### Table B. FDA-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weight >10 Kg Who Are Antiretroviral Treatment-Naive or Treatment-Experienced With No DRV Resistance-Associated Mutations

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose (once daily with food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to &lt;11 kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DRV 350 mg (3.6 mL&lt;sup&gt;b&lt;/sup&gt;) plus RTV 64 mg (0.8 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>11 to &lt;12 kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DRV 385 mg (4 mL&lt;sup&gt;b&lt;/sup&gt;) plus RTV 64 mg (0.8 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>12 to &lt;13 kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DRV 420 mg (4.2 mL) plus RTV 80 mg (1 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>13 to &lt;14 kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DRV 455 mg (4.6 mL&lt;sup&gt;b&lt;/sup&gt;) plus RTV 80 mg (1 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>14 to &lt;15 kg</td>
<td>DRV 490 mg (5 mL&lt;sup&gt;b&lt;/sup&gt;) plus RTV 80 mg (1 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>15 to &lt;30 kg</td>
<td>DRV 600 mg (tablet or combination of tablets or 6 mL) plus RTV 100 mg (tablet or 1.25 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>30 to &lt;40 kg</td>
<td>DRV 675 mg (combination of tablets or 6.8 mL&lt;sup&gt;b,d&lt;/sup&gt;) plus RTV 100 mg (tablet or 1.25 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>DRV 800 mg (tablet or combination of tablets or 8 mL&lt;sup&gt;d&lt;/sup&gt;) plus RTV 100 mg (tablet or 1.25 mL&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The dose in children weighing 10–15 kg is 35 mg/kg DRV and 7 mg/kg RTV per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.

<sup>b</sup> RTV 80 mg/mL oral solution.

<sup>c</sup> The 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.

<sup>d</sup> The 6.8-mL and 8-mL DRV doses can be taken as two (3.4 mL and 4 mL, respectively) administrations with the included oral dosing syringe, or as one syringe when provided by pharmacy or medical office.

### Once-Daily Administration in Children Aged <12 Years

As part of the TMC114-C228 trial that evaluated twice-daily dosing in treatment-experienced children aged 3 to <12 years, once-daily dosing of darunavir for 2 weeks with PK evaluation was conducted as a sub-study, after which the participants switched back to the twice-daily regimen. The ritonavir-boosted darunavir dosage for once-daily use in the trial, based on PK simulation (which did not include a relative bioavailability factor), was 40 mg/kg of darunavir co-administered with approximately 7 mg/kg of ritonavir once daily for children weighing <15 kg, and ritonavir-boosted darunavir 600 mg/100 mg once daily for children weighing ≥15 kg. The PK data obtained from 10 children aged 3 to 6 years in this sub-study (Table C) were included as part of the population PK modeling and simulation, which proposed the FDA-approved dose for once-daily darunavir with ritonavir in children aged 3 to <12 years.
Once-Daily Administration in Adolescents Age ≥12 Years

A sub-study of once-daily dosing of darunavir 800 mg with ritonavir 100 mg in 12 treatment-naive adolescents (aged 12–17 years and ≥40 kg body weight) demonstrated darunavir exposures similar to those seen in adults treated with once-daily darunavir (see Table D). In this study, the proportion of patients with viral load <50 copies/mL and <400 copies/mL at 48 weeks was 83.3% and 91.7%, respectively. Interestingly, no relationship was observed between darunavir AUC_{24h} and C_{0h} and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those in adults with once-daily dosing in another study in which a single dose darunavir 800 mg with ritonavir 100 mg tablets was administered to 24 subjects with median age 19.5 years (14–23 years). However, darunavir exposures were slightly below the lower target concentrations in adolescent patients age 14 to 17 years (n = 7) within the cohort, suggesting the potential need for higher doses in younger adolescents. A single case report suggests the potential therapeutic benefit of virologic suppression using an increased darunavir dose with standard ritonavir booster following therapeutic drug monitoring in a highly treatment-experienced adolescent patient.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3–6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Once-Daily Darunavir Sub-Study (n=10)</th>
<th>Adult Study (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV AUC_{24h} geometric mean, ng<em>h/mL (SD</em>)</td>
<td>115 (40.6)</td>
<td>89.7 (27.0)</td>
</tr>
<tr>
<td>DRV C_{0h} geometric mean, ng/mL (SD*)</td>
<td>3029 (1715)</td>
<td>2027 (1168)</td>
</tr>
</tbody>
</table>

*SD = standard deviation

Table D. Darunavir Pharmacokinetics with Once-Daily Administration (Adolescents Aged ≥12 Years and Adults Aged >18 Years)

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Dose of DRV/RTV</th>
<th>AUC_{24h} (mcg*h/mL) median</th>
<th>C_{0h} (ng/mL) median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 12–17 years (mean 14.6)</td>
<td>12</td>
<td>800/100 mg</td>
<td>86.7</td>
<td>2,141</td>
</tr>
<tr>
<td>Aged 14–23 years (mean 19.5)</td>
<td>24</td>
<td>800/100 mg</td>
<td>69.5</td>
<td>1,300</td>
</tr>
<tr>
<td>Adults aged &gt;18 years (2 studies)*</td>
<td>335/280</td>
<td>800/100 mg</td>
<td>87.8–87.9</td>
<td>1,896–2,041</td>
</tr>
</tbody>
</table>

* Product label

The efficacy of once-daily darunavir has been established only within a small cohort of adolescent patients with 48 weeks data on virologic and immunologic outcomes.

Formulations:

Palatability

Darunavir oral suspension is better tasting than the ritonavir oral solution needed for PK boosting, which is seen as a greater challenge to palatability. In a Phase II initial approval study, 27 of the 80 participants switched from the ritonavir liquid solution to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills. Switching to the higher dose of ritonavir for the palatability of the boosting drug can be considered if the liquid formulation represents a barrier.

References

Opportunistic Infections (CROI); 2012; Seattle, WA.


12. King J, Hazra R, et al. Pharmacokinetics of darunavir 800 mg with ritonavir 100mg once daily in HIV+ adolescents and young adults. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 2013; Atlanta, GA.

Fosamprenavir (FPV, Lexiva) (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

**Formulations**

<table>
<thead>
<tr>
<th>Tablets: 700 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral suspension: 50 mg/mL</td>
</tr>
</tbody>
</table>

**Dosing Recommendations**

**Pediatric Dose (Aged >6 Months to 18 Years):**

- Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but not recommended by The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants at least 4 weeks of age and for treatment-experienced infants at least 6 months of age; however, the Panel does not recommend use in infants younger than 6 months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks gestation or greater.

**Aged ≥6 Months to 18 Years:**

**Twice-Daily Dosage Regimens by Weight for Pediatric Patients at Least 6 Months of Age Using Lexiva Oral Suspension with Ritonavir**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose Fosamprenavir Plus Ritonavir Both twice daily* with food</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 kg</td>
<td>fosamprenavir 45 mg/kg plus ritonavir 7 mg/kg</td>
</tr>
<tr>
<td>11 kg to &lt;15 kg</td>
<td>fosamprenavir 30 mg/kg plus ritonavir 3 mg/kg</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg</td>
<td>fosamprenavir 23 mg/kg plus ritonavir 3 mg/kg</td>
</tr>
<tr>
<td>≥20 kg</td>
<td>fosamprenavir 18 mg/kg plus ritonavir 3 mg/kg</td>
</tr>
</tbody>
</table>

* Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

**Selected Adverse Events**

- Diarrhea, nausea, vomiting
- Skin rash (fosamprenavir has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

**Special Instructions**

- Fosamprenavir tablets with ritonavir should be taken with food. Pediatric patients should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine should take fosamprenavir at least 1 hour before or after antacid or didanosine use.
- Fosamprenavir contains a sulfonamide moiety. The potential for cross sensitivity between fosamprenavir and other drugs in the sulfonamide class is unknown. Fosamprenavir should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well before use. Refrigeration is not required.

**Metabolism**

- The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.
- Amprenavir is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.
**Note:** When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing ≥39 kg. Ritonavir pills can be used in patients weighing ≥33 kg. Once-daily dosing is not recommended for any pediatric patient.

**Adolescent/Adult (Aged >18 Years) Dose:**
- Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

**HRV-Naive Patients**
Boosted with Ritonavir, Twice-Daily Regimen:
- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.

Boosted with Ritonavir, Once-Daily Regimen:
- Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily.

**Protease Inhibitor (PI)-Experienced Patients:**
- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.
- Note: Once-daily administration of fosamprenavir plus ritonavir is not recommended.

**Fosamprenavir in Combination with Efavirenz (Adult):**
- Only fosamprenavir boosted with ritonavir should be used in combination with efavirenz.

**Twice-Daily Regimen:**
- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily plus efavirenz 600 mg once daily.

**PI-Naive Patients Only, Once-Daily Regimen:**
- Fosamprenavir 1400 mg plus ritonavir 300 mg plus efavirenz 600 mg, all once daily.

**Drug Interactions** (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)
- Fosamprenavir has the potential for multiple drug interactions.
- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.
**Major Toxicities**

- **More common:** Vomiting, nausea, diarrhea, perioral paresthesia, headache, rash, and lipid abnormalities.

- **Less common (more severe):** Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.

- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.

- **Pediatric specific:** Vomiting was more frequent in children than in adults in clinical trials of fosamprenavir with ritonavir, (20%–36% vs. 10%, respectively) and in trials of fosamprenavir without ritonavir (60% vs. 16%, respectively). Neutropenia was also more common in children across all the trials (15% vs. 3%, respectively).

**Resistance**


**Pediatric Use**

**Approval**

Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) recommends use only in children aged 6 months or older. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naive children aged 2 to 5 years, the Panel does not recommend unboosted fosamprenavir for this—or any other—age group because of low exposures and because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.

**Efficacy and Pharmacokinetics**

Dosing recommendations for fosamprenavir are based on 3 pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In 2 open-label trials in both treatment-experienced and treatment-naive children from ages 2 to 18 years, fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children; therefore, once-daily dosing is not recommended for pediatric patients.

**Pharmacokinetics in Infants**

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naive infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months. Exposures in those younger than age 6 months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir. Given these low exposures, limited data, large volumes, unpleasant taste, and the availability of alternatives for infants and young children, the Panel does not recommend fosamprenavir use in infants younger than 6 months.
<table>
<thead>
<tr>
<th>Population</th>
<th>Dose</th>
<th>$\text{AUC}_{0-24}$ (mcg·hr/mL) Except Where Noted</th>
<th>$C_{\text{min}}$ (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt;6 months</td>
<td>45 mg fosamprenavir/10 mg ritonavir per kg twice daily</td>
<td>26.6$^a$</td>
<td>0.86</td>
</tr>
<tr>
<td>Children aged 2 to &lt;6 years</td>
<td>30 mg fosamprenavir per kg twice daily (no ritonavir)</td>
<td>22.3$^a$</td>
<td>0.513</td>
</tr>
<tr>
<td>Children weighing &lt;11 kg</td>
<td>45 mg fosamprenavir/7 mg ritonavir per kg twice daily</td>
<td>57.3</td>
<td>1.65</td>
</tr>
<tr>
<td>Children weighing 15 to &lt;20 kg</td>
<td>23 mg fosamprenavir/3 mg ritonavir per kg twice daily</td>
<td>121.0</td>
<td>3.56</td>
</tr>
<tr>
<td>Children weighing ≥20 kg</td>
<td>18 mg fosamprenavir/3 mg ritonavir per kg twice daily (maximum 700/100 mg)</td>
<td>72.3–97.9</td>
<td>1.98–2.54</td>
</tr>
<tr>
<td>Adults</td>
<td>1400 mg fosamprenavir twice daily (no ritonavir)</td>
<td>33</td>
<td>0.35</td>
</tr>
<tr>
<td>Adults</td>
<td>1400 mg fosamprenavir/100–200 mg ritonavir once daily</td>
<td>66.4–69.4</td>
<td>0.86–1.45</td>
</tr>
<tr>
<td>Adults</td>
<td>700 mg fosamprenavir/100 mg ritonavir twice daily</td>
<td>79.2</td>
<td>2.12</td>
</tr>
</tbody>
</table>

$^a$ $\text{AUC}_{0-12}$ (mcg·hr/mL)

**Note:** Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies, therefore, area under the curve and $C_{\text{min}}$ are not available.

**References**


**Indinavir (IDV, Crixivan)** (Last updated November 1, 2012; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

**Formulations**

Capsules: 100 mg, 200 mg, and 400 mg

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**Dosing Recommendations**

**Neonate/Infant Dose:**
- Not approved for use in neonates/infants.
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

**Pediatric Dose:**
- Not approved for use in children.
- A range of indinavir doses (234–500 mg/m$^2$ body surface area) boosted with low-dose ritonavir has been studied in children (see text below).

**Adolescent/Adult Dose:**
- 800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours

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**Selected Adverse Events**

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

---

**Special Instructions**

- When given in combination with ritonavir, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If co-administered with didanosine, give indinavir and didanosine ≥1 hour apart on an empty stomach.
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

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**Metabolism**

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate
- **Dosing in patients with hepatic impairment**: Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.
Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Metabolism**: CYP3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with indinavir.

Major Toxicities

- **More common**: Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritus, and rash. Nephrolithiasis/uro lithiasis with indinavir crystal deposits.
- **Less common (more severe)**: Fat maldistribution.
- **Rare**: New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).
- **Pediatric specific**: The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/indinavir.html).

Pediatric Use

Approval

Indinavir has not been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Although indinavir was one of the first protease inhibitors to be studied in children, its use in pediatrics has never been common and is currently very rare.

Dosing

Both unboosted and ritonavir-boosted indinavir have been studied in HIV-infected children. Data in children indicate that an unboosted indinavir dose of 500 to 600 mg/m² body surface area given every 8 hours results in peak blood concentrations and area under the curve slightly higher than those in adults but considerably lower trough concentrations. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults. Studies in small groups of children of a range of ritonavir-boosted indinavir doses have shown that indinavir 500 mg/m² body surface area plus ritonavir 100 mg/m² body surface area twice daily is probably too high, that indinavir 234 to 250 mg/m² body surface area plus low-dose ritonavir twice daily is too low, and that indinavir 400 mg/m² body surface area plus ritonavir 100 to 125 mg/m² body surface area twice daily results in exposures approximating those seen with 800 mg indinavir/100 mg ritonavir twice daily in adults, albeit with considerable inter-individual variability and high rates of toxicity.

Toxicity

The cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%). This is likely due to the difficulty in maintaining adequate hydration in children. Finally, a large analysis of more than 2,000 HIV-infected children from PACTG 219
demonstrated a hazard ratio of 1.7 for risk of renal dysfunction in children receiving combination antiretroviral therapy with indinavir.12

References


Dosing Recommendations

Neonatal Dose (<14 Days):
• No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days because of potential toxicities.

Dosing for Individuals not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir Infant Dose (14 Days–12 Months):
• Once-daily dosing is not recommended.
• 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area twice daily (approximates 16 mg/4 mg ritonavir-boosted lopinavir per kg body weight twice daily).
  Note: This dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). (Also see text for transitioning infants to lower mg per m² dose).

Pediatric Dose (>12 Months to 18 Years):
• Once-daily dosing is not recommended.
• 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily (maximum dose 400 mg/100 mg twice daily except as noted below). For patients with body weight <15 kg, this approximates 13 mg/3.25 mg ritonavir-boosted lopinavir per kg body weight twice daily; and for patients with body weight ≥15 to 45 kg this dose approximates 11 mg/2.75 mg ritonavir-boosted lopinavir per kg body weight twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients with possible decreased lopinavir susceptibility (see text below).

Selected Adverse Events
• Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
• Asthenia
• Hyperlipidemia, especially hypertriglyceridemia
• Elevated transaminases
• Hyperglycemia
• Fat maldistribution
• Possible increased bleeding in patients with hemophilia
• PR interval prolongation
• QT interval prolongation and torsades de pointes
• Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below)

Special Instructions
• Ritonavir-boosted lopinavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
• Ritonavir-boosted lopinavir tablets must be swallowed whole. Do not crush or split tablets.
• Ritonavir-boosted lopinavir oral solution should be administered with food because a high-fat meal increases absorption.
• The poor palatability of ritonavir-boosted lopinavir oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
• Ritonavir-boosted lopinavir oral solution can be kept at room temperature up to 77ºF (25ºC) if used within 2 months. If kept refrigerated (2º to 8ºC or 36º to 46ºF)
• 230 mg/57.5 mg ritonavir-boosted lopinavir/m² of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients <15 kg, this dose approximates 12 mg/3 mg ritonavir-boosted lopinavir per kg body weight given twice daily and for patients ≥15 kg to 40 kg, this dose approximates 10 mg/2.5 mg ritonavir-boosted lopinavir per kg body weight given twice daily.

Weight-Band Dosing for 100 mg/25 mg Ritonavir-Boosted Lopinavir Pediatric Tablets for Children/Adolescents

<table>
<thead>
<tr>
<th>Dosing target</th>
<th>Recommended number of 100-mg/25-mg ritonavir-boosted lopinavir tablets given twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>300 mg/m²/dose given twice daily</td>
</tr>
<tr>
<td>15 to 20 kg</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20 to 25 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;25 to 30 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30 to 35 kg</td>
<td>4ᵃ</td>
</tr>
<tr>
<td>&gt;35 to 45 kg</td>
<td>4ᵃ</td>
</tr>
<tr>
<td>&gt;45 kg</td>
<td>4ᵃ or 5ᵇ</td>
</tr>
</tbody>
</table>

ᵃ Four of the 100 mg/25 mg ritonavir-boosted lopinavir tablets can be substituted by 2 tablets each containing 200 mg/50 mg ritonavir-boosted lopinavir in children capable of swallowing a larger size tablet.

ᵇ In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nefilavir, for body weight >45 kg, the Food and Drug Administration (FDA)-approved adult dose is 500 mg/125 mg ritonavir-boosted lopinavir twice daily, given as a combination of 2 tablets of 200/50 mg ritonavir-boosted lopinavir and 1 tablet of 100 mg/25 mg ritonavir-boosted lopinavir. Alternatively, 3 tablets of 200/50 mg ritonavir-boosted lopinavir can be used for ease of dosing.

Adult Dose (>18 Years):
• 800 mg/200 mg ritonavir-boosted lopinavir once daily, or
• 400 mg/100 mg ritonavir-boosted lopinavir twice daily.
• Do not use once-daily dosing in children or adolescents, or in patients receiving concomitant therapy with nevirapine.

Metabolism
• Cytochrome P (CYP) 3A4 inhibitor and substrate.
• Dosing of ritonavir-boosted lopinavir in patients with hepatic impairment; ritonavir-boosted lopinavir is primarily metabolized by the liver. Caution should be used when administering lopinavir to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
• In the co-formulation of ritonavir-boosted lopinavir, the ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.
efavirenz, fosamprenavir, or nelfinavir, or in patients with three or more lopinavir-associated mutations (see Special Instructions for list).

**In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):**

- 400 mg/100 mg ritonavir-boosted lopinavir twice daily.

**Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir.**

**Note:** These drugs induce lopinavir metabolism and reduce lopinavir plasma levels; increased ritonavir-boosted lopinavir dosing is required with concomitant administration of these drugs.

- Once-daily dosing should **not** be used.

**Pediatric Dose (>12 Months to 18 Years):**

- 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

**Adult Dose (>18 Years):**

- Food and Drug Administration (FDA)-approved dose is 500 mg/125 mg ritonavir-boosted lopinavir twice daily, given as a combination of 2 tablets of 200/50 mg ritonavir-boosted lopinavir and 1 tablet of 100 mg/25 mg ritonavir-boosted lopinavir. **Alternatively,** 3 tablets of 200/50 mg ritonavir-boosted lopinavir can be used for ease of dosing. Once-daily dosing should **not** be used.

**Ritonavir-boosted Lopinavir in Combination with Saquinavir Hard-Gel Capsules (Invirase) or in Combination with Maraviroc:**

- Saquinavir and maraviroc doses may need modification (See sections on SQV and MVC).

**Drug Interactions** (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)

- **Metabolism:** CYP450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.

Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with lopinavir/ritonavir. In patients treated with lopinavir/ritonavir, fluticasone (a commonly
used inhaled and intranasal steroid) should be avoided and an alternative used.

**Major Toxicities**

- **More common:** Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia
- **Less common (more severe):** Fat maldistribution
- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases). PR interval prolongation.
  
  QT interval prolongation and torsades de pointes may occur.

  - **Special populations—neonates:** Ritonavir-boosted lopinavir should not be used in the immediate postnatal period in premature infants because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency, life-threatening bradyarrhythmias and cardiac dysfunction, and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with ritonavir-boosted lopinavir.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/LPV.html).

**Pediatric Use**

**Approval**

Ritonavir-boosted lopinavir is Food and Drug Administration (FDA)-approved for use in children. Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

**Pharmacokinetics**

**General Considerations**

There is some controversy about the dosing of ritonavir-boosted lopinavir in children. Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m². For the adult dose of 400/100 mg ritonavir-boosted lopinavir, the appropriate pediatric dose would be approximately 230/57.5 mg ritonavir-boosted lopinavir per m². However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. To achieve similar C_{trough} to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area. Lopinavir exposures in infants are compared to those in older children and adults as shown in the table below.
Models suggest that diet, body weight and postnatal age are important factors in lopinavir PK, with improved bioavailability as dietary fat increases over the first year of life⁷ and with clearance slowing by age 2.3 years.¹¹ A study from the UK and Ireland in children aged 5.6 to 12.8 years at the time of ritonavir-boosted lopinavir initiation that compared outcomes in children treated with 230 mg/m²/dose versus 300 mg/m²/dose suggests that the higher doses were associated with long-term viral load suppression.¹²

### Pharmacokinetics and Dosing

#### Aged 6 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

Lower trough concentrations have been observed in children receiving 230 mg/57.5 mg ritonavir-boosted lopinavir per m² of body surface area when compared to the 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice-daily dose. (see table and Verweel, Burger, 2007) Therefore, some clinicians choose to initiate therapy in children aged 6 months to 12 years using 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the drug label-recommended 230 mg/57.5 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily.

For infants receiving 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily, immediate dose reduction at age 12 months is not recommended; many practitioners would allow patients to “grow into” the 230 mg/57.5 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily dosage as they gain weight over time. Some would continue the infant dose (300 mg/m² of body surface area per dose twice daily) while on LPV/r liquid formulation.

#### Aged 6 Weeks to 6 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

The PK of the oral solution at approximately 300 mg/75 mg ritonavir-boosted lopinavir per m² of body surface area per dose twice daily was evaluated in infants younger than age 6 weeks⁶ and infants aged 6 weeks to 6 months.⁵

Even at this higher dose, pre-dose (Cₜᵣᵩₐₜ) levels were highly variable but were lower in infants than in children older than age 6 months and were lowest in the youngest infants aged 6 weeks or younger compared with those ages 6 weeks to 6 months. By age 12 months, lopinavir AUC was similar to that found in older children.⁷ Because infants grow rapidly in the first months of life, it is important to optimize lopinavir dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg/m² body surface area in older children and adolescents,¹³ some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m² body surface area dose to allow for projected growth between clinic visits.

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**Note:** Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

**Key to Acronyms:** AUC = area under the curve; LPV = lopinavir

<table>
<thead>
<tr>
<th></th>
<th>Adults⁹</th>
<th>Children⁸</th>
<th>Children⁸</th>
<th>Infants at 12 Months⁷,ₐ</th>
<th>Infants 6 weeks–6 months⁵</th>
<th>Infants &lt;6 weeks⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>19</td>
<td>12</td>
<td>15</td>
<td>20</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td><strong>Dose Lopinavir</strong></td>
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<td>230 mg/m²</td>
<td>300 mg/m²</td>
<td>300 mg/m²</td>
<td>300 mg/m²</td>
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</tr>
<tr>
<td><strong>AUC mcg·hr/mL</strong></td>
<td>92.6</td>
<td>72.6</td>
<td>116.0</td>
<td>101.0</td>
<td>74.5</td>
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</tr>
<tr>
<td><strong>Cₘₐₓ mcg/mL</strong></td>
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<td>8.2</td>
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</tr>
<tr>
<td><strong>Cₘᵟᵦ mcg/mL</strong></td>
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<td>6.5</td>
<td>3.8</td>
<td>2.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

⁶ Data generated in study cited but not reported in final manuscript; data in table according to an e-mail from Edmund Capparelli, PharmD (April 18, 2012)

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*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection O-85*
Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

In both children and adults the lopinavir C\textsubscript{trough} is reduced by concurrent treatment with NNRTIs or concomitant fosamprenavir or nelfinavir. Higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg ritonavir-boosted lopinavir per m\textsuperscript{2} body surface area per dose twice daily plus nevirapine, the mean lopinavir C\textsubscript{trough} was 3.77 ± 3.57 mcg/mL.\textsuperscript{8} Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of ritonavir-boosted lopinavir, but the variability in concentration is much higher in children than adults.\textsuperscript{8,14} In a study of 15 HIV-infected children 5.7 to 16.3 years treated with the combination of 300 mg/75 mg ritonavir-boosted lopinavir per m\textsuperscript{2} body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily there was a 34-fold inter-individual variation in lopinavir trough concentrations, and 5 of 15 (33\%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.\textsuperscript{15} A PK study in 20 children aged 10 to 16 years treated with the combination of ritonavir-boosted lopinavir 300 mg/75 mg per m\textsuperscript{2} body surface area twice daily plus efavirenz 350 mg/m\textsuperscript{2} body surface area once daily showed only 1 (6.6\%) patient with subtherapeutic lopinavir trough concentrations,\textsuperscript{16} perhaps because of the use of a lower efavirenz dose of approximately 11 mg/kg body weight,\textsuperscript{16} compared to efavirenz 14 mg/kg body weight in the Bershoeff trial.\textsuperscript{15}

Dosing
Once Daily

Once-daily dosing of ritonavir-boosted lopinavir 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV infection in therapy-naive adults older than age 18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM). There is high inter-individual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus as demonstrated in studies of ARV-naive children and adolescents.\textsuperscript{17-20} Compared with the soft-gel formulation of ritonavir-boosted lopinavir, the tablet formulation has lower variability in trough levels\textsuperscript{20,21} but the Panel remains concerned about the long-term effectiveness of once-daily ritonavir-boosted lopinavir in children.

Dosing and Its Relation to Efficacy

Ritonavir-boosted lopinavir is effective in treatment-experienced patients with severe immune suppression,\textsuperscript{22,23} although patients with greater prior exposure to ARVs may have slower reductions in virus load to undetectable concentrations\textsuperscript{23,24} and less robust response in CD4 percentage.\textsuperscript{25} Twice daily doses of lopinavir used in this cohort were 230 to 300 mg/m\textsuperscript{2} body surface area in 39\% of patients, 300 to 400 mg/m\textsuperscript{2} body surface area in 35\%, and greater than 400 mg/m\textsuperscript{2} body surface area per dose in 4\%.\textsuperscript{25}

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just before a dose, or C\textsubscript{trough}) to the susceptibility of the HIV-1 isolate (EC\textsubscript{50}). The ratio of C\textsubscript{trough} to EC\textsubscript{50} is called the inhibitory quotient (IQ), and in both adults and children treated with ritonavir-boosted lopinavir, virus load reduction is more closely associated with IQ than with either the C\textsubscript{trough} or EC\textsubscript{50} alone.\textsuperscript{26-28} A study of the practical application of the IQ to guide therapy using higher doses of ritonavir-boosted lopinavir in children and adolescents to reach a target IQ of 15 showed the safety and tolerability of doses of 400 mg/100 mg ritonavir-boosted lopinavir per m\textsuperscript{2} body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine or efavirenz) and 480 mg/120 mg ritonavir-boosted lopinavir per m\textsuperscript{2} body surface area per dose twice daily (with nevirapine or efavirenz).\textsuperscript{13} Results of a modeling study suggest that standard doses of ritonavir-boosted lopinavir may be inadequate for treatment-experienced children and suggest the potential utility of TDM when ritonavir-boosted lopinavir is used in children previously treated with protease inhibitors.\textsuperscript{29}
**Formulations**

**Palatability**

The poor palatability of the oral solution can be a significant challenge to medication adherence for some children and families. Numbing of the taste buds with ice chips before or after administration of the solution, masking of the taste by administration with sweet or tangy foods, chocolate syrup, or peanut butter, for example, or by flavoring the solution by the pharmacist prior to dispensing, are examples of interventions that may improve tolerability.

**Do Not Use Crushed Tablets**

Ritonavir-boosted lopinavir tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, C\text{max}, and C\text{trough} compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.\(^{30}\) In a PK study using a generic adult formulation of ritonavir-boosted lopinavir manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C\text{trough} measurements.\(^{21}\)

**Toxicity**

**Weight Gain**

Compared with children treated with NNRTI-based regimens, those treated with ritonavir-boosted lopinavir may have less robust weight gain and smaller increases in CD4 percentage.\(^{31-33}\) The poor weight gain associated with ritonavir-boosted lopinavir is not understood, but may be related to aversion to the taste of the liquid formulation or decreased appetite.

**References**


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection


**Nelfinavir (NFV, Viracept)**  
*Last updated November 1, 2012; last reviewed February 12, 2014*

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

### Formulations

**Tablets:** 250 mg and 625 mg

### Dosing Recommendations

**Neonate/Infant Dose:**
- Nelfinavir should not be used for treatment in children aged <2 years.

**Pediatric Dose (Aged 2–13 Years):**
- 45–55 mg/kg twice daily

**Adolescent/Adult Dose:**
- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily
- Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.

### Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia
- Serum transaminase elevations

### Special Instructions

- Administer nelfinavir with meal or light snack.
- If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
- Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, patients should mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.

### Metabolism

- CYP2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

### Drug Interactions

(See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Metabolism:** Cytochrome P (CYP) 2C19 and 3A4 substrate. Metabolized to active M8 metabolite. CYP3A4 inhibitor. However, ritonavir boosting does not significantly increase nelfinavir concentrations and co-administration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir.
- Before administering nelfinavir, carefully review a patient’s medication profile for potential drug interactions.
**Major Toxicities**

- **More common:** Diarrhea (most common), asthenia, abdominal pain, rash, and lipid abnormalities.
- **Less common (more severe):** Exacerbation of chronic liver disease, fat redistribution.
- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevations in transaminases.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/NFV.html](http://hivdb.stanford.edu/pages/GRIP/NFV.html)).

**Pediatric Use**

**Approval**

Nelfinavir is a protease inhibitor (PI) approved for use in combination with 2 nucleoside reverse transcriptase inhibitors in children aged >2 years. Nelfinavir is not recommended for treatment of children aged <2 years (see the Perinatal Guidelines).

**Efficacy in Pediatric Clinical Trials**

Nelfinavir in combination with other antiretroviral drugs has been extensively studied in HIV-infected children. In randomized trials of children aged 2 to 13 years receiving nelfinavir as part of triple combination antiretroviral therapy (cART), the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient’s age or prior history of ART, the number of drugs included in the combination regimen, and dose of nelfinavir used.

**Pharmacokinetics: Exposure-Response Relationships**

The relatively poor ability of nelfinavir to control plasma viremia in infants and children in clinical trials may be related to lower potency compared with other PIs or non-nucleoside reverse transcriptase inhibitors, as well as highly variable drug exposure, metabolism, and poor patient acceptance of available formulations.

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increased by as much as five fold) and decreases pharmacokinetic (PK) variability relative to the fasted state. Drug exposure may be even more unpredictable in pediatric patients than in adults because of increased clearance of nelfinavir observed in children, and difficulties in taking nelfinavir with sufficient food to improve bioavailability. A pediatric powder formulation, no longer available, was poorly tolerated when mixed with food or formula. In the PENTA-7 trial, 35% (7 of 20) of infants started on powder at initiation of therapy were switched from the powder to crushed tablets because of difficulty administering the oral formulation to the infants. A slurry made by dissolving nelfinavir tablets in water or other liquids can be administered to children who are unable to swallow tablets. The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.

Nelfinavir is metabolized by multiple CYP-450 enzymes including CYP3A4 and CYP2C19. M8, the major oxidative metabolite, has *in vitro* antiviral activity comparable to the parent drug. The variability of drug exposure at any given dose is much higher for children than adults, which has been attributed at least in part to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children. Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir PKs and the virologic responses to combination therapy in HIV-1-infected children. These findings suggest that CYP2C19 genotypes are important determinants of nelfinavir PKs and virologic response in HIV-1-infected children.
Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults, an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration ($C_{\text{min}}$) <1.0 mcg/mL.\textsuperscript{16-18}

The antiviral response to nelfinavir is significantly less in children younger than age 2 years than in older children.\textsuperscript{6,8,19} Infants have even lower drug exposures and higher variability in plasma concentrations than children with body weights <25 kg; the presence of lower peak drug concentrations and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be contributing factors.\textsuperscript{20,21} In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had Week 48 HIV RNA concentrations <50 copies/mL, compared with only 29% of those with morning trough <0.8 mcg/mL.\textsuperscript{22} It is of note that the median age of the group with C\textsubscript{trough} <0.8 mcg/mL was 3.8 years, while the median age of the group with C\textsubscript{trough} >0.8 mcg/mL was 8.3 years.\textsuperscript{22} Therapeutic drug monitoring (TDM) of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir.\textsuperscript{16,23} Similarly, better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing;\textsuperscript{15,24} doses higher than those recommended in adults may be required in some patients. Given the higher variability of nelfinavir plasma concentrations in infants and children, nelfinavir is not recommended for use in children younger than age 2 years.

References


Ritonavir (RTV, Norvir) (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral Solution (Contains 43% Alcohol by Volume): 80 mg/mL
Capsules: 100 mg
Tablets: 100 mg

Dosing Recommendations

Ritonavir as a Pharmacokinetic (PK) Enhancer:
- The major use of ritonavir is as a PK enhancer of other protease inhibitors (PIs) used in pediatric patients and in adolescents and adults. The recommended dose of ritonavir varies and is specific to the drug combination selected. See dosing information for specific PIs.

In the Unusual Situation When Ritonavir is Prescribed as Sole PI:
- See manufacturer guidelines.

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Paresthesia (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

Special Instructions

- Administer ritonavir with food to increase absorption and reduce GI side effects.
- If ritonavir is prescribed with didanosine, administer the drugs 2 hours apart.
- Refrigerate ritonavir capsules only if the capsules will not be used within 30 days or cannot be stored below 77° F (25° C). Ritonavir tablets are heat stable.
- Do not refrigerate ritonavir oral solution; store at room temperature (68–77° F or 20–25° C). Shake the solution well before use.
- Ritonavir oral solution has limited shelf life; use within 6 months.
- Patients who have persistent or significant nausea with the capsule may benefit from switching to the tablet. Also, the tablet is smaller than the capsule and thus easier to swallow.
• **To Increase Tolerability Of Ritonavir Oral Solution In Children:**
  - Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
  - Before administration, give a child ice chips; a Popsicle; or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds; or give peanut butter to coat the mouth.
  - After administration, give a child strong-tasting foods such as maple syrup or cheese.

**Metabolism**

- Cytochrome P (CYP) 3A4 and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.
- **Dosing of ritonavir in patients with hepatic impairment:** Ritonavir is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Data are unavailable on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.

**Drug Interactions** (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Metabolism:** Ritonavir is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). There is potential for multiple drug interactions with ritonavir.
- Before ritonavir is administered, a patient’s medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.
- Avoid concomitant use of intranasal or inhaled fluticasone. Use caution when prescribing ritonavir with other inhaled steroids because of reports of adrenal insufficiency.¹

**Major Toxicities**

- **More common:** Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, lipid abnormalities.
- **Less common (more severe):** Exacerbation of chronic liver disease, fat maldistribution.
- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.²
Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic enhancer of other protease inhibitors (PIs).

Pediatric Use

Approval

Ritonavir has been approved by the Food and Drug Administration (FDA) for use in the pediatric population.

Efficacy: Effectiveness in Practice

Use of ritonavir as the sole PI in combination antiretroviral therapy (cART) in children is not recommended. Although ritonavir has been well studied in children, its use as a sole PI for therapy is limited because ritonavir is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. Also, ritonavir as a sole PI is associated with a higher risk of virologic failure than efavirenz or ritonavir-boosted lopinavir. In addition, poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is six capsules or tablets twice daily) limit its use as a sole PI. Concentrations are highly variable in children younger than aged 2 years, and doses of 350 to 450 mg/m² twice daily may not be sufficient for long-term suppression of viral replication in this age group.

However, in both children and adults, ritonavir is recommended as a PK enhancer to boost the second PI in an ART regimen. Ritonavir acts by inhibiting the metabolism of the second (boosted) PI by the liver, thereby increasing the plasma concentration of the second (boosted) PI.

Dosing

Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, atazanavir and a PI co-formulation, ritonavir-boosted lopinavir, are available (see individual PIs for more specific information).

Toxicity

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily. Potentially life-threatening arrhythmias in premature newborn infants treated with ritonavir-boosted lopinavir have been reported; thus, ritonavir-boosted lopinavir should not be used in this group of patients. Co-administration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how co-administering any of these drugs with ritonavir will affect the PR interval. In addition, ritonavir should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as those with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

References


Saquinavir (SQV, Invirase) (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations
Hard-Gel Capsules: 200 mg
Film-Coated Tablets: 500 mg

Dosing Recommendations

Neonate/Infant Dose:
• Not approved for use in neonates/infants.

Pediatric Dose:
• Not approved for use in children.

Investigational Doses in Treatment-Experienced Children:
• Saquinavir must be boosted with ritonavir.

Aged <2 Years:
• No dose has been determined.

Aged ≥2 Years (Conditional Dosing Based on Limited Data; See Text):
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose Saquinavir plus Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to &lt;15 kg</td>
<td>saquinavir 50 mg/kg plus ritonavir 3 mg/kg, both twice daily</td>
</tr>
<tr>
<td>15 to 40 kg</td>
<td>saquinavir 50 mg/kg plus ritonavir 2.5 mg/kg, both twice daily</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>saquinavir 50 mg/kg plus ritonavir 100 mg, both twice daily</td>
</tr>
</tbody>
</table>

Aged ≥7 Years in Combination with Ritonavir-Boosted Lopinavir for Salvage Therapy (Conditional Dosing Based On Limited Data, See Text):
• Saquinavir 750 mg/m² (max 1600 mg) and saquinavir 50 mg/kg each have been used in combination with ritonavir-boosted lopinavir, both twice daily.

Adolescent (Aged ≥16 years)/Adult Dose:
• Saquinavir should only be used in combination with ritonavir or ritonavir-boosted lopinavir (never unboosted).
• Saquinavir 1000 mg + ritonavir 100 mg, both twice daily
• Saquinavir 1000 mg + ritonavir-boosted lopinavir 400/100 mg, both twice daily

Selected Adverse Events
• Gastrointestinal intolerance, nausea, and diarrhea
• Headache
• Elevated transaminases
• Hyperlipidemia
• Hyperglycemia
• Fat maldistribution
• Increased bleeding episodes in patients with hemophilia
• PR interval prolongation, QT interval prolongation and ventricular tachycardia (torsades de pointes) have been reported.

Special Instructions
• Administer within 2 hours after a full meal.
• Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
• Pre-therapy electrocardiogram is recommended and saquinavir is contraindicated in patients with a prolonged QT interval.

Metabolism
• Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor, 90% metabolized in the liver.
• Use in patients with hepatic impairment: Use with caution.
**Drug Interactions** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](http://www.iasusa.org/resistance_mutations/index.html))

- Saquinavir is both a substrate and inhibitor of the CYP3A4 system. **Potential exists for multiple** drug interactions. **Co-administration of saquinavir is contraindicated with drugs** **that are highly dependent on the CYP3A clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events.**

- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions.

**Major Toxicities**

- **More common:** Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash, and lipid abnormalities.

- **Less common (more severe):** Exacerbation of chronic liver disease, lipodystrophy.

- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and **ventricular tachycardia** (torsades de pointes).

**Resistant**

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/SQV.html](http://hivdb.stanford.edu/pages/GRIP/SQV.html)).

**Pediatric Use**

**Approval**

Saquinavir is not Food and Drug Administration (FDA)-approved for use in children.

**Efficacy**

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors in HIV-infected children. Ritonavir-boosted saquinavir and saquinavir/lopinavir/ritonavir regimens were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications.

**Pharmacokinetics**

Studies suggest that saquinavir should not be used without boosting by ritonavir or ritonavir-boosted lopinavir. A pharmacokinetic (PK) analysis of 5 children aged younger than 2 years and 13 children aged 2 to 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir demonstrated that drug exposure was lower in children aged <2 years whereas drug exposure was adequate in those aged 2 to 5 years. For this reason, saquinavir should not be administered to children aged <2 years. In children aged ≥2 years, a dose of 50 mg/kg twice daily (maximum dose = 1000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 to <15 kg) or 2.5 mg/kg twice daily (patients weighing 15–40 kg) resulted in area under the curve and steady-state trough plasma concentration (C_{trough}) values similar to those in older children and adults.

In a study of 18 children (median age 14.2 years, range 7.7–17.6 years) evaluating the addition of saquinavir (750 mg/m^2 body surface area every 12 hours, maximum dose 1600 mg) to a regimen containing ritonavir-boosted lopinavir dosed at 400/100 mg/m^2 body surface area twice daily (for patients not concurrently taking a non-nucleoside reverse transcriptase inhibitor [NNRTI]) or ritonavir-boosted lopinavir 480/120 mg/m^2 body surface area twice daily for patients concurrently administered an NNRTI, the addition of saquinavir was well tolerated and did not appear to alter lopinavir PKs. Saquinavir required dose adjustment in four
patients (decreased in three, increased in one).9

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance (saquinavir was dosed at 50 mg/m² body surface area and ritonavir-boosted lopinavir was dosed at 230/57.5 mg/m² body surface area, all twice daily). After 96 weeks, 74% of the children achieved an undetectable plasma RNA load at <50 copies/mL. Therapeutic drug monitoring was used to establish adequate minimum plasma concentration (C_{min}) values and to aid with alterations in drug dosage based upon toxicity. Most C_{min} values for saquinavir were above the desired trough value of 0.1 mg/L. The average C_{min} throughout 96 weeks for saquinavir was 1.37 mg/L, and when saquinavir doses were adjusted, most were decreased by an average of 21% (8 mg/kg).7,8

**Toxicity**

In a healthy adult volunteer study, ritonavir-boosted saquinavir use was associated with increases in both QT and PR intervals.11,12 Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Ritonavir-boosted saquinavir is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval. An ECG is recommended before initiation of therapy with saquinavir and should be considered during therapy.

**References**


infected children 4 months to <6 years old. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA.


Tipranavir (TPV, APTIVUS)  (Last updated November 1, 2012; last reviewed February 12, 2014)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations
Oral solution: 100 mg tipranavir/mL, with 116 International Units (IU) vitamin E/mL
Capsules: 250 mg

Dosing Recommendations

Note: Tipranavir must be used with ritonavir boosting. The ritonavir boosting dose used for tipranavir is higher than that used for other protease inhibitors (PIs).

Pediatric Dose (Aged <2 Years):
• Not approved for use in children aged <2 years.

Pediatric Dose (Aged 2–18 Years):
Note: Not recommended for treatment-naive patients.

Body Surface Area Dosing:
• Tipranavir 375 mg/m² plus ritonavir 150 mg/m², both twice daily.

Maximum Dose:
• Tipranavir 500 mg plus ritonavir 200 mg, both twice daily.

Weight-Based Dosing:
• Tipranavir 14 mg/kg plus ritonavir 6 mg/kg, both twice daily.

Maximum Dose:
• Tipranavir 500 mg plus ritonavir 200 mg, both twice daily.

Adult Dose:
Note: Not recommended for treatment-naive patients.
• Tipranavir 500 mg (two 250-mg capsules) plus ritonavir 200 mg, both twice daily.

Selected Adverse Events
• Rare cases of fatal and non-fatal intracranial hemorrhage
• Skin rash (more common in children than adults)
• Nausea, vomiting, diarrhea
• Hepatotoxicity
• Hyperlipidemia
• Hyperglycemia
• Fat maldistribution
• Possible increased bleeding episodes in patients with hemophilia

Special Instructions
• Administer tipranavir and ritonavir together with food.
• Tipranavir oral solution contains 116 IU vitamin E/mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
• Tipranavir contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
• Store tipranavir oral solution at room temperature 25° C (77° F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
• Store unopened bottles of oral tipranavir capsules in a refrigerator at 2° C to 8° C (36°–46° F). Once bottle is opened, capsules can be kept at room temperature (maximum of 77° F or 25° C) if used within 60 days.
• Use tipranavir with caution in patients who may be at increased risk of intracranial
hemorrhage: risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, use of anticoagulant or antiplatelet agents (including vitamin E).
• Use of tipranavir is contraindicated in patients with moderate or severe hepatic impairment.

**Metabolism**

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate.
- **Dosing in patients with renal impairment:** No dose adjustment required.
- **Dosing in patients with hepatic impairment:** No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

**Drug Interactions** *(See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)*

- Tipranavir has the potential for multiple drug interactions. Co-administration of ritonavir-boosted tipranavir with drugs that are highly dependent on CYP3A for clearance or are potent CYP3A inducers is contraindicated.

- Before tipranavir is administrated, a patient’s medication profile should be carefully reviewed for potential drug interactions.

- Tipranavir should be used with caution in patients who are receiving medications known to increase the risk of bleeding, such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

**Major Toxicities**

- **More common:** Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Elevated transaminases, cholesterol, and triglycerides.

- **Less common (more severe):** Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis.

- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of intracranial hemorrhage. Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TPV.html).
Pediatric Use

Approval and General Considerations

Tipranavir is Food and Drug Administration (FDA)-approved for use in children aged ≥2 years who are treatment-experienced and infected with HIV strains resistant to more than one protease inhibitor (PI).\(^1\) The use of tipranavir is limited by the high pill burden imposed on patients taking tipranavir capsules, including the burden of taking a higher dose of boosting ritonavir than is required with other PIs. This increased dose of ritonavir is associated with greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events that limit its use to patients with few treatment options. However, tipranavir is approved for use in children as young as age 2 years and is available in a liquid formulation.

Efficacy

FDA approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of ritonavir-boosted tipranavir in HIV-infected children (PACTG 1051/BI-1182.14).\(^2\) This study enrolled treatment-experienced children (with the exception of 3 treatment-naive patients) aged 2 to 18 years (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children in 3 age strata were randomized to 2 different doses of tipranavir/ritonavir: ritonavir-boosted tipranavir 290 mg/115 mg per m\(^2\) body surface area (low dose, 58 patients) or 375 mg/150 mg/m\(^2\) body surface area (high dose, 57 patients) twice daily, plus optimized background therapy. All children initially received the oral solution but patients who were aged 12 years or older and receiving the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily were eligible to switch to tipranavir capsules after Week 4. At baseline, resistance to all commercially available PIs was present in greater than 50% of patient isolates, and the ritonavir-boosted tipranavir mutation scores increased with age.\(^2\) At 48 weeks, 39.7% of patients receiving the low dose and 45.6% of those receiving the high dose had viral loads <400 copies/mL. The groups did not differ in percentage of patients who achieved viral loads <50 copies/mL. HIV RNA levels <400 copies/mL tended to be seen in a greater proportion of the youngest patients (70%), who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 T lymphocyte count of 100 cells/mm\(^3\) and 59 cells/mm\(^3\) in low- and high-dose groups, respectively.

In a multivariate model, three variables (listed in order) predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100,000 copies/mL. GIQ is calculated by dividing the tipranavir trough concentration by the number of tipranavir resistance-conferring mutations genotyped from a patient’s HIV strain. The GIQ was consistently greater in the high-dose group. Based on these findings and the increased number of AIDS-defining events in the low-dose group, high-dose ritonavir-boosted tipranavir has been recommended.

Pharmacokinetics

Pharmacokinetic evaluation of the liquid formulation at steady state in children was assessed.\(^3\) In children aged 2 to <12 years, at a dosage of ritonavir-boosted tipranavir 290/115 mg/m\(^2\) body surface area, tipranavir trough concentrations were consistent with those achieved in adults receiving standard ritonavir-boosted tipranavir 500 mg/200 mg dosing. However, children aged 12 to 18 years required a higher dose (375/150 mg/m\(^2\) body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard ritonavir-boosted tipranavir dose. Population PK analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age.\(^3\) Based on these studies, the final dose of ritonavir-boosted tipranavir 375/150 mg/m\(^2\) body surface area twice daily is recommended.

Toxicity

Adverse effects were similar between treatment groups in the multicenter, pediatric study.\(^2\) Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs because of adverse events. The most common adverse events were gastrointestinal disturbances; 37%
of participants had vomiting and 24% had diarrhea. Moderate or severe laboratory toxicity (primarily increase in gamma glutamyl transpeptidase and creatine phosphokinase) was seen in 11% of children. Four patients (all in the low-dose group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus high-dose group reached statistical significance \( P = 0.04 \).

Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir/mL of solution. The recommended dose of tipranavir (14 mg/kg body weight) results in a vitamin E dose of 16 IU/kg body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%). Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.

References


Entry and Fusion Inhibitors

Enfuvirtide (ENF, T-20, Fuzeon)
Maraviroc (MVC, Selzentry)
**Enfuvirtide (ENF, T-20, Fuzeon)** (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

### Formulations

**Lyophilized Powder for Injection:**
- 108-mg vial of enfuvirtide. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

**Convenience Kit:**
- 60 single-use vials of enfuvirtide (90-mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes

### Dosing Recommendations

**Pediatric/Adolescent Dose (Aged 6–16 Years):**
- **Children Aged <6 Years:** Not approved for use in children aged <6 years
- **Children Aged ≥6 Years:** 2 mg/kg (maximum dose, 90 mg [1 mL]) twice daily injected subcutaneously (SQ) into the upper arm, anterior thigh, or abdomen

**Adolescent (Aged >16 Years)/Adult Dose:**
- 90 mg (1 mL) twice daily injected SQ into the upper arm, anterior thigh, or abdomen

### Selected Adverse Events

- Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in up to 98% of patients.
- Increased rate of bacterial pneumonia (unclear association)
- Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.

### Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of SQ injections. Enfuvirtide injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject enfuvirtide immediately or keep refrigerated in the original vial until use. Reconstituted enfuvirtide must be used within 24 hours.
- Enfuvirtide must be given SQ; severity of reactions increases if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions apply ice or heat after injection or gently massage injection site.
to better disperse the dose. There are reports of injection-associated neuralgia and paresthesia when alternative delivery systems, such as needle-free injection devices, are used.

- Advise patient/caregiver of the possibility of a HSR; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a HSR.

**Metabolism**

- Catabolism to constituent amino acids.

**Drug Interactions** (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- There are no known significant drug interactions with enfuvirtide.

**Major Toxicities**

- **More common**: Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients.

- **Less common (more severe)**: Increased rate of bacterial pneumonia (unclear association).\(^1\) Pediatric studies have lacked the statistical power to answer questions concerning enfuvirtide use and increased risk of pneumonia.

- **Rare**: Hypersensitivity reactions (HSRs) (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing HSRs should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with HSRs.

- **Pediatric specific**: Local site cellulitis requiring antimicrobial therapy (up to 11% in certain subgroups of patients in pediatric studies).\(^2\)

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/pages/GRIP/enfuvirtide.html](http://hivdb.stanford.edu/pages/GRIP/enfuvirtide.html)).

**Pediatric Use**

**Approval**

Although enfuvirtide is Food and Drug Administration (FDA)-approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high rate of injection site reactions. Use in deep salvage regimens\(^3\) has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).
Pharmacokinetics

A single-dose pharmacokinetic (PK) evaluation study of enfuvirtide, given SQ to 14 HIV-infected children aged 4 to 12 years (PACTG 1005), identified that enfuvirtide 60 mg/m² of body surface area per dose resulted in a target trough concentration that approximated the “equivalent” of a 90-mg dose delivered SQ to an adult (1000 mg/mL). In a second pediatric study of 25 children aged 5 to 16 years, a 2-mg/kg dose (maximum 90 mg) of enfuvirtide given twice daily, yielded drug concentrations similar to 60 mg/m² of body surface area dose independent of age group, body weight, body surface area, and sexual maturation. The Food and Drug Administration (FDA)-recommended dose of enfuvirtide for children aged 6 to 16 years is 2 mg/kg (maximum 90 mg) administered SQ twice daily. Further data are needed for dosing in children aged <6 years.

Efficacy

The safety and antiretroviral (ARV) activity of twice-daily SQ enfuvirtide administration at 60 mg/m² per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children aged 4 to 12 years who had failed to achieve viral suppression on multiple prior ARV regimens (PACTG 1005). At 24 weeks 71% of the children had a >1.0 log reduction in viral load; 43% and 21% had HIV RNA levels suppressed to <400 copies/mL and <50 copies/mL, respectively. However, only 36% of children maintained virologic suppression (>1.0 log decrease in HIV RNA) at Week 96. Most children had local injection site reactions. Significant improvements in CD4 T lymphocyte (CD4) percentages and height z scores were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase I/II study of enfuvirtide (2.0 mg/kg SQ, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children aged 3 years to 16 years for 48 weeks. Only 64% of the children completed 48 weeks of therapy. The median decrease in HIV RNA was -1.17 log₁₀ copies/mL (n = 32) and increase in CD4 count was 106 cells/mm³ (n = 25). At Week 8, treatment responses as measured by several plasma HIV RNA parameters were superior in younger children (aged <11 years) compared with adolescents. Median increases in CD4 cell count were 257 cells/mm³ in children and 84 cells/mm³ in adolescents. Local skin reactions were common in all age groups (87% of study participants). The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen.

References


### Maraviroc (MVC, Selzentry)

(Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

#### Formulations

**Tablets:**
- 150 mg and 300 mg

#### Dosing Recommendations

**Neonate/Infant Dose:**
- Not approved for use in neonates/infants.

**Pediatric Dose:**
- Not approved for use in children aged <16 years.
- A pediatric clinical trial is under way.

**Adolescent (Aged ≥16 Years)/Adult Dose**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>When given with potent CYP3A inhibitors (with or without CYP3A inducers)</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>including protease inhibitors (except ritonavir-boosted tipranavir)</td>
<td></td>
</tr>
<tr>
<td>When given with nucleoside reverse transcriptase inhibitors, enfuvirtide,</td>
<td>300 mg twice daily</td>
</tr>
<tr>
<td>ritonavir-boosted tipranavir, nevirapine, raltegravir, and drugs that are</td>
<td></td>
</tr>
<tr>
<td>not potent CYP3A inhibitors or inducers</td>
<td></td>
</tr>
<tr>
<td>When given with potent CYP3A inducers including efavirenz and etravirine</td>
<td>600 mg twice daily</td>
</tr>
<tr>
<td>(without a potent CYP3A inhibitor)</td>
<td></td>
</tr>
</tbody>
</table>

#### Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Orthostatic hypotension (especially in patients with severe renal insufficiency).

#### Special Instructions

- Conduct testing with HIV tropism assay (see Antiretroviral Drug-Resistance Testing in the main body of the guidelines) before using maraviroc to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Use maraviroc in patients with only CCR5-tropic virus. Do not use if CXCR4 or mixed/dual-tropic HIV is present.
- Maraviroc can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering maraviroc to patients with underlying cardiac disease.

#### Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate
- **Dosing of maraviroc in patients with hepatic impairment:** Use caution when administering maraviroc to patients with hepatic impairment. Because maraviroc is metabolized by the liver, concentrations in patients with hepatic impairment may be increased.
• Do not use maraviroc in patients with creatinine clearance <30 mL/min who are receiving potent CYP3A4 inhibitors or inducers.

• Dosing of maraviroc in patients with renal impairment: Refer to the manufacturer’s prescribing information.

Drug Interactions (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

• Absorption: Absorption of maraviroc is somewhat reduced with ingestion of a high-fat meal; however, maraviroc can be given with or without food.

• Metabolism: Maraviroc is a CYP3A4 and p-glycoprotein (Pgp) substrate and requires dosage adjustments when administered with CYP- or Pgp-modulating medications.

• Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with maraviroc.

Major Toxicities

• More common: Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.

• Less common (more severe): Hepatotoxicity that may be preceded by evidence of a systemic allergic reaction (such as pruritic rash, eosinophilia or elevated immunoglobulin) has been reported. Serious adverse events occurred in less than 2% of maraviroc-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html). Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

Pediatric Use

The pharmacokinetics (PK), safety, and efficacy of maraviroc in patients aged <16 years have not been established. A dose-finding and efficacy study is under way in children aged 2 to 17 years. In this trial, maraviroc dose is based upon body surface area and the presence or absence of a potent CYP3A4 inhibitor in the background regimen. Preliminary PK data are encouraging in those on a potent CYP3A4 inhibitor, but low exposures were seen in those not on a potent CYP3A4 inhibitor. Enrollment of and follow up with participants in this trial continues.

References


**Integrase Inhibitors**

Dolutegravir (DTG, Tivicay, GSK1349572)
Elvitegravir (EVG)
Raltegravir (RAL, Isentress)
**Dolutegravir (DTG, Tivicay, GSK1349572)** (Last updated February 12, 2014; last reviewed February 12, 2014)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

**Formulations**

**Tablet:** 50 mg

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**Dosing Recommendations**

**Neonate/Infant Dose:**
- Not approved for use in neonates/infants

**Children Aged <12 Years:**
- Not approved for use in children aged <12 years. A clinical trial in treatment-experienced children aged <12 years is under way.

**Children Aged ≥12 Years and Weighing At Least 40 kg (Treatment-Naive or Treatment-Experienced/Integrase Strand Transfer Inhibitor [INSTI]-Naive):**
- 50 mg once daily
- If co-administered with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin, then 50 mg twice daily should be given.

**Adult Dose**

<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive or treatment-experienced/INSTI-naive</td>
<td>50 mg once daily</td>
</tr>
<tr>
<td>Treatment-naive or treatment-experienced/ INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin</td>
<td>50 mg twice daily</td>
</tr>
<tr>
<td>INSTI-experienced with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance*</td>
<td>50 mg twice daily</td>
</tr>
</tbody>
</table>

* Combinations that do not include metabolic inducers should be considered where possible.

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**Selected Adverse Events**

- Insomnia
- Headache

**Special Instructions**

- May be taken without regard to meals
- Should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications
- Poor virologic response to 50 mg dolutegravir twice daily may occur if INSTI-resistance Q148 substitution is present along with 2 or more additional INSTI-resistance mutations: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

**Metabolism**

- UGT1A1 and cytochrome P450 (CYP) 3A substrate
- **Dosing in patients with hepatic impairment:** No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Dolutegravir is not recommended in patients with severe hepatic impairment because of lack of data.
- **Dosing in patients with renal impairment:** No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment or in INSTI-experienced patients with mild or moderate renal impairment.
- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min)
because dolutegravir concentrations will be decreased (the cause of this decrease is unknown).

**Drug Interactions:**

- **Metabolism:** Dolutegravir is a UGT1A1 and CYP 3A substrate and may require dosage adjustments when administered with UGT1A1 or CYP 3A-modulating medications. Because etravirine significantly reduces plasma concentrations of dolutegravir, dolutegravir should not be administered with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteracts this effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data.

- Before dolutegravir is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions.

**Major Toxicities:**

- More common: Insomnia and headache

- Less common (more severe): Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations ([http://www.iasusa.org/resistance_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html)), and the Stanford University HIV Drug Resistance database offers a discussion of integrase strand transfer inhibitor (INSTI) mutations ([http://hivdb.stanford.edu/DR/INIResiNote.html](http://hivdb.stanford.edu/DR/INIResiNote.html)). Poor virologic response to 50 mg dolutegravir twice daily may occur if INSTI-resistance Q148 substitution is present along with 2 or more additional INSTI-resistance mutations (see table above for list).

**Pediatric Use**

**Approval**

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other antiretroviral drugs for children aged 12 years and older, weighing at least 40 kg, and who are treatment-naive or treatment-experienced and INSTI-naive.

**Efficacy and Pharmacokinetics**

IMPAACT P1093 is an ongoing open-label trial of HIV-infected children with the plan to enroll down to age 4 weeks. FDA approval of dolutegravir down to age 12 years was based on data from 23 treatment-experienced, INSTI-naive adolescents. Intensive pharmacokinetic (PK) evaluations were performed on the first 10 participants (9 weighing ≥40 kg and receiving 50 mg, 1 weighing 37 kg and receiving 35 mg) and revealed comparable exposures to those seen in adults receiving 50 mg once daily.1 Nine of 10 participants achieved HIV RNA concentration <400 copies/mL at week 4 (optimal background therapy was added 5 to 10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 24 weeks, 70% had achieved HIV RNA concentration <50 copies/mL. No safety or tolerability concerns were identified.2 In addition, children aged ≥6 to <12 years are undergoing PK and longer-term follow up in P1093, using investigational tablets of lower strengths (or the 50 mg tablet if they
weigh at least 40 kg). An oral pediatric granule formulation will also be studied.

References


### Dosing Recommendations

**Pediatric Dose (aged <18 years):**
- Not Food and Drug Administration (FDA)-approved or recommended for use in children aged <18 years.

**Adult Dose (aged ≥18 years):**
- 1 tablet once daily in antiretroviral (ARV) treatment-naive adults.

### Selected Adverse Events
- Diarrhea, nausea, flatulence
- Renal insufficiency
- Cobicistat alters tubular secretion of creatinine, and therefore, may decrease creatinine-based estimates of glomerular filtration rate without a true change in glomerular filtration.
- Decreased bone mineral density (BMD).

### Special Instructions
- Administer with food.
- Monitor estimated creatinine clearance, urine glucose, and urine protein; in patients at risk of renal impairment, also monitor serum phosphate. Patients with increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of FTC or TDF. Severe acute exacerbation of HBV can occur when FTC or TDF are discontinued; therefore, monitor hepatic function for several months after therapy with FTC or TDF is stopped.
- Not recommended for use with other ARV drugs.

### Metabolism
- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl) <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.
Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- **Metabolism:** Stribild contains elvitegravir and cobicistat. Elvitegravir is metabolized by cytochrome P (CYP) 3A4 and is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, it inhibits ATP-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions.

- **Renal elimination:** Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided.

- **Protease inhibitors:** Stribild should not be administered concurrent with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A.

- Not recommended for use with other ARV drugs.

Major Toxicities

- **More common:** Nausea, diarrhea, and flatulence.

- **Less common (more severe):** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors including tenofovir disoproxil fumarate (tenofovir) and emtricitabine. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

Pediatric Use

**Approval**

Elvitegravir is only available as the fixed-dose combination product Stribild, which contains elvitegravir/cobicistat/emtricitabine/tenofovir. Stribild is not FDA-approved for use in children aged <18 years. There are currently no data on its use in individuals aged <18 years, although studies in participants as young as age 12 years are ongoing.

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor added as a pharmacokinetic enhancer. Cobicistat slows elvitegravir metabolism and allows once-daily administration of the combination. Stribild is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive adults aged ≥18 years based on trials showing non-inferiority to regimens of emtricitabine/tenofovir plus atazanavir/ritonavir, or emtricitabine/tenofovir plus efavirenz. There is cross-resistance between elvitegravir and raltegravir. Cobicistat alters the renal tubular secretion of creatinine, so creatinine-based calculations of estimated glomerular filtration rate (eGFR) will be altered, even though the actual GFR might be only minimally changed. Adults who experience a confirmed increase in serum creatinine greater than 0.4 mg/dL from baseline should be closely monitored for renal toxicity by following creatinine for further increases and urinalysis for evidence of proteinuria or glycosuria.
References


Dosing Recommendations

Neonate Dose:
- Not approved for use in neonates. **Note:** Metabolism by UGT1A1 is immature in neonates. Neonatal dose will be studied in full-term infants in IMPAACT P1110.

Infant/Pediatric Dose

**Oral Suspension Dosing Table**
Children at least 4 weeks of age and weighing 3 kg to < 20 kg:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Volume (Dose) of Suspension to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to &lt;4</td>
<td>1 mL (20 mg) twice daily</td>
</tr>
<tr>
<td>4 to &lt;6</td>
<td>1.5 mL (30 mg) twice daily</td>
</tr>
<tr>
<td>6 to &lt;8</td>
<td>2 mL (40 mg) twice daily</td>
</tr>
<tr>
<td>8 to &lt;11</td>
<td>3 mL (60 mg) twice daily</td>
</tr>
<tr>
<td>11 to &lt;14</td>
<td>4 mL (80 mg) twice daily</td>
</tr>
<tr>
<td>14 to &lt;20</td>
<td>5 mL (100 mg) twice daily</td>
</tr>
</tbody>
</table>

* The weight-based dosing recommendation for the oral suspension is based on approximately 6 mg/kg/dose twice daily. **Note:** Maximum dose of oral suspension is 5 ml (100 mg) twice daily.

Children Aged 2 to <12 Years:
- <25 kg: Chewable tablet twice daily (maximum of 300 mg twice daily). See table below for chewable tablet dose.
- ≥25 kg: 400-mg film-coated tablet twice daily **or** chewable tablets twice daily. See table for chewable tablet dose.

Selected Adverse Events
- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

Special Instructions
- Can be given without regard to food.
- Chewable tablets may be chewed or swallowed whole.

**Film-coated tablets, chewable tablets, and oral suspension are not interchangeable.** Chewable tablets and oral suspension have better bioavailability than the film-coated tablets.

- Chewable tablets should be stored in the original package with desiccant to protect from moisture.
- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.

- Oral suspension is provided with a kit which includes 2 mixing cups, 2 dosing syringes, and 60 foil packets. Detailed instructions are provided in Instructions for Use document. Each foil, single-use packet contains 100 mg of raltegravir, which will be suspended in 5 mL of water for final concentration of 20 mg/mL. Dose should be administered...
**Adolescent (Aged ≥ 12 Years)/Adult Dose:**

- **400-mg film-coated tablet twice daily**

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**Chewable Tablet Dosing Table**

Dosing of chewable tablets in children aged 2 to <12 years:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dose</th>
<th>Number of Chewable Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to &lt;14</td>
<td>75 mg twice daily</td>
<td>3 X 25 mg twice daily</td>
</tr>
<tr>
<td>14 to &lt;20</td>
<td>100 mg twice daily</td>
<td>1 X 100 mg twice daily</td>
</tr>
<tr>
<td>20 to &lt;28</td>
<td>150 mg twice daily</td>
<td>1.5 X 100 mg b twice daily</td>
</tr>
<tr>
<td>28 to &lt;40</td>
<td>200 mg twice daily</td>
<td>2 X 100 mg twice daily</td>
</tr>
<tr>
<td>≥40</td>
<td>300 mg twice daily</td>
<td>3 X 100 mg twice daily</td>
</tr>
</tbody>
</table>

* a The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

* b The 100-mg chewable tablet can be divided into equal halves.

**Note:** Maximum dose of chewable tablets is 300 mg twice daily.

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**Drug Interactions** (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)

- **Metabolism:** The major route of raltegravir elimination is mediated through glucuronidation by uridine diphosphate glucotransferase (UGT1A1).

- Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir whereas inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.

- In adults, an increased dose of raltegravir is recommended when co-administered with rifampin. The appropriate dose adjustment is not known in children.

- Efavirenz and etravirine may decrease raltegravir concentrations.

- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with raltegravir.

- Raltegravir plasma concentrations may be reduced when administered with antacids containing divalent metal cations such as magnesium hydroxide, aluminum hydroxide, or calcium carbonate. Co-administration or administration of raltegravir within 2 hours of aluminum and/or magnesium hydroxide-containing antacids resulted in significantly reduced raltegravir plasma levels and is not recommended.

**Major Toxicities:**

- **More common:** Nausea, headache, dizziness, diarrhea, fatigue, itching, and insomnia

- **Less common:** Abdominal pain, vomiting. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening aspartate aminotransferase (AST), alanine aminotransferase (ALT),...
or total bilirubin than are patients who are not coinfected.

- **Rare**: Moderate to severe increase in creatine phosphokinase. Myopathy and rhabdomyolysis: Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis have been reported. Thrombocytopenia.

**Resistance**

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/INIResiNote.html).

**Pediatric Use**

**Approval**

Raltegravir is FDA-approved for use in infants and children aged ≥ 4 weeks and weight ≥3 kg. Current pediatric approval and dosing recommendations are based upon evaluations in 122 patients aged ≥ 4 weeks to 18 years enrolled in IMPAACT P1066.

**Efficacy and Pharmacokinetics**

**Children Aged 2 to 18 Years**

IMPAACT P1066 is a Phase I/II open label multicenter study to evaluate the pharmacokinetic (PK) profile, safety, tolerability, and efficacy of various formulations of raltegravir in combination antiretroviral treatment (cART)-experienced, HIV-infected children and adolescents aged 2 to 18 years in combination with an optimized background cART regimen. Subjects receive either the 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing at least 25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 to <12 years). In IMPAACT P1066, the initial dose-finding stage includes intensive PK evaluation in various age cohorts: (aged 12 to <19 years, 6 to <12 years, 2 to <6 years). Dose selection is based upon achieving target PK parameters similar to those seen in adults: PK targets are geometric mean (GM) area under the curve of 14–25 µMxh and GM 12-hour concentration >33 nM. Additional subjects are then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. Ninety-three (97%) subjects completed 24 weeks of treatment with 54% achieving HIV RNA <50 copies/mL with a mean CD4 T lymphocyte (CD4) count (percent [%]) increase of 119 cells/mm³ (3.8%). Ninety-one subjects completed 48 weeks of treatment with 57% achieving HIV RNA <50 copies/mL with a mean CD4 count (percent [%]) increase of 156 cells/mm³ (4.6%). In subjects who experienced virologic failure, development of drug resistance and/or poor adherence were contributing factors. The frequency, type, and severity of drug-related adverse reactions through week 48 were comparable to those observed in adult studies. Observed adverse reactions considered drug-related included one patient with grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; one patient with a grade 2 allergic rash; and one patient with grade 3 ALT and grade 4 AST laboratory elevations. There were no discontinuations due to adverse events and no drug-related deaths.

In 19 HIV-infected children and adolescents with multidrug-resistant virus in the HIV Spanish Pediatric Cohort (CoRISe), good virologic response and improved CD4 counts were observed when raltegravir was included in an optimized regimen. Additional experience from the French expanded access program in treatment-experienced adolescents support the good virologic and immunologic results observed in P1066.

**Infants/Toddlers Aged At Least 4 Weeks to <2 Years**

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the oral suspension in combination with an optimized background regimen. All subjects had received prior antiretrovirals as part of prevention of perinatal transmission and/or treatment of HIV infection, and 69% had baseline plasma HIV-1 RNA exceeding 100,000 copies/mL. Twenty-three (88%) completed 48 weeks of treatment with 44% achieving HIV RNA <50 copies/mL with a mean CD4 cell count (percent [%]) increase of

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**
PK parameters were similar to those achieved for the older cohorts in P1066.

**Neonates Aged <4 Weeks**

There are no data on the safety and dosing of raltegravir in neonates aged <4 weeks. Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth and it is likely that raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for UGT and albumin binding sites.

Washout PK of raltegravir in neonates born to HIV-infected pregnant women was studied in P1097. The neonatal plasma half-life was highly variable, ranging from 9.3 to 184 hours, suggesting potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of raltegravir. IMPAACT P1110 is a phase I trial that will evaluate the safety and PK of raltegravir in HIV-1 exposed neonates at high risk of acquiring HIV-1 infection.

**Formulations**

The PK of raltegravir were compared in HIV-infected adult patients receiving intact whole 400-mg tablets and patients who chewed the 400-mg film-coated tablets because of swallowing difficulties. Drug absorption was significantly higher in the group who chewed the tablets, although palatability was rated as poor.

The raltegravir chewable tablet and oral suspension have higher oral bioavailability than the film-coated tablet based on a comparative study in healthy adult volunteers. Interpatient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets. Because of the differences in the bioavailability of the chewable and film-coated tablets, the dosing recommendations are different and these products are **not interchangeable**.

**References**


## Appendix B: Acronyms

(Last updated February 12, 2014; last reviewed February 12, 2014)

<table>
<thead>
<tr>
<th>Acronym/Abbreviation</th>
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<td>lamivudine</td>
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<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
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<td>abacavir</td>
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<td>alkaline phosphatase</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>ANC</td>
<td>absolute neutrophil count</td>
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<td>antiretroviral</td>
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<td>bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<td>blood urea nitrogen</td>
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<td>combination antiretroviral therapy</td>
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<td>complete blood count</td>
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<td>CHER Trial</td>
<td>The Children with HIV Early Antiretroviral Therapy Trial</td>
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<td>CHIPS</td>
<td>Collaborative HIV Pediatric Study</td>
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<td>CK</td>
<td>creatine kinase</td>
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<td>C_{max}</td>
<td>maximum plasma concentration</td>
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<tr>
<td>C_{min}</td>
<td>minimum plasma concentration</td>
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<td>CrCl</td>
<td>creatinine clearance</td>
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<td>computed tomography</td>
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<td>diabetes mellitus</td>
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<td>depot medroxyprogesterone acetate</td>
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<td>directly observed therapy</td>
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<td>darunavir</td>
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<td>ENV, ENF</td>
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<td>François-Xavier Bagnoud Center</td>
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<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
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<tr>
<td>G-CSF</td>
<td>granulocyte colony-stimulating factor</td>
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<td>gamma glutamyl transpeptidase</td>
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<td>gastrointestinal</td>
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<td>genotypic inhibitory quotient</td>
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<td>HAART</td>
<td>highly active antiretroviral therapy</td>
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<td>HAV</td>
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<tr>
<td>HBV</td>
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<td>HDL</td>
<td>high-density lipoprotein</td>
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<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
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<tr>
<td>Hgb</td>
<td>hemoglobin</td>
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<tr>
<td>HHS</td>
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<td>HIVMA</td>
<td>HIV Medicine Association</td>
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<td>HPPMCS</td>
<td>HIV Paediatric Prognostic Markers Collaborative Study</td>
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<td>HRSA</td>
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<td>HSR</td>
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<td>IAS-USA</td>
<td>International Antiviral Society-USA</td>
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<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>mean inhibitory concentration</td>
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<td>ICH</td>
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<td>INSTI</td>
<td>integrase strand transfer inhibitor</td>
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<td>inhibitory quotient</td>
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<td>IRIS</td>
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<td>intravenous immune globulin</td>
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<td>LDL</td>
<td>low-density lipoprotein</td>
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<td>low-density lipoprotein cholesterol</td>
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<td>lopinavir</td>
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<td>ritonavir-boosted lopinavir</td>
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<td>MAC</td>
<td><em>Mycobacterium avium</em> complex</td>
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<td>Acronym</td>
<td>Term</td>
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<tr>
<td>m-DOT</td>
<td>modified directly observed therapy</td>
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<td>MEMS</td>
<td>Medication Event Monitoring System</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>msec</td>
<td>milliseconds</td>
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<td>MVC</td>
<td>maraviroc</td>
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<td>NA-ACCORD</td>
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<td>NFV</td>
<td>nelfinavir</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse transcriptase inhibitor/non-nucleoside analogue reverse transcriptase inhibitor</td>
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<td>non-HDL-C</td>
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<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor/nucleoside analogue reverse transcriptase inhibitor</td>
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<tr>
<td>NVP</td>
<td>nevirapine</td>
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<tr>
<td>OARAC</td>
<td>Office of AIDS Research Advisory Council</td>
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<tr>
<td>OBR</td>
<td>optimized background regimen</td>
</tr>
<tr>
<td>OBT</td>
<td>optimized background therapy</td>
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<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
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<tr>
<td>OI</td>
<td>opportunistic infection</td>
</tr>
<tr>
<td>PBMC</td>
<td>peripheral blood mononuclear cells</td>
</tr>
<tr>
<td>PCP</td>
<td><em>Pneumocystis jiroveci</em> pneumonia</td>
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<td>PCR</td>
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<td>PENTA</td>
<td>Paediatric European Network for Treatment of AIDS</td>
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<td>PG</td>
<td>plasma glucose</td>
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<tr>
<td>Pgp</td>
<td>p-glycoprotein</td>
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<td>PI</td>
<td>protease inhibitor</td>
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<td>PIDS</td>
<td>Pediatric Infectious Diseases Society</td>
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<tr>
<td>PK</td>
<td>pharmacokinetic</td>
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<tr>
<td>PPI</td>
<td>proton-pump inhibitor</td>
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<tr>
<td>PR</td>
<td>protease</td>
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<td>PUFA</td>
<td>polyunsaturated fatty acid</td>
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<td>RAL</td>
<td>raltegravir</td>
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<td>RBV</td>
<td>ribavirin</td>
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<td>random plasma glucose</td>
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<td>enfuvirtide</td>
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<td>tuberculosis</td>
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<tr>
<td>TC</td>
<td>total cholesterol</td>
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<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
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<td>TDM</td>
<td>therapeutic drug monitoring</td>
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<td>TEN</td>
<td>toxic epidermal necrolysis</td>
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<tr>
<td>TG</td>
<td>triglyceride</td>
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<tr>
<td>THAM</td>
<td>tris–hydroxymethyl-aminomethane</td>
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<tr>
<td>TMP-SMX</td>
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<td>TPV</td>
<td>tipranavir</td>
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<td>TPV/r</td>
<td>ritonavir-boosted tipranavir</td>
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<td>UA</td>
<td>urinalysis</td>
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<td>uridine diphosphate glucoronosyltransferase</td>
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<td>upper limit of normal</td>
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<td>ZDV</td>
<td>zidovudine</td>
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Table A. Likelihood of Developing AIDS or Death Within 12 Months, by Age and CD4 T-Cell Percentage or \( \log_{10} \) HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

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<thead>
<tr>
<th>CD4 Percentage</th>
<th>( \log_{10} ) HIV RNA Copy Number</th>
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<td>10%</td>
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<tr>
<td>20%</td>
<td>5.0</td>
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<tr>
<td>25%</td>
<td>4.0</td>
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<td>30%</td>
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</table>

Percent Mortality (95% Confidence Interval)

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<th>Age</th>
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<th>20%</th>
<th>25%</th>
<th>30%</th>
<th>6.0</th>
<th>5.0</th>
<th>4.0</th>
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<td>6 Months</td>
<td>28.7</td>
<td>12.4</td>
<td>8.5</td>
<td>6.4</td>
<td>9.7</td>
<td>4.1</td>
<td>2.7</td>
</tr>
<tr>
<td>1 Year</td>
<td>19.5</td>
<td>6.8</td>
<td>4.5</td>
<td>3.3</td>
<td>8.8</td>
<td>3.1</td>
<td>1.7</td>
</tr>
<tr>
<td>2 Years</td>
<td>11.7</td>
<td>3.1</td>
<td>2.0</td>
<td>1.5</td>
<td>8.2</td>
<td>2.5</td>
<td>1.1</td>
</tr>
<tr>
<td>5 Years</td>
<td>4.9</td>
<td>0.9</td>
<td>0.6</td>
<td>0.5</td>
<td>7.8</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>10 Years</td>
<td>2.1</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>7.7</td>
<td>2.0</td>
<td>0.6</td>
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Percent Developing AIDS (95% Confidence Interval)

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<th>25%</th>
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<th>6.0</th>
<th>5.0</th>
<th>4.0</th>
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<td>51.4</td>
<td>31.2</td>
<td>24.9</td>
<td>20.5</td>
<td>23.7</td>
<td>13.6</td>
<td>10.9</td>
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<tr>
<td>1 Year</td>
<td>40.5</td>
<td>20.9</td>
<td>15.9</td>
<td>12.8</td>
<td>20.9</td>
<td>10.5</td>
<td>7.8</td>
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<tr>
<td>2 Years</td>
<td>28.6</td>
<td>12.0</td>
<td>8.8</td>
<td>7.2</td>
<td>18.8</td>
<td>8.1</td>
<td>5.3</td>
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<tr>
<td>5 Years</td>
<td>14.7</td>
<td>4.7</td>
<td>3.7</td>
<td>3.1</td>
<td>17.0</td>
<td>6.0</td>
<td>3.2</td>
</tr>
<tr>
<td>10 Years</td>
<td>7.4</td>
<td>2.2</td>
<td>1.9</td>
<td>1.8</td>
<td>16.2</td>
<td>5.1</td>
<td>2.2</td>
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</table>


Table B. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Cell Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>50–99</th>
<th>100–199</th>
<th>200–349</th>
<th>350–499</th>
<th>500+</th>
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<tbody>
<tr>
<td>Rate of Death Per 100 Patient-Years</td>
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<td>21.4</td>
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Rate of AIDS or Death per 100 Patient-Years

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Table C. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4 T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children

<table>
<thead>
<tr>
<th>Baseline HIV RNAc (Copies/mL)</th>
<th>Baseline CD4 Percentage</th>
<th>Deathsb</th>
<th>No. Patientsd</th>
<th>Number</th>
<th>Percentage</th>
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<tr>
<td>≤100,000</td>
<td>≥15%</td>
<td></td>
<td>103</td>
<td>15</td>
<td>(15%)</td>
</tr>
<tr>
<td></td>
<td>&lt;15%</td>
<td></td>
<td>24</td>
<td>15</td>
<td>(63%)</td>
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<tr>
<td>&gt;100,000</td>
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<td>89</td>
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<td>(36%)</td>
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<tr>
<td></td>
<td>&lt;15%</td>
<td></td>
<td>36</td>
<td>29</td>
<td>(81%)</td>
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</table>

a Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.
b Mean follow-up: 5.1 years.
c Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.
d Mean age: 3.4 years.


Figure A. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

![Figure A](http://example.com/figureA.png)

Figure modified from Lancet 2003;362:1605-1611
Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

Figure modified from *Lancet* 2003;362:1605-1611

Figure C. Death Rate per 100 Person-Years in HIV-Infected Children Aged 5 Years or Older in the HIV Paediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study*
Figure D. Estimated Probability of AIDS Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

Figure modified from *Lancet* 2003;362:1605-1611

Figure E. Estimated Probability of Death Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

Figure modified from *Lancet* 2003;362:1605-1611
Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Register for e-mail notification of guideline updates at http://aidsinfo.nih.gov/e-news.
Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Developed by the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Perinatal Guidelines:


It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo website (http://aidsinfo.nih.gov).

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/8/2014
What’s New in the Guidelines  (Last updated March 28, 2014; last reviewed March 28, 2014)

Key changes to the Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions to Reduce Perinatal HIV Transmission in the United States are summarized below. Some content has been reorganized and revised to enhance usability. Text, appendices, and references have been updated to include new data and publications where relevant. The terms “mother-to-child transmission (MTCT)” and “prevention of mother-to-child transmission (PMTCT)” have been replaced with “perinatal transmission” and “prevention of perinatal transmission,” respectively. All changes are highlighted throughout the guidelines.

Preconception Counseling and Care for HIV-Infected Women of Childbearing Age

- The Panel recommends that all HIV-infected women contemplating pregnancy be on a maximally suppressive antiretroviral (ARV) regimen (AII).
- HIV-infected women who do not desire pregnancy should be offered effective and appropriate contraceptive methods. They can use all available contraceptive methods, including hormonal contraception and emergency contraception, as appropriate.
- Further discussion about drug interactions between ARV agents and hormonal contraceptives has been added, including revised and updated Table 3: Drug Interactions between Antiretroviral Agents and Hormonal Contraceptives.

Reproductive Options for HIV-Concordant and Serodiscordant Couples

- The Panel recommends that HIV-infected partner(s) in HIV-seroconcordant and HIV-serodiscordant couples planning pregnancy attain maximum viral suppression before attempting conception (AIII).
- The Panel notes that periconception administration of ARV pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission (CIII). A new table has been added reviewing clinical trials of PrEP (see Table 4: Clinical Trials of Pre-Exposure Prophylaxis).
- The Panel also notes that no studies exist about the utility of PrEP in an uninfected individual whose infected partner is receiving combination antiretroviral therapy (cART) and has a suppressed viral load.
- Pregnancy is not a contraindication to PrEP.

General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

- This section incorporates content previously included in separate, earlier sections (Mechanisms of Action of Antiretroviral Prophylaxis in Reducing Perinatal Transmission of HIV and Perinatal Transmission of HIV and Maternal HIV RNA Copy Number).

Nevirapine and Hepatic/Rash Toxicity

- Language has been strengthened to indicate that in patients with pre-existing liver disease, use of ARV medications other than nevirapine should be considered.

Recommendations for Use of Antiretroviral Drugs during Pregnancy

- A new table has been added indicating cART regimen choices for ARV-naive HIV-infected pregnant women and including the rationale for the choices (see Table 6: What to Start: Initial Combination Regimens for Antiretroviral Naive-Pregnant Women).
Table 7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy has been redesigned, streamlined, and updated to summarize information about formulation, dosing, and recommendations for use of individual ARV drugs in pregnancy. More detailed information on individual drugs is found in Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy.

- The Preferred dual nucleoside analogue reverse transcriptase inhibitors (NRTI) for ARV-naive pregnant women have been expanded to include abacavir plus lamivudine and tenofovir plus emtricitabine or lamivudine in addition to zidovudine plus lamivudine.
- The Preferred protease inhibitors (PIs) for ARV-naive pregnant women remain ritonavir-boosted atazanavir and ritonavir-boosted lopinavir. Alternative PIs include ritonavir-boosted darunavir and ritonavir-boosted saquinavir.
- The Preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) for ARV-naive pregnant women is now efavirenz, initiated after the first 8 weeks of pregnancy. Nevirapine is the alternative NNRTI for ARV-naive pregnant women.
- Raltegravir has been moved to the Alternative category for ARV-naive pregnant women, for consideration particularly when drug interactions with PI-based regimens are a concern.
- Drugs for which data are currently insufficient in pregnancy to recommend routine use in ARV-naive women include dolutegravir, elvitegravir/cobicistat/tenofovir/emtricitabine fixed drug combination, ritonavir-boosted fosamprenavir, maraviroc, and rilpivirine.

HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Treatment
- The Panel discusses the use of raltegravir in late pregnancy in women with high viral load, but because the efficacy and safety of this approach have only been described in anecdotal reports, the Panel does not routinely recommend this approach.

HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment
- The Panel discusses updated data related to virologic response to cART in women who previously received cART but subsequently stopped therapy and were on no ARV drugs prior to re-starting cART in the current pregnancy.

HIV/Hepatitis C Coinfection
- The Panel discusses availability of new anti-hepatitis C drugs and the lack of data on these new agents in pregnancy. Interferon alfa and pegylated interferon are not recommended in pregnancy and ribavirin should not be used in pregnancy (AII). Because management of HIV/hepatitis C coinfection in pregnancy is complex, consultation with an expert in management of these conditions is recommended.

HIV-2 Infection and Pregnancy
- The Panel discusses difficulties in diagnosis of HIV-2 and difficulties with the currently available tests in the United States; confirmatory testing for HIV-2 can be obtained from the Centers for Disease Control and Prevention.
- No validated HIV-2 genotype or phenotype resistance assays are available in the United States; European experts have developed a rule set and an automated tool for HIV-2 drug resistance analyses that is freely available on the Internet (see http://www.hiv-grade.de).
Monitoring of the Woman and Fetus during Pregnancy

- While monitoring of CD4 T lymphocyte (CD4) cell count during pregnancy is generally recommended every 3 months, this can be reduced to 6-month intervals in patients on cART with consistently suppressed viral load who have immune reconstitution (CD4 cell count increase well above the threshold for risk of opportunistic infection) (CIII).

Intrapartum Antiretroviral Therapy/Prophylaxis

- The HIV RNA threshold for requiring administration of intravenous (IV) zidovudine during labor (in addition to continuing antepartum cART) has been modified to be consistent with the threshold for scheduled cesarean delivery and based on additional data summarized in the section.
- IV zidovudine should be administered to HIV-infected women with HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery (AI), but it is not required for HIV-infected women receiving combination ARV regimens who have HIV RNA ≤1,000 copies/mL consistently during late pregnancy and near delivery and no concerns regarding adherence to the regimen.

Postpartum Follow-Up of HIV-Infected Women

- The Panel’s discussion about continuing cART postpartum has been revised to highlight collaborative decision-making between provider and patient, the importance of ensuring continuity of treatment from the antepartum to the postpartum period, and to reflect the current adult ARV treatment guidelines.
  - Decisions about continuing cART after delivery should be made in consultation with a woman and her HIV provider, ideally before delivery (AIII). cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission, although the strength and evidence for this recommendation vary by pretreatment CD4 cell count.

Infant Antiretroviral Prophylaxis

- A 4-week neonatal zidovudine chemoprophylaxis regimen can be considered when the mother has received standard cART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence (BII).
- The Panel provides information on the case of a functional cure in an infant. The Panel notes that further investigation is ongoing and clinical trials are planned to address whether administration of a three-drug regimen in therapeutic doses to HIV-exposed high-risk infants could alter the establishment and long-term persistence of HIV infection. Investigation also is ongoing and clinical trials are planned to assess the safety of such an approach in infants, particularly in the setting of preterm delivery for which pharmacokinetic data on most drugs are lacking.
- The NICHD/HPTN 040/P1043 two-drug infant prophylaxis regimen of 6 weeks of zidovudine plus 3 doses of nevirapine in the first week of life continues to be the general recommendation for infant prophylaxis for infants born to mothers who did not receive antepartum ARV drugs or received only intrapartum drugs (AI); the regimen should be initiated as soon after delivery as possible. Decisions about use of alternative combination ARV prophylaxis regimens in infants should be made in consultation with a pediatric HIV specialist before delivery, if possible, and should be accompanied by a discussion with the mothers about potential risks and benefits of this approach.

Appendix A. Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal Transmission of HIV

- Content about lessons from clinical trials and the table Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal Transmission of HIV has been moved from the beginning of the document to a new Appendix.
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### Members of the Panel

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<tr>
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<th>Institution</th>
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<th>Name</th>
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* Moved to Office of Global AIDS Coordinator, State Department

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<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carolyn Burr, RN, EdD</td>
<td>François-Xavier Bagnoud Center, Rutgers School of Nursing, Newark, NJ</td>
</tr>
<tr>
<td>Deborah Storm, MSN, PhD</td>
<td>François-Xavier Bagnoud Center, Rutgers School of Nursing, Newark, NJ</td>
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Financial Disclosure List for Members of the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission  
(Last updated March 28, 2014; last reviewed March 28, 2014)

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<tr>
<th>Name</th>
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<td>Cu-Uvin, Susan</td>
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<td>Deyo, Stephanie</td>
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<td>Flynn, Patricia M.</td>
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<td>Fowler, Mary Glenn</td>
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<td>Jamieson, Denise</td>
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<td>Lazenby, Gweneth</td>
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<td>Levison, Judy</td>
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<td>Maupin, Robert</td>
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<td>Mirochnick, Mark</td>
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Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/8/2014
## Financial Disclosure List for Members of the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission

(Last updated March 28, 2014; last reviewed March 28, 2014)

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<th>Name</th>
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<tr>
<td>Mofenson, Lynne</td>
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<td>Nesheim, Steve</td>
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<td>Prioleau, Fatima Y.</td>
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<td>Ross, Polly E.</td>
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<td>Shapiro, Alan</td>
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<td>Siberry, George</td>
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<td>Spector, Stephen A.</td>
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<td>Squires, Kathleen E.</td>
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<td>Watts, D. Heather</td>
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<td>Weinberg, Geoffrey A.</td>
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**Key to Acronyms:** DSMB = Data Safety Monitoring Board; ES = Executive Secretary; ExOM = Ex Officio Member; HHS = Member from Department of Health and Human Services; M = Member; N/A = Not applicable; NVO = Nonvoting Observer
Introduction (Last updated March 28, 2014; last reviewed March 28, 2014)

Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal transmission of HIV have evolved considerably in the United States over the last 25 years, reflecting changes in the epidemic and the science of prevention. With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral (ARV) prophylaxis, scheduled cesarean delivery, and avoidance of breastfeeding, the rate of perinatal transmission of HIV has dramatically diminished to less than 2% in the United States and Europe.

These guidelines update the July 31, 2012, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. The Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel), a working group of the Office of AIDS Research Advisory Council (OARAC), develops these guidelines. The guidelines provide health care providers with information for discussion with HIV-infected pregnant women to enable the patient/provider team to make informed decisions regarding the use of ARV drugs during pregnancy and use of scheduled cesarean delivery to reduce perinatal transmission of HIV. The recommendations in the guidelines are accompanied by discussion of various circumstances that commonly occur in clinical practice and the factors influencing treatment considerations. The Panel recognizes that strategies to prevent perinatal transmission and concepts related to management of HIV in pregnant women are rapidly evolving and will consider new evidence and adjust recommendations accordingly. The updated guidelines are available from the AIDSinfo website (http://aidsinfo.nih.gov).

Health care providers considering the use of ARV agents for HIV-infected women during pregnancy must take into account two separate—but related—issues:

1. ARV treatment of maternal HIV infection; and
2. ARV chemoprophylaxis to reduce the risk of perinatal transmission of HIV.

The benefits of ARV drugs for a pregnant woman must be weighed against the risks of adverse events to the woman, fetus, and newborn. Combination drug regimens are considered the standard of care both for treatment of HIV infection and for prevention of perinatal transmission of HIV. After provider counseling and discussion about ARV drug use during pregnancy, a pregnant woman’s informed choice on whether to take ARV drugs for her treatment, for prevention of perinatal transmission, and/or to follow other medical recommendations intended to reduce perinatal transmission of HIV should be respected. Coercive and punitive policies are potentially counterproductive; they may undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize fetal and neonatal well-being.

The current guidelines have been structured to reflect the management of an individual mother-child pair and are organized into a brief discussion of preconception care followed by principles for management of a woman and her infant during the antepartum, intrapartum, and postpartum periods. Although perinatal transmission of HIV occurs worldwide, these recommendations have been developed for use in the United States. Alternative strategies may be appropriate in other countries. Policies and practices in other countries regarding the use of ARV drugs for reduction of perinatal transmission of HIV may differ from the recommendations in these guidelines and will depend on local considerations, including availability and cost of ARV drugs, accessibility of facilities for safe intravenous infusions during labor, and local recommendations regarding breastfeeding by HIV-infected women.
### Guidelines Development Process

<table>
<thead>
<tr>
<th>Topic</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>Goal of the Guidelines</strong></td>
<td>Provide guidance to HIV care practitioners on the optimal use of ARV agents in pregnant women for treatment of HIV infection and for prevention of perinatal transmission of HIV in the United States.</td>
</tr>
<tr>
<td><strong>Panel Members</strong></td>
<td>The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (such as training in either obstetrics/gynecology or women’s health) and interventions for prevention of perinatal transmission (such as specialized training in pediatric HIV infection) as well as community representatives with knowledge of HIV infection in pregnant women and interventions for prevention of perinatal transmission. The U.S. government representatives, appointed by their agencies, include at least 1 representative from each of the following Department of Health and Human Services agencies: the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. A list of all Panel members can be found on Page IV of the guidelines.</td>
</tr>
<tr>
<td><strong>Financial Disclosures</strong></td>
<td>All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDSinfo website (<a href="http://aidsinfo.nih.gov">http://aidsinfo.nih.gov</a>).</td>
</tr>
<tr>
<td><strong>Users of the Guidelines</strong></td>
<td>Providers of care to HIV-infected pregnant women and to HIV-exposed infants.</td>
</tr>
<tr>
<td><strong>Developer</strong></td>
<td>Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—a working group of OARAC.</td>
</tr>
<tr>
<td><strong>Funding Source</strong></td>
<td>Office of AIDS Research, NIH</td>
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<td><strong>Evidence for Recommendations</strong></td>
<td>The recommendations in these guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.</td>
</tr>
<tr>
<td><strong>Recommendation Grading</strong></td>
<td>See Table 2.</td>
</tr>
<tr>
<td><strong>Method of Synthesizing Data</strong></td>
<td>Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. A structured literature search is conducted by staff from the HIV/AIDS National Resource Center at the Francois-Xavier Bagnoud Center (through funding from HRSA) and provided to the Panel working group. The members review and synthesize the available data and propose recommendations to the entire Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals receiving endorsement from a consensus of members are included in the guidelines as official Panel recommendations.</td>
</tr>
<tr>
<td><strong>Other Guidelines</strong></td>
<td>These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines outline the use of ARV agents in non-pregnant HIV-infected adults and adolescents, HIV-infected children, and people who experience occupational or non-occupational exposure to HIV. The guidelines described are also available on the AIDSinfo website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>). Preconception management for non-pregnant women of reproductive age is briefly discussed in this document. However, for more detailed discussion on issues of treatment of non-pregnant adults, the Working Group defers to the designated expertise offered by Panels that have developed those guidelines.</td>
</tr>
<tr>
<td><strong>Update Plan</strong></td>
<td>The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, new dosing formulations, or changes in dosing frequency), significant new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and accompanying recommendations on the AIDSinfo website until the guidelines can be updated with appropriate changes. Updated guidelines are available on the AIDSinfo website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>).</td>
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### Table 1. Outline of the Guidelines Development Process

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Guidelines Development Process

Table 1. Outline of the Guidelines Development Process, cont’d

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<td>Public Comments</td>
<td>A 2-week public comment period follows release of the updated guidelines on the AIDSinfo website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at <a href="mailto:contactus@aidsinfo.nih.gov">contactus@aidsinfo.nih.gov</a>.</td>
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</table>

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommended statement is rated with a letter of A, B, or C that represents the strength of the recommendation and with a numeral I, II, or III, according to the quality of evidence.

Table 2. Rating Scheme for Recommendations

<table>
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<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
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<tbody>
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<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

References

4. Taylor A, Little K, Zhang X. Estimated perinatal antiretroviral exposures, cases prevented, and infected infants in the era of antiretroviral prophylaxis in the US. Conference on Retroviruses and Opportunistic Infections (CROI); 2012; Boston, MA.
Overview

The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists, and other national organizations recommend offering all women of childbearing age comprehensive family planning and the opportunity to receive preconception counseling and care as a component of routine primary medical care. The purpose of preconception care is to improve the health of each woman before conception by identifying risk factors for adverse maternal or fetal outcome, providing education and counseling targeted to patients’ individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes.1 Preconception care is not something that occurs in a single clinical visit but, rather, a process of ongoing care and interventions integrated into primary care to address the needs of women during the different stages of reproductive life. Because more than half of all pregnancies in the United States are unintended2-6 it is important that comprehensive family planning and preconception care be integrated into routine health visits. Providers should initiate and document a nonjudgmental conversation with all women of reproductive age concerning their reproductive desires because women may be reluctant to bring this up themselves.7-9 HIV care providers who routinely care for women of reproductive age play an important role in promoting preconception health and informed reproductive decisions.

The fundamental principles of preconception counseling and care are outlined in the CDC Preconception Care Work Group’s Recommendations to Improve Preconception Health and Health Care. In addition to the general components of preconception counseling and care that are appropriate for all women of reproductive age, HIV-infected women have specific needs that should be addressed.10-12 Because many HIV-infected women are aware of their HIV status before becoming pregnant, issues that impact pregnancy can be addressed before conception during their routine medical care for HIV disease. In addition to the principles outlined by the CDC Preconception Care Work Group,13 the following components of preconception counseling and care are specifically recommended for HIV-infected women. Health care providers should:

- Discuss reproductive options; actively assess women’s pregnancy intentions on an ongoing basis throughout the course of care; and, when appropriate, make referrals to experts in HIV and women’s health, including experts in reproductive endocrinology and infertility when necessary.14,15
- Counsel on safe sexual practices that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted diseases, and reduce the potential to acquire more virulent or resistant
strains of HIV.

- Counsel on eliminating alcohol, illicit drug use, and cigarette smoking.

- Counsel women contemplating pregnancy to take a daily multivitamin that contains 400 ug of folic acid to help prevent certain birth defects.

- Educate and counsel women about risk factors for perinatal transmission of HIV, strategies to reduce those risks, potential effects of HIV or of antiretroviral (ARV) drugs given during pregnancy on pregnancy course and outcomes, and the recommendation that HIV-infected women in the United States not breastfeed because of the risk of transmission of HIV to their infant and the availability of safe and sustainable infant feeding alternatives.

- When prescribing combination antiretroviral therapy (cART) to women of childbearing age, consider the regimen’s effectiveness, an individual’s hepatitis B disease status, the drugs’ potential for teratogenicity, should pregnancy occur, and possible adverse outcomes for mother and fetus.16-18

- Use the preconception period in women who are contemplating pregnancy to adjust cART to exclude efavirenz or other drugs with teratogenic potential.

- Make a primary treatment goal for women who are on cART and who are planning a pregnancy to attain a stable, maximally suppressed maternal viral load prior to conception to decrease the risk of perinatal transmission of HIV and of HIV transmission to an uninfected partner.

- Evaluate and appropriately manage therapy-associated side effects such as hyperglycemia, anemia, and hepatotoxicity that may adversely impact maternal-fetal health outcomes.

- Evaluate the need for appropriate prophylaxis or treatment for opportunistic infections, including safety, tolerability, and potential toxicity of specific agents when used in pregnancy.

- Administer medical immunizations for influenza, pneumococcal or hepatitis A and B vaccines, and other vaccines as indicated (see http://www.cdc.gov/vaccines/acip/committee/guidance/rec-vac-preg.html).

- Encourage sexual partners to receive counseling and HIV testing and, if infected, to seek appropriate HIV care.

- Offer all women who do not desire pregnancy effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. HIV-infected women can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs).19 Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy (see Table 3 below).

- Offer emergency contraception as appropriate, including emergency contraceptive pills and the copper IUD. Concerns about drug interactions between ARVs and emergency contraceptive pills containing estrogen and a progestin, or containing levonorgestrel only, may be similar to concerns when those formulations are used for regular contraception.20 There are no data on potential interactions between ARVs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is predominantly metabolized by CYP3A4, so interactions can be expected.

Data on drug interactions between ARV agents and hormonal contraceptives primarily come from drug labels and limited studies,21-28 and the clinical implications have not been well studied. The magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy or increase contraceptive-associated adverse effects is unknown. No studies have addressed differences in pregnancy rates in women using hormonal contraception and ARVs compared to those not using ARVs. Hormonal contraceptives can be used with cART in women without other contraindications. Additional or alternative methods of contraception may be recommended when drug interactions are known. For women using ritonavir-boosted protease inhibitors who are on combination hormonal contraceptives (e.g., pills, patches, rings) or progestin-only pills, use of an
alternative or additional method of contraception is recommended. Implants generally can be used, but providers may also consider use of an alternative method or recommend the additional use of a reliable barrier method. Depot medroxyprogesterone acetate (DMPA) can be used without restriction because of its relative higher dose and limited studies that have shown no significant interaction between DMPA and ARVs.22,24

Because no high-quality, definitive, evidence-based studies exist on pregnancy rates among women on different hormonal contraceptives and ARVs, the dosing recommendations in Table 3 are based on consensus expert opinion. Whenever possible, we based our recommendations on available data regarding pharmacokinetic (PK) interactions between ARVs and combined hormonal methods, DMPA and etonogestrel implants. The lowest decrease in PK for which we recommended use of an alternative method was 14% decrease in norethindrone (with ritonavir-boosted darunavir) and 19% decrease in ethinyl estradiol (ritonavir-boosted atazanavir). For women using atazanavir without ritonavir boosting (ethinyl estradiol increase 48%, norethindrone increase 110%), we recommend use of oral contraceptives containing ≤30 ug ethinyl estradiol. The panel did not recommend any ethinyl estradiol dose change for etravirine (ethinyl estradiol increase 22%), rilpivirine (ethinyl estradiol increase 14%), or indinavir (ethinyl estradiol increase 25%, norethindrone increase 26%).

All recommendations in the following table are based on consensus expert opinion.

### Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (CIII).

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels</th>
<th>Dosing Recommendation/ Clinical Comment for Combined Hormonal Methods and Progestin-Only Pills</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
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<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
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</tbody>
</table>
| EFV | Oral Ethinyl Estradiol/ Norgestimate:  
• No effect on ethinyl estradiol concentrations  
• ↓ active metabolites of norgestimate (levonorgestrel AUC ↓ 83%; norelgestromin AUC ↓ 64%)  
**Implant:**  
• ↓ etonogestrel  
Levonorgestrel (Emergency contraception) AUC ↓ 58% | Use alternative or additional contraceptive method. | No additional contraceptive protection is needed. | Use alternative or additional contraceptive method. |
| ETR | Ethinyl estradiol AUC ↑ 22%  
Norethindrone:  
• No significant effect | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. |
| NVP | Ethinyl estradiol AUC ↓ 20%  
Norethindrone AUC ↓ 19%  
DMPA:  
• No significant change | Can consider an alternative method or a reliable method of barrier contraception in addition to this method. | No additional contraceptive protection is needed. | Can consider an alternative method or a reliable method of barrier contraception in addition to this method. |
| RPV | Ethinyl estradiol AUC ↑ 14%  
Norethindrone:  
• No significant change | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. |
Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (CIII).

<table>
<thead>
<tr>
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<th>Dosing Recommendation/ Clinical Comment for Combined Hormonal Methods and Progestin-Only Pills</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP/r</td>
<td>↓ Ethinyl estradiol AUC ↓ 19% ↑ Norgestimate ↑ 85%</td>
<td>Use alternative or additional contraceptive method. No additional contraceptive protection is needed.</td>
<td>Can consider an alternative method or a reliable method of barrier contraception in addition to this method.</td>
<td></td>
</tr>
<tr>
<td>DRV/r</td>
<td>Ethinyl estradiol AUC ↓ 44% Norethindrone AUC ↓ 14%</td>
<td>Use alternative or additional contraceptive method. No additional contraceptive protection is needed.</td>
<td>Can consider an alternative method or a reliable method of barrier contraception in addition to this method.</td>
<td></td>
</tr>
<tr>
<td>FPV/r</td>
<td>Ethinyl estradiol AUC ↓ 37% Norethindrone AUC ↓ 34%</td>
<td>Use alternative or additional contraceptive method. No additional contraceptive protection is needed.</td>
<td>Can consider an alternative method or a reliable method of barrier contraception in addition to this method.</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>Ethinyl estradiol AUC ↓ 42% Norethindrone AUC ↓ 17%</td>
<td>Use alternative or additional contraceptive method. No additional contraceptive protection is needed.</td>
<td>Can consider an alternative method or a reliable method of barrier contraception in addition to this method.</td>
<td></td>
</tr>
<tr>
<td>SQV/r</td>
<td>↓ Ethinyl estradiol</td>
<td>Use alternative or additional contraceptive method. No additional contraceptive protection is needed.</td>
<td>Can consider an alternative method or a reliable method of barrier contraception in addition to this method.</td>
<td></td>
</tr>
<tr>
<td>TPV/r</td>
<td>Ethinyl estradiol AUC ↓ 48% Norethindrone: • No significant change</td>
<td>Use alternative or additional contraceptive method. No additional contraceptive protection is needed.</td>
<td>Can consider an alternative method or a reliable method of barrier contraception in addition to this method.</td>
<td></td>
</tr>
</tbody>
</table>

**PIs without RTV**

| ATV      | Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110% | No additional contraceptive protection is needed. Oral contraceptive should contain ≤30 ug of ethinyl estradiol or use alternative method. Oral contraceptives containing <25 ug ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied. No additional contraceptive protection is needed. | No additional contraceptive protection is needed. |

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<sup>a</sup> DMPA: Depo-Provera.
## Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (CIII).

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels</th>
<th>Dosing Recommendation/ Clinical Comment for Combined Hormonal Methods and Progestin- Only Pills</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPV</strong></td>
<td>Amprenavir:</td>
<td>Use alternative contraceptive method. Use of fosamprenavir alone with ethinyl estradiol/norethindrone may lead to loss of virologic response.</td>
<td>No additional contraceptive protection is needed. Use alternative contraceptive method.</td>
<td>No additional contraceptive protection is needed. Use alternative contraceptive method.</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir with Ethinyl Estradiol/ Norethindrone:</td>
<td>↓ Amprenavir (AUC 22%, C&lt;sub&gt;min&lt;/sub&gt; 20%)</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
<tr>
<td><strong>IDV</strong></td>
<td>Ethinyl estradiol AUC ↑ 25% Norethindrone AUC ↑ 26%</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
<tr>
<td><strong>NFV</strong></td>
<td>Ethinyl estradiol AUC ↓ 47% Norethindrone AUC ↓ 18%</td>
<td>Use alternative or additional contraceptive method.</td>
<td>No additional contraceptive protection is needed.</td>
<td>Use alternative or additional contraceptive method.</td>
</tr>
<tr>
<td><strong>MVC</strong></td>
<td>No significant effect on ethinyl estradiol or levonorgestrel</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>No significant effect</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
<tr>
<td><strong>DTG</strong></td>
<td>No significant effect on norgestimate or ethinyl estradiol</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
<tr>
<td><strong>EVG/ COBI</strong></td>
<td>Norgestimate AUC ↑ 2.26 Ethinyl estradiol AUC ↓ 0.75</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
</tbody>
</table>

*Because the hormonal levels achieved with DMPA are substantially higher than are required for contraception, any small reduction in hormonal level due to ARVs is unlikely to reduce contraceptive effectiveness.*

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; C<sub>min</sub> = minimum plasma concentration; COBI = cobicistat; DMPA = depot medroxyprogesterone acetate; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = ritonavir-boosted saquinavir; TPV/r = ritonavir-boosted tipranavir

References


Reproductive Options for HIV-Concordant and Serodiscordant Couples  (Last updated March 28, 2014; last reviewed March 28, 2014)

For couples in which one or both are HIV-infected, optimal health should be attained before attempting conception. The infected partner should be on combination antiretroviral therapy (cART) and have achieved maximal suppression of HIV infection.

For concordant or serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple. Before attempting to conceive, both partners should be screened for genital tract infections. If any such infections are identified, they should be treated because genital tract inflammation is associated with genital tract shedding of HIV.1-5

Serodiscordant Couples

Before conception is attempted, maximal viral suppression is recommended for individuals who are on combination antiretroviral therapy (cART). Observational studies have demonstrated a decreased rate of transmission of HIV in heterosexual serodiscordant couples among whom the index partners were on cART compared with those not on therapy.6-8 HPTN 052 was a randomized clinical trial designed to evaluate whether immediate versus delayed initiation of ART by HIV-infected individuals with CD4 T lymphocyte (CD4) cell counts of 350 to 550 cells/mm³ could prevent sexual transmission of HIV among serodiscordant couples. Most of the participants were from Africa (54%), with 30% from Asia and 16% from North and South America. Data from this study showed that earlier initiation of cART led to a significant reduction in
transmission of HIV to the uninfected partner. Of 28 cases of HIV infection documented to be genetically linked to the infected partner, 27 occurred in the 877 couples in which the HIV-infected partner delayed initiation of ART until the CD4 cell count fell below 250 cells/mm³, whereas only 1 case of HIV infection occurred in the 886 couples with an HIV-infected partner who began immediate cART; 17 of the 27 transmissions in the delayed-therapy group occurred in individuals with CD4 cell counts >350 cells/mm³. The majority of transmissions (82%) were observed in participants from Africa. These are the first data from a randomized trial to demonstrate that provision of treatment to infected individuals can reduce the risk of transmission to their uninfected sexual partners. Based on the results from HPTN 052, initiation of cART would be recommended for the infected partner in a serodiscordant couple who has a CD4 cell count of ≤550 cells/mm³ if the couple wishes to conceive. Initiation of cART is also recommended for HIV-infected individuals with CD4 cell counts >550 cells/mm³, although the benefit of cART in reducing sexual transmission from individuals with higher CD4 cell counts has not been determined.

It is important to recognize that no single method (including treatment of the infected partner) is fully protective against transmission of HIV. Effective cART that decreases plasma viral load to undetectable levels is also associated with decreased concentration of virus in genital secretions. In a prospective study of 2,521 African HIV-infected serodiscordant couples, higher genital HIV RNA concentrations were associated with greater risk of heterosexual HIV-1 transmission and this effect was independent of plasma HIV concentrations. Each log₁₀ increase in genital HIV-1 RNA levels increased the risk of female-to-male or male-to-female HIV transmission by 1.7-fold. Discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus. In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract. Thus, maximal plasma viral suppression may not completely eliminate risk of heterosexual transmission. Although use of cART may not eliminate all risk of sexual transmission, it may contribute to lowering risk in couples who have decided to conceive through unprotected intercourse despite known risks.

Reducing the risk of perinatal transmission is another potential rationale for starting cART before conception in HIV-infected women. Data suggest that early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission, but that does not completely eliminate the risk of perinatal transmission. In addition, reports are mixed on the possible effects of cART on prematurity and low birthweight, with some but not all data suggesting that such outcomes may be more frequent in women on ARV drugs at conception.

The implications of initiating therapy before conception solely for prevention of sexual and/or perinatal transmission should be discussed with the couple. These issues include willingness and ability of the HIV-infected partner to commit to potential lifelong therapy, the potential risks versus benefits of stopping or continuing the regimen after conception in the male or postpartum in the female, and the need for strict adherence to achieve maximal viral suppression. Consultation with an expert in HIV care is strongly recommended.

For HIV-discordant couples in which the female is the HIV-infected partner, the safest form of conception is artificial insemination, including the option to self-inseminate with the partner’s sperm during the peri-ovulatory period. Condom use should be advised at all times.

For HIV-discordant couples in which the male is the HIV-infected partner, the use of donor sperm from an HIV-uninfected male with artificial insemination is the safest option. When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or in vitro fertilization has been reported to be effective in avoiding seroconversion in uninfected women and offspring in several studies. Sperm preparation should utilize optimal methods that can detect the presence of HIV. Couples should also consider the cost and other possible complications of in vitro fertilization. More data are needed to demonstrate the complete efficacy of these techniques, and couples should be cautioned about the potential risk of transmission of HIV to the uninfected partner and to their offspring. Semen analysis is recommended for HIV-infected males before conception is attempted because
HIV, and possibly cART, may be associated with a higher prevalence of semen abnormalities such as low sperm count, low motility, higher rate of abnormal forms, and low semen volume. If such abnormalities are present, the uninfected female partner may be exposed unnecessarily and for prolonged periods to her partner’s infectious genital fluids when the likelihood of getting pregnant naturally is low or nonexistent.22-25

Discordant couples who do not have access to assisted reproduction services and who still want to try to conceive after comprehensive counseling should be advised that timed, peri-ovulatory unprotected intercourse after the infected partner has achieved maximal viral suppression (with use of condoms at all other times) may reduce but not completely eliminate the risk of sexual transmission.20 HIV-uninfected women who become pregnant should be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV and the possible risk of perinatal transmission (see Monitoring of HIV Uninfected Pregnant Women with a Partner Known to be HIV Infected).

Periconception pre-exposure prophylaxis (PrEP) may offer an additional option to minimize risk of transmission of HIV within discordant couples. PrEP is use of ARV medications by an HIV-uninfected individual to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. Many studies have demonstrated that PrEP reduces the risk of HIV acquisition in both men and women, with minimal risk of incident ARV resistance. Others did not show benefit, which is likely related to adherence issues.9,26-31 Table 4 summarizes clinical trials of PrEP.32

**Table 4. Clinical Trials of Pre-Exposure Prophylaxis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Population</th>
<th>Location</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF2</td>
<td>1,219 sexually active adults; 55% male, 45% female; 94 % unmarried; approximately 90% aged 21–29 years</td>
<td>Botswana</td>
<td>Daily oral TDF/FTC</td>
<td>63% protection</td>
<td>&gt;30% did not complete study; cannot draw definitive conclusions for women and men separately.</td>
</tr>
<tr>
<td>PIP</td>
<td>4,758 heterosexual serodiscordant couples; 38% negative-female, 68% negative-male partner; 98% married; median age 33 years</td>
<td>Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia</td>
<td>Daily oral TDF or TDF/FTC</td>
<td>67% protection with TDF alone; 75% protection with TDF/FTC</td>
<td>Discordant couples may be a distinct, unique population.</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>1,951 heterosexual women aged 18–35 years at high risk of infection</td>
<td>Kenya, South Africa, Tanzania</td>
<td>Daily oral TDF/FTC</td>
<td>Trial discontinued for futility in April 2011.</td>
<td>Adherence assessment with monthly clinical samples to measure drug concentration is pending.</td>
</tr>
<tr>
<td>VOICE</td>
<td>5,029 heterosexual women aged 18–45 years in high-prevalence areas</td>
<td>Uganda, South Africa, Zimbabwe</td>
<td>Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel</td>
<td>No study drug significantly reduced the risk of HIV acquisition: HIV incidence was 5.7 per 100 person years. Effectiveness was -48.8% for TDF; -4.2% for TDF/FTC; and 14.7% for TDF gel.</td>
<td>Adherence to study drugs was low: TFV was detected in 30% of the oral TDF arm; 29% in the oral TDF/FTC arm; and 25% in the TDF gel arm.</td>
</tr>
</tbody>
</table>
Table 4. Clinical Trials of Pre-Exposure Prophylaxis (page 2 of 2)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Population</th>
<th>Location</th>
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<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052</td>
<td>1,763 heterosexual serodiscordant couples; 50% negative-female, 50% negative-male partner; 94% married; 61% aged 26–40 years</td>
<td>Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand</td>
<td>Immediate or delayed cART in HIV-infected partner</td>
<td>96% protection</td>
<td>Suppression of viraemia on therapy assured by routine monitoring.</td>
</tr>
</tbody>
</table>

Key to Acronyms: cART = combination antiretroviral therapy; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; FTC = emtricitabine

Source: Adapted from Kashuba et al., Antiretroviral-based HIV prevention studies: Lancet 379(9835): 2409-2411

PrEP may offer an additional strategy for safer conception. Couples should be advised to use condoms at all times except during periovulatory intercourse. Several studies evaluating the efficacy of PrEP in heterosexual discordant couples planning pregnancy are ongoing but complete data are not yet available. One study evaluated timed intercourse with PrEP in 46 heterosexual HIV-discordant couples with an HIV-uninfected female partner. The male HIV-infected partners were receiving cART and had undetectable plasma HIV RNA levels. One dose of oral tenofovir was taken by the women at luteinizing hormone peak and a second oral dose was taken 24 hours later. None of the women became HIV infected and pregnancy rates were high, reaching a plateau of 75% after 12 attempts.33

Only combination tenofovir/emtricitabine is being evaluated currently in ongoing heterosexual PrEP trials. Adherence is critical. The use of continued PrEP is recommended for anyone who is at ongoing risk of HIV acquisition.

Pregnancy is not a contraindication to PrEP. However, the use of daily oral PrEP during pregnancy and lactation has not been well studied in HIV-uninfected women with HIV-infected partners. Condom use should be encouraged in pregnancy because several studies have reported increased incidence of HIV acquisition during pregnancy which may also lead to increased perinatal transmission. Continuation of PrEP during pregnancy can be considered.34-38 Currently, there is no reported increase in congenital anomalies among children born to women exposed to tenofovir (2.4%) or to emtricitabine (2.5%) during pregnancy, including in the first trimester.39

It will be important to have outcome studies that examine adverse events, including risk of congenital abnormalities. In addition, the utility of daily oral PrEP when the HIV-infected partner is receiving cART has not been studied. If clinicians elect to use PrEP for HIV-uninfected women or men in serodiscordant couples, the couples should be educated about the potential risks and benefits and all available alternatives for safer conception. Laboratory testing for HIV infection, baseline renal function, and chronic hepatitis B virus (HBV) infection should be performed before initiating PrEP. Hepatitis B-uninfected individuals should be vaccinated. Individuals receiving PrEP should be monitored for potential side effects such as renal dysfunction and clinical toxicities. They should be educated about symptoms associated with acute HIV infection and advised to contact their providers immediately for further evaluation, should symptoms occur. HIV-uninfected partners should undergo frequent HIV testing to detect HIV infection quickly. If HIV infection is documented, the PrEP ARV agents should be discontinued to minimize selection of drug-resistant virus and measures should be instituted to prevent perinatal transmission if pregnancy has occurred and attempts at conception stopped if it has not. Refer patient to HIV specialist immediately. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.40 Clinicians are strongly encouraged to register HIV-uninfected women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

Concordant Couples

Both partners should be on cART with maximum viral suppression before attempting conception. Periovulatory unprotected intercourse (with use of condoms at all other times) is a reasonable option. The
risk of HIV superinfection or infection with a resistant virus is negligible when both partners are on cART and have fully suppressed plasma viral loads.41

The National Perinatal HIV Hotline (1-888-448-8765) is a resource for a list of institutions offering reproductive services for HIV concordant/serodiscordant couples.

The Centers for Disease Control and Prevention has issued guidelines for the use of PrEP in sexually active heterosexual adults.42

**Monitoring of HIV-Uninfected Pregnant Women with Partners Known to Be HIV-Infected**

Clinicians may increasingly be seeing HIV-uninfected women who present during pregnancy and indicate that their partners are HIV-infected. They, like all pregnant women, should be notified that HIV screening is recommended and they will receive an HIV test as part of the routine panel of prenatal tests unless they decline. These women also should receive a second HIV test during the third trimester, preferably before 36 weeks’ gestation, as is recommended for high-risk women. Furthermore, pregnant women who present in labor without results of third-trimester testing should be screened with a rapid HIV test on the labor and delivery unit. If at any time during pregnancy a clinician suspects that a pregnant woman may be in the “window” period of seroconversion (i.e., she has signs or symptoms consistent with acute HIV infection), then a plasma HIV RNA test should be used in conjunction with an HIV antibody test. If the plasma HIV RNA is negative, it should be repeated in 2 weeks. All HIV-uninfected pregnant women with HIV-infected partners should always use condoms during sexual intercourse to prevent acquisition of HIV. Women should be counseled regarding the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash, myalgia, arthralgia, diarrhea, headache) and the importance of seeking medical care and testing if they experience such symptoms.

Pregnancy is not a contraindication to PrEP and should be considered in HIV-seronegative pregnant women who are at ongoing risk of HIV acquisition. However, the use of daily oral PrEP during pregnancy and lactation has not been well studied (see section on Serodiscordant Couples).

Women who test HIV seropositive on either conventional or rapid HIV tests should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate cART and consideration of elective cesarean delivery according to established guidelines (see Transmission and Mode of Delivery). In cases where confirmatory test results are not readily available, such as with rapid testing during labor, it is still appropriate to initiate interventions to reduce perinatal transmission (see Infant Antiretroviral Prophylaxis).

Women with HIV-infected partners who test HIVseronegative should continue to be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV. Women with primary HIV infection during pregnancy or lactation are at high risk of transmitting HIV to their infants.43,44

**References**


5. Homans J, Christensen S, Stiller T, et al. Permissive and protective factors associated with presence, level, and


Antepartum Care  (Last updated March 28, 2014; last reviewed March 28, 2014)

General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

Panel’s Recommendations

- Initial evaluation of HIV-infected pregnant women should include assessment of HIV disease status and recommendations regarding initiation of combination antiretroviral therapy (cART) or the need for any modification if currently receiving cART (AIII). The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.

- All pregnant HIV-infected women should receive cART to prevent perinatal transmission regardless of plasma HIV RNA copy number or CD4 T lymphocyte count (AI).

- Combined antepartum, intrapartum, and infant antiretroviral (ARV) prophylaxis is recommended because ARV drugs reduce perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and providing infant pre- and post-exposure prophylaxis (AI).

- The known benefits and potential risks of ARV use during pregnancy should be discussed with all HIV-infected women (AIII).

- In counseling patients, the importance of adherence to their ARV regimens should be emphasized (AI).

- ARV drug-resistance studies should be performed before starting or modifying ARV drug regimens in women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) (AIII). When HIV is diagnosed later in pregnancy, cART should be initiated promptly without waiting for results of resistance testing (BIII).

- Coordination of services among prenatal care providers, primary care and HIV specialty care providers, and when appropriate, mental health and drug abuse treatment services, and public assistance programs, is essential to ensure that infected women adhere to their ARV drug regimens (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

In addition to the standard antenatal assessments for all pregnant women, the initial evaluation of those who are HIV infected should include assessment of HIV disease status and recommendations for HIV-related medical care. This initial assessment should include the following:

- Review of prior HIV-related illnesses and past CD4 T lymphocyte (CD4) cell counts and plasma HIV RNA levels;

- Current CD4 cell count;

- Current plasma HIV RNA copy number;

- Assessment of the need for prophylaxis against opportunistic infections such as Pneumocystis jirovecii pneumonia and Mycobacterium avium complex (see Adult and Adolescent Opportunistic Infections Guidelines);

- Screening for hepatitis C virus and tuberculosis in addition to standard screening for hepatitis B virus (HBV) infection;

- Assessment of the need for immunizations per guidelines from the American College of Obstetricians and Gynecologists, with particular attention to hepatitis A, HBV, influenza, pneumococcus, and Tdap immunizations;¹²

- Complete blood cell count and renal and liver function testing;

- HLA-B*5701 testing if abacavir use is anticipated (see Table 7);

- History of prior and current antiretroviral (ARV) drug use, including prior ARV use for prevention of perinatal transmission or treatment of HIV and history of adherence problems;
• Results of prior and current HIV ARV drug-resistance studies;
• History of **adverse** effects or toxicities from prior ARV regimens; and
• Assessment of supportive care needs such as mental health services, substance abuse treatment, and smoking cessation.

**The National Perinatal HIV Hotline**
The National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service providing free clinical consultation to providers caring for HIV-infected women and their infants.

**HIV RNA and Transmission**
ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of CD4 cell counts and HIV RNA levels. Although the risk of perinatal transmission in women with undetectable plasma HIV RNA levels appears to be extremely low, transmission has been reported even in women with very low or undetectable levels of maternal HIV RNA on combination antiretroviral therapy (cART). Although there is a general correlation between viral loads in plasma and in the genital tract, discordance between blood and genital tract virus has also been reported; low-level cervico-vaginal HIV RNA and DNA shedding has been detected even in women treated with cART who have undetectable plasma viral load, particularly in the presence of genital tract coinfections. Penetration of ARV drugs into the female genital tract has been shown to vary between drugs. If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV RNA levels may not always be an accurate indicator of risk.

**Mechanism of Action of Antiretrovirals in Prevention of Perinatal Transmission**
ARV drugs can reduce perinatal transmission through a number of mechanisms. Antenatal drug administration decreases maternal viral load in blood and genital secretions. Another mechanism of protection is infant pre-exposure prophylaxis achieved by administering ARV drugs that cross the placenta from mothers to infants and produce adequate systemic drug levels in the infants. Infant post-exposure prophylaxis is achieved by administering drugs to infants after birth, providing protection from cell-free or cell-associated virus that may have entered the fetal/infant systemic circulation during labor and delivery. The importance of the pre- and post-exposure components of prophylaxis in reducing perinatal transmission is demonstrated by the efficacy of interventions that involve administration of ARVs only during labor and/or to the newborns. Therefore, combined antepartum, intrapartum, and infant ARV prophylaxis is recommended to prevent perinatal transmission of HIV.

**General Principles of Drug Selection**
In general, guidelines for the use of combination antiretroviral therapy (cART) for the benefit of maternal health during pregnancy are the same as for women who are not pregnant, with some modifications based on concerns about specific drugs and limited experience during pregnancy with newer drugs.

The known benefits and known and unknown risks of ARV drug use during pregnancy should be considered and discussed with women. Results from preclinical and animal studies and available clinical information about use of the various agents during pregnancy also should be discussed (see Table 7 and Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). Potential risks of these drugs should be placed into perspective by reviewing the substantial benefits of ARV drugs for maternal health and in reducing the risk of transmission of HIV to infants. Counseling of pregnant women about ARV use should be noncoercive, and providers should help them make informed decisions regarding use of ARV drugs.

Discussions with women about initiation of cART drug regimens should include information about:
• Maternal risk of disease progression and the benefits and risks of initiation of therapy for maternal health;
• Benefit of cART for preventing perinatal transmission of HIV;\textsuperscript{19}
• Benefits of therapy for reducing sexual transmission to discordant partners when viral suppression is maintained;\textsuperscript{20}
• The need for strict adherence to the prescribed drug regimen to avoid resistance;
• Potential adverse effects of ARV drugs for mothers, fetuses, and infants, including potential interactions with other medications the women may already be receiving; and
• The limited long-term outcome data for both women who use cART during pregnancy for prophylaxis of transmission and stop the regimen postpartum and for infants with in utero drug exposure.

Transplacental passage of ARVs is an important mechanism of infant pre-exposure prophylaxis. Thus, when selecting an ARV regimen for a pregnant woman, at least one nucleoside/nucleotide reverse transcriptase inhibitor agent with high placental transfer should be included as a component of the cART regimen (see Table 7).\textsuperscript{21-24}

In women with plasma HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL), ARV drug-resistance studies should be performed before starting cART. When HIV is diagnosed later in pregnancy, however, cART should be initiated promptly without waiting for results of resistance testing (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Counseling should emphasize the importance of adherence to the ARV drug regimen to minimize the development of resistance.

Support services, mental health services, smoking cessation, and drug abuse treatment may be required, depending on a woman’s individual circumstances. Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure that infected women adhere to their ARV drug regimens.

All HIV-infected pregnant women should be started on cART during pregnancy to minimize the risk of transmission. Providers should work with women to develop long-range plans regarding continuity of medical care. Considerations regarding postpartum continuation of cART for maternal therapeutic indications are the same as for nonpregnant individuals.

Medical care of HIV-infected pregnant women requires coordination and communication between HIV specialists and obstetrical providers. General counseling should include current knowledge about risk factors for perinatal transmission. Risk of perinatal transmission of HIV has been associated with potentially modifiable factors, including cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy.\textsuperscript{25-29} Besides improving maternal health, cessation of cigarette smoking and drug use, treatment of genital tract infections, and use of condoms with sexual intercourse during pregnancy may reduce risk of perinatal transmission. In addition, the Centers for Disease Control and Prevention and American Academy of Pediatrics recommends that HIV-infected women in the United States (including those receiving cART) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk\textsuperscript{30,31} and avoid premastication of food for their infants, a potential risk factor for transmission.\textsuperscript{32}

References


Teratogenicity  (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel's Recommendations

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see http://www.APRegistry.com) (AIII).

- Nonpregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens (AIII).
  - Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health (BIII).

- Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz can be continued in pregnant women receiving an efavirenz-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment) (CIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself but also on the dose ingested; the gestational age of the fetus at exposure; the duration of exposure; the interaction with other agents to which the fetus is exposed; and, to an unknown extent, the genetic makeup of mother and fetus.

Information regarding the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Data are limited for antiretroviral (ARV) drugs, particularly when used in combination antiretroviral therapy (cART). Drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of in vitro and animal in vivo screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans.1 Limited data exist regarding placental passage, pharmacokinetics and safety in pregnancy, and long-term safety for exposed infants for the Food and Drug Administration (FDA)-approved ARV drugs (see Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). In general, reports of birth defects in fetuses/infants of women enrolled in observational studies who receive ARV regimens during pregnancy are reassuring and find no difference in rates of birth defects for first-trimester compared with later exposures.2-4 However, concerns have been raised about the risk of several ARV agents.

Most studies evaluating a possible association between ARV exposure and birth defects do not evaluate folate levels. Folate antagonists (e.g., trimethoprim-sulfamethoxazole), which may be associated with an increased risk of birth defects with first trimester use, may be prescribed to women with advanced HIV disease. Therefore, it may be important to consider the role of folate antagonists as well as folic acid supplementation when evaluating any potential association between ARV drugs and birth defects.5

Significant malformations were observed in 3 of 20 infant cynomolgus monkeys receiving efavirenz from gestational Days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human exposure at therapeutic dosage.6 The malformations included anencephaly and unilateral anophthalmia in one, microphthalmia in another, and cleft palate in the third. Among pregnancies prospectively reported to
the Antiretroviral Pregnancy Registry through July 2013 that had exposure to efavirenz-based regimens, a 2.3% incidence of overall birth defects was seen with first-trimester exposure, a proportion not significantly different from that observed among U.S. births in the general population. Defects reported prospectively included one report of myelomeningocele and a separate report of anophthalmia. The case of anophthalmia included severe oblique facial clefts and amniotic banding that is known to be associated with anophthalmia. In addition, six cases of central nervous system defects, including myelomeningocele, have been retrospectively reported in infants born to mothers receiving efavirenz during the first trimester. However, retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

A meta-analysis including data from 21 studies reporting on 1,437 first-trimester exposures found no increased risk of overall birth defects in infants born to women on efavirenz during the first trimester compared with those on other ARV drugs during the first trimester (relative risk [RR] 0.85; 95% confidence interval [CI], 0.61–1.20). One neural tube defect was observed, giving an incidence of 0.07% (95% CI, 0.002–0.39). However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a two- to three-fold increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02%–0.2%).

In contrast to the meta-analysis, the Pediatric AIDS Clinical Trials Protocols (PACTG) 219 and 219C studies reported a higher defect rate in infants with first-trimester exposure to efavirenz compared with those without first-trimester efavirenz exposure (adjusted odds ratio 4.31; 95% CI, 1.56–11.86). However, only 32 infants had efavirenz exposure. PACTG protocol P1025 is a companion study of PACTG 219 with considerable overlap in cases enrolled. Although P1025 reports a significant increased risk of congenital anomalies in infants born between 2002 and 2007 with first-trimester exposure to efavirenz, there is overlap in the defect cases between the 2 studies and only 41 infants are included in this analysis. Thus, additional data are needed on first-trimester efavirenz exposures to be able to more conclusively determine if risk of neural tube defects or other malformations is elevated.

Although a causal relationship has not been established between these events and the use of efavirenz, in light of similar findings in primates, efavirenz has been classified as FDA Pregnancy Category D. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first 8 weeks of pregnancy (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens. Alternate cART regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman’s health. However, the Panel now recommends that efavirenz can be continued in women who present for care in the first trimester and are receiving efavirenz-based cART that is effective in suppressing viral replication. This is because the neural tube closes at 36 to 39 days after the last menstrual period; hence the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (and pregnancy is rarely recognized before 5–6 weeks), and unnecessary changes in ARV drugs during pregnancy may be associated with a loss of virologic control and, thus, increased risk of transmission to the infant. For more details, see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment.

Tenofovir has not demonstrated teratogenicity in rodents or monkeys. In infant monkeys with in utero exposure to tenofovir at maternal doses resulting in levels approximately 25 times those used in humans, low birth weights and reductions in fetal bone porosity were seen. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose-, exposure-, age-, and species-specific. Data from the Antiretroviral Pregnancy Registry show a birth defect incidence of 2.4% in 1,612 women with first-trimester tenofovir exposure, similar to that in the general population.
population. An Italian study assessed growth patterns, bone health, and markers of bone metabolism in 33 infants with \textit{in utero} exposure to tenofovir and found no difference compared with infants born to HIV-infected women who had not been exposed to tenofovir. A larger study from the United States included 2,029 HIV-exposed but uninfected infants, 449 (21\%) of whom had \textit{in utero} exposure to tenofovir. Although there were no differences in anthropomorphic parameters at birth, at age 1 year, infants exposed to tenofovir-based regimens had slight but significantly lower adjusted mean length and head circumference for age z-score than those without exposure to tenofovir.

A modest (but statistically significant) increase in overall birth defect rates for didanosine and nelfinavir is observed when compared with the U.S. population-based Metropolitan Atlanta Congenital Defects Program (MACDP). The lower bounds of the CIs for didanosine and nelfinavir (3.0\%, 2.9\%, respectively) are slightly above the higher bound (2.76\%) for the MACDP rate. No specific pattern of defects has been detected with either didanosine or nelfinavir, and the clinical relevance of this statistical finding is unclear. The Registry will continue to monitor didanosine and nelfinavir for any signal or pattern of birth defects.

See \textit{Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy} to obtain detailed information on individual drugs.

Health care providers who are caring for HIV-infected pregnant women and their newborns are strongly advised to report instances of prenatal exposure to ARV drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. This registry is an epidemiologic project to collect observational, non-experimental data regarding ARV exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting physician.

Referrals should be directed to:

\textbf{Antiretroviral Pregnancy Registry}  
Research Park  
1011 Ashes Drive  
Wilmington, NC 28405  
Telephone: 1–800–258–4263  
Fax: 1–800–800–1052  
\url{http://www.APRegistry.com}

\textbf{References}


Nevirapine and Hepatic/Rash Toxicity  (Last updated March 28, 2014; last reviewed March 28, 2014)

Increases in hepatic transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. Signs and symptoms of systemic toxicity may be nonspecific and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, or hepatomegaly with or without initially abnormal hepatic transaminases. Development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than in men. The degree of risk of rash and hepatic toxicity also appears to vary with CD4 T lymphocyte (CD4) cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts >250 cells/mm³ were 9.8 times more likely than women with lower CD4 cell counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity; a single-center study also found higher CD4 cell counts to be associated with increased risk of severe nevirapine-associated skin rash. CD4 cell counts >250 cells/mm³ predicted rash illness, but not liver enzyme elevation, among pregnant and non-pregnant women initiating nevirapine-based combination antiretroviral therapy (cART) in 3 U.S. university clinics. Other international cohorts of non-pregnant women have experienced hepatotoxicity and rash at similar rates as in U.S. studies, but not in association with CD4 cell counts >250 cells/mm³. In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine; severe or life-threatening rash has occurred in approximately 2% of patients receiving nevirapine.

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of cART raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared with other antiretroviral (ARV) drugs. However, more recent data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy. A meta-analysis of data from 3,582 pregnant women included in 20 studies did not find any evidence of increased risk of nevirapine-related adverse events in pregnant women compared with non-pregnant adults. Nevertheless, if nevirapine is used in pregnancy, health care providers should be aware of potential hepatotoxicity with or without rash and should conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of nevirapine use. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through Month 4, and every 1 to 3 months thereafter (see the Hepatotoxicity section of the table on Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects in the Adult and Adolescent Antiretroviral Guidelines). In patients with pre-existing liver disease, ARV medications other than nevirapine should be considered. If nevirapine is selected, monitoring should be performed more frequently when initiating nevirapine and monthly thereafter. Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe

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<td>• Nevirapine-based regimens should be initiated in women with CD4 T lymphocyte (CD4) cell counts &gt;250 cells/mm³ only if the benefits clearly outweigh the risks because of the drug’s potential for causing hepatic toxicity/hypersensitivity reaction (AII).</td>
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<tr>
<td>• Women who become pregnant while receiving nevirapine-containing regimens and who are tolerating the regimen well can continue on the therapy regardless of CD4 cell count (AII).</td>
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Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
Transaminase elevations (i.e., more than 5 times the upper limit of normal) should stop nevirapine and not receive nevirapine again in the future.

Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV. Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well can continue therapy, regardless of CD4 cell count.

**References**


Nucleoside Reverse Transcriptase Inhibitor Drugs and Mitochondrial Toxicity

Panel’s Recommendations

- The combination of stavudine and didanosine should not be prescribed during pregnancy because of reports of lactic acidosis and maternal/neonatal mortality with prolonged use in pregnancy (AII).
- Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to antiretroviral (ARV) drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings (AII).
- Long-term clinical follow-up is recommended for any child with in utero exposure to ARV drugs (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Nucleoside reverse transcriptase inhibitor (NRTI) drugs are known to induce mitochondrial dysfunction because the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction. The relative potency of the NRTI drugs in inhibiting mitochondrial gamma DNA polymerase in vitro is highest for zalcitabine, followed by didanosine, stavudine, zidovudine, lamivudine, abacavir, and tenofovir. In one study, didanosine and didanosine-containing regimens were associated with the greatest degree of mitochondrial suppression. Toxicity related to mitochondrial dysfunction has been reported to occur in infected patients receiving long-term treatment with NRTI drugs and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested. These toxicities may be of particular concern for pregnant women and infants with in utero exposure to NRTI drugs.

Lactic acidosis with microvesicular hepatic steatosis is a toxicity related to NRTI drugs that is thought to be related to mitochondrial toxicity; it has been reported to occur in infected individuals treated with NRTI drugs for longer than 6 months. In a report from the Food and Drug Administration Spontaneous Adverse Event Program, typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness. Metabolic acidosis with elevated serum lactate levels and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight.

During Pregnancy

Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance. These syndromes have similarities to rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: acute fatty liver and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in development of acute fatty liver of pregnancy and HELLP syndrome and possibly contribute to susceptibility to antiretroviral (ARV)-associated mitochondrial toxicity. HELLP syndrome also can occur postpartum in women with severe preeclampsia.

The frequency of this syndrome in pregnant HIV-infected women receiving NRTI drugs is unknown but a number of case reports of severe (1) or fatal (3) outcomes have been reported including several cases with didanosine/stavudine used in combination during pregnancy. Nonfatal cases of lactic acidosis also have been reported in pregnant women receiving combination stavudine/didanosine. Because of these reports of maternal mortality secondary to lactic acidosis with prolonged use of the combination of stavudine and didanosine by HIV-infected pregnant women, clinicians should not prescribe this ARV combination during pregnancy.

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/8/2014
pregnancy. Likewise, combination stavudine/didanosine also is not recommended for non-pregnant adults. It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for non-pregnant individuals receiving NRTI drugs. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving NRTI drugs to be alert for early signs of this syndrome.

In addition to low platelets and elevated liver enzymes, other laboratory findings reported in HIV-infected pregnant women on ARV drugs include depletion of mtDNA in the placenta but without evidence of ultrastructural damage to placental cells. The clinical significance of reduced mtDNA in placentas exposed to ARV drugs remains unknown. A recent report by Hernandez et al. assessed mitochondrial and apoptotic parameters in mononuclear cells from maternal peripheral blood and infant cord blood from 27 HIV-infected, ARV-treated pregnant women and their infants and 35 uninfected controls and their infants. Reduced newborn mtDNA levels, decreased maternal and fetal mitochondrial protein synthesis, and reduced maternal glycerol-3-phosphate and complex III function were observed in HIV- and ARV-exposed mothers and infants compared with uninfected controls. Maternal mtDNA depletion was particularly seen in HIV-infected pregnant women who had cumulative exposure to NRTIs of more than 100 months, suggesting NRTI-mediated injury. Also, Jitratkosol et al. reported increased prevalence of AG/TG mtDNA mutations among HIV-infected pregnant women receiving combination antiretroviral therapy (cART). However, no clinical adverse outcomes were linked to these findings in either pregnant women or their infants.

**In Utero Exposure**

It has been suggested that mitochondrial dysfunction may develop in infants with in utero exposure to NRTI drugs. Data from a French cohort of 1,754 uninfected infants born to HIV-infected women who received ARV drugs during pregnancy identified 8 infants with in utero or neonatal exposure to either zidovudine/lamivudine (4) or zidovudine alone (4) who developed indications of mitochondrial dysfunction after the first few months of life. Two of these infants (both exposed to zidovudine/lamivudine) contracted severe neurologic disease and died; 3 had mild-to-moderate symptoms; and 3 had no symptoms but had transient laboratory abnormalities.

In a larger cohort of 4,392 uninfected children (including the children in the previous study) followed within the French Pediatric Cohort or identified within a French National Register, the 18-month incidence of clinical symptoms of mitochondrial dysfunction was 0.26% and 0.07% for mortality. All children had perinatal exposure to ARV drugs; risk was higher among infants exposed to cART (primarily zidovudine/lamivudine) than to zidovudine alone. The children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or episodes of significant hyperlactatemia, and deficits in mitochondrial respiratory chain complex enzyme function on biopsy of muscle. The same group also has reported an increased risk of simple febrile seizures in the first 18 months of life and persistently lower (but clinically insignificant) neutrophil, lymphocyte, and platelet counts in infants with in utero exposure to NRTIs. More recently, in continued follow-up of the French Perinatal Cohort, researchers reported severe neurologic symptoms in the first 2 years of life as a rare event (0.3% to 0.5%).

Other clinical studies from the United States and Europe generally have not duplicated the French reports. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring in children born to HIV-infected women and followed from 1986 to 1999 in 5 large, prospective U.S. perinatal cohorts. No deaths similar to those reported from France or with clinical findings attributable to mitochondrial dysfunction were identified in a database of more than 16,000 uninfected children born to HIV-infected women with and without exposure to ARV drugs. However, most of the infants with exposure to ARVs had been exposed to zidovudine alone and only a relatively small proportion (approximately 6%) had been exposed to zidovudine/lamivudine.

The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort.
with median follow-up of 2.2 years (maximum 16 years); 1,008 had perinatal exposure to ARV drugs. No association was found between clinical manifestations suggestive of mitochondrial abnormalities and perinatal exposure to ARV drugs. Of the 4 children with seizures in this cohort, none had perinatal exposure to ARV drugs. In a report from a long-term follow-up study in the United States (PACTG 219/219C), 20 children with possible symptoms of mitochondrial dysfunction were identified in a cohort of 1,037 uninfected infants born to HIV-infected mothers. Definitive diagnosis was not available because none of the children had biopsies for mitochondrial function. Three of the 20 children had no exposure to ARV drugs. In the 17 remaining children, although overall exposure to NRTIs was not associated with symptoms, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester. Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were found in stored specimens from these children, but the clinical significance of these observations remains unknown.

Laboratory abnormalities without clinical symptoms have been reported in infants with perinatal exposure to ARV drugs compared with unexposed infants in a number of studies, most of which are limited by small numbers of subjects. In one study, mtDNA quantity was lower in cord and peripheral white blood cells at ages 1 and 2 years in 20 infants born to HIV-infected women compared with 30 infants born to uninfected women and was lowest in 10 HIV-exposed infants with zidovudine exposure compared with 10 without zidovudine exposure. In a subsequent study, mitochondrial changes were evaluated in umbilical cord endothelial cells and cord blood from human infants and monkeys with in utero exposure to various NRTI-containing regimens. Similar morphologic changes and mtDNA depletion were seen in the human and monkey infants. In the monkey study, mitochondrial damage demonstrated a gradient, with greatest damage with stavudine/ lamivudine > zidovudine/didanosine > zidovudine/lamivudine > lamivudine. In a Canadian study of 73 ARV-exposed infants and 81 controls with blood samples during the first 8 months of life, investigators found that in the first weeks of life, blood mtDNA levels were higher and blood mitochondrial RNA levels were lower in the HIV- and ARV-exposed infants compared with infants without HIV and ARV exposure.

Aldrovandi et al. reported that peripheral blood mononuclear cell mtDNA levels were lower at birth in HIV-exposed, ARV-exposed infants compared with infants without HIV and ARV exposure. However, among the HIV-exposed infants, those with combination ARV drug exposure in utero had higher mtDNA levels than those exposed only to zidovudine in utero. Umbilical cord mtDNA sequence variants were 3-fold higher among HIV- and zidovudine-exposed infants compared with infants born to HIV-uninfected mothers. Most recently, Jitratkosol et al. reported blood mtDNA mutations in HIV-exposed infants and Hernandez et al. reported subclinical mitochondrial dysfunction with decreased mtDNA levels and mtDNA protein synthesis.

Transient hyperlactatemia during the first few weeks of life was reported in 17 HIV-exposed infants with perinatal exposure to ARV drugs; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up. Similarly, the French Perinatal Cohort Study has reported asymptomatic hyperlactatemia in one-third of zidovudine-exposed newborns, which resolved following perinatal exposure to the drug. Clinically asymptomatic hematoletic findings have been reported by several investigators in uninfected infants with in utero exposure to ARV regimens in the United States and Europe, and infants with exposure to triple-combination ARV regimens were found to be at increased risk of lowered hemoglobin compared with those with perinatal exposure to zidovudine or zidovudine/lamivudine. Similar hematologic findings of anemia have also been reported in a Botswana study. Dryden-Peterson et al. reported that 12.5% of breastfed infants of mothers on ARV drugs during pregnancy and during breastfeeding in Botswana experienced at least 1 episode of Grade 3 or Grade 4 reduced hemoglobin by age 6 months compared with 5.3% of breastfed infants exposed to zidovudine in utero followed by daily infant zidovudine for 6 months and 2.5% of infants who were exposed to the drug in utero and for 1 month post-birth and were formula fed. The Botswana study group has also reported decreased birth weight and decreased weight for age and length for age in the first several months of life in infants exposed to ARV drugs.

Echocardiographic abnormalities have been reported among 136 ARV drug- and HIV-exposed uninfected infants compared with 216 HIV-exposed, uninfected infants without ARV drug exposure in the NHLBI
CHAART-1 study.\textsuperscript{41} In infants up to age 2 years, prenatal ARV exposure was associated with reduced left ventricular mass, dimension, and septal wall thickness z-scores and increased left ventricular fractional shortening and contractility compared with lack of ARV drug exposure. These findings were more prominent in female than in male infants.

The clinical significance of these differences in mtDNA, lactate levels, and hematologic and cardiac laboratory findings remains unclear. \textbf{Furthermore, not all studies have reported similar findings.}\textsuperscript{42} Additional long-term studies are needed to validate the findings and assess whether they affect long-term growth and development of infants exposed to ARV drugs. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and must be balanced against the proven benefit of ARV prophylaxis in significantly reducing perinatal transmission.\textsuperscript{24,43,44}

Development of new diagnostic techniques, including use of flow cytometry assays to screen for mitochondrial function, may lead to more accurate assessment of mitochondrial toxicity.\textsuperscript{45} Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings. Current recommendations emphasize the need for long-term clinical follow-up for any child with \textit{in utero}, peripartum, or postnatal exposure to ARV drugs used for prevention of perinatal transmission.

\textbf{References}


Combination Antiretroviral Drug Regimens and Pregnancy Outcome

(Last updated March 28, 2014; last reviewed March 28, 2014)

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<td>• Clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving protease-inhibitor (PI)-based combination antiretroviral therapy; however, given the clear benefits of such regimens for both a woman’s health and prevention of perinatal transmission, PIs should not be withheld for fear of altering pregnancy outcome (AII).</td>
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Early data were conflicting as to whether receipt of combination antiretroviral therapy (cART) during pregnancy is associated with adverse pregnancy outcomes and, in particular, preterm delivery. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study investigated the effects of cART in a population of 3,920 pregnant women who delivered between 1986 and 2000. Adjusting for CD4 T lymphocyte (CD4) cell count and intravenous drug use, they found a roughly twofold increase in the odds of preterm delivery for infants exposed to combination regimens with or without protease inhibitors (PIs) compared with no drugs; women receiving combination regimens that had been initiated before pregnancy were twice as likely to deliver prematurely as those who started drugs during the third trimester. However, PI-based combination regimens were received by only 108 (3%) of the women studied; confounding by severity or indication may have biased the results (i.e., sicker women may have received PIs more often, but their advanced HIV infection may have actually caused the preterm births). Exposure to nucleoside reverse transcriptase inhibitor (NRTI) single-drug prophylaxis (primarily zidovudine) was not associated with prematurity.

An updated report from the European Collaborative Study, based on an adjusted analysis that included 2,279 pregnant women who delivered between 1986 and 2004, found a 1.9-fold increased risk of delivery at less than 37 weeks with cART started during pregnancy and a 2.1-fold increased risk with cART started prior to pregnancy compared with mono- or dual-NRTI prophylaxis. In this report, 767 women received cART during pregnancy, although the proportion receiving PIs was not specified. The risk of delivery before 34 weeks’ gestation was increased by 2.5-fold for those starting cART during pregnancy and 4.4-fold for those entering pregnancy on cART.

In contrast, in an analysis of 7 prospective clinical studies that included 2,123 HIV-infected pregnant women who delivered infants between 1990 and 1998 and had received antenatal antiretroviral (ARV) regimens and 1,143 women who did not receive antenatal ARV drugs, the use of multiple ARV drugs compared with no drugs or treatment with 1 drug was not associated with increased rates of preterm birth, low birth weight, low Apgar scores, or stillbirth. Nor were any significant associations between adverse pregnancy outcome and use of ARV drugs by class or by category (including cART) found in an analysis from the Women and Infants Transmission Study, including 2,543 HIV-infected women (some of whom were included in the previous meta-analysis).

More recent data have continued to be conflicting as to whether preterm delivery is increased with cART. Table 5 reviews results from studies that have evaluated the association of ARV drug use during pregnancy and preterm delivery. Multiple studies have detected small but significant increases (odds ratio [OR] 1.2–1.8 in the largest studies) in preterm birth with PI- or non-PI-based cART as well. However, other recent studies that have controlled for maternal and pregnancy characteristics as well as factors related to HIV infection have shown no increase in adverse outcomes including preterm delivery and low birth weight in association with PI-containing drug regimens. A meta-analysis of 14 European and American clinical studies found no increase in risk of preterm birth with either exposure to any ARV drug compared to no
drugs or to cART including PIs compared with no drugs. However, a significant but modest increased risk of preterm birth (OR 1.35; 95% confidence interval [CI], 1.08–1.70) was found in women who received combination regimens with PIs compared with cART without PIs. Other reports have found increased rates of preterm birth when cART is compared with dual regimens and when cART regimens containing non-nucleoside reverse transcriptase inhibitors were compared with other forms of cART.

Other variables may confound these observational studies. Some studies have found increased rates of preterm birth if cART is begun before conception or earlier in pregnancy compared with later in pregnancy, which itself may reflect confounding by severity or indication. Recent studies have assessed spontaneous preterm birth only, excluding delivery that was initiated at a preterm gestation because of medical or obstetrical reasons, and found no association between ARV and preterm birth. However, a recent U.S. study found an increased risk of spontaneous and overall preterm birth with exposure to PI-containing cART in the first trimester compared to exposure only after the first trimester to PI- or non-PI-containing cART. Exposure to non-PI-containing regimens in the first trimester was not associated with increased risk of preterm birth. In an analysis of HIV-infected women enrolled in the ANRS French Perinatal Cohort from 1990 to 2009, preterm delivery rates were seen to increase over time, and preterm delivery was associated with cART versus either mono- or dual-ARV regimens and were highest in those who had initiated ARV drugs before pregnancy. A restricted analysis within this cohort of PI-based cART comparing boosted to unboosted PIs showed an association with induced preterm delivery for boosted PI regimens (adjusted odds ratio [AOR] 2.03; 95% CI, 2.06–3.89) that was not seen with spontaneous preterm birth. Boosted PI regimens were also associated with both medical and obstetrical complications, raising the possibility that the association with induced preterm delivery was mediated through these complications.

A secondary analysis of data collected during a randomized, controlled clinical trial conducted in Botswana in women with CD4 cell counts >200 cells/mm³—267 randomized to receive lopinavir/ritonavir/zidovudine/lamivudine (PI group) and 263 randomized to receive abacavir/zidovudine/lamivudine (NRTI group) begun between 26 and 34 weeks’ gestation for prevention of perinatal transmission and not for maternal health indications—did show an association between PI-containing ARV regimens and preterm delivery. In logistic regression analysis, use of combination PI-based ARV regimens was the most significant risk factor for preterm delivery (OR 2.03; 95% CI, 1.26–3.27). Those receiving the latest initiation of ARV drugs had the highest preterm delivery rates. However the 20% background rate for preterm delivery in this population was not different from that seen in the PI group, and there was no difference between the 2 groups in neonatal morbidity and mortality. An observational study also from Botswana found that use of cART from before conception was not associated with very preterm delivery (AOR 0.78), which could not be assessed in the controlled clinical trial.

Clinicians should be aware of a possible increased risk of preterm birth with use of cART; however, given the clear benefits for maternal health and reduction in perinatal transmission, these agents should not be withheld because of the possibility of increased risk of preterm delivery. Until more information is known, HIV-infected pregnant women who are receiving cART for their HIV infection should continue their provider-recommended regimens. They should receive careful, regular monitoring for pregnancy complications including preterm delivery and for potential toxicities.
Table 5. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 3)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total on ARV Drugs</th>
<th>Types of ARV Regimens Compared (Numbers)</th>
<th>Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Collaborative and Swiss Mother and Child HIV Cohort Study; 1986–2000&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3,920/896</td>
<td>• Mono (573) &lt;br&gt; • Multi, no PI (215) &lt;br&gt; • PI-multi (108)</td>
<td>• YES (compared with no ARV) &lt;br&gt; • Multi: 1.82 (1.13–2.92) &lt;br&gt; • PI-multi: 2.60 (1.43–4.7)</td>
<td>• Increase in PTD if ARV begun before pregnancy versus in third trimester</td>
</tr>
<tr>
<td>United States; 1990–1998&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3,266/2,123</td>
<td>• Mono (1,590) &lt;br&gt; • Multi (396) &lt;br&gt; • PI-multi (137)</td>
<td>• NO (compared with mono) &lt;br&gt; • Multi: 0.95 (0.60–1.48) &lt;br&gt; • PI-multi: 1.45 (0.81–2.50)</td>
<td>• 7 prospective clinical studies</td>
</tr>
<tr>
<td>European Collaborative Study; 1986–2004&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4,372/2,033</td>
<td>• Mono (704) &lt;br&gt; • Dual (254) &lt;br&gt; • Multi (1,075)</td>
<td>• YES (compared with mono/dual) &lt;br&gt; • Multi in pregnancy: 1.88 (1.34–2.65) &lt;br&gt; • Multi prepregnancy: 2.05 (1.43–2.95)</td>
<td></td>
</tr>
<tr>
<td>United States; 1990–2002&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2,543/not given</td>
<td>Early (&lt;25 Weeks): &lt;br&gt; • Mono (621) &lt;br&gt; • Multi (≥2 without PI or NNRTI) (198) &lt;br&gt; • Multi (with PI or NNRTI) (357)</td>
<td>• NO (compared with mono) &lt;br&gt; • No association between any ARV and PTD</td>
<td>• PTD decreased with ARV compared with no ARV.</td>
</tr>
<tr>
<td>United States; 1990–2002&lt;sup&gt;23&lt;/sup&gt;</td>
<td>1,337/999</td>
<td>• Mono (492) &lt;br&gt; • Multi (373) &lt;br&gt; • PI-multi (134)</td>
<td>• YES (compared with other multi) &lt;br&gt; • PI-multi: 1.8 (1.1–3.03)</td>
<td>• PI-multi reserved for advanced disease, those who failed other multi-ARV regimens.</td>
</tr>
<tr>
<td>Brazil, Argentina, Mexico, Bahamas; 2002–2005&lt;sup&gt;24&lt;/sup&gt;</td>
<td>681/681</td>
<td>• Mono/dual NRTI (94) &lt;br&gt; • Multi-NNRTI (257) &lt;br&gt; • Multi-PI (330)</td>
<td>• NO (compared with mono/dual NRTI) &lt;br&gt; • No association between any ARV regimen and PTD</td>
<td>• All on ARV for at least 28 days during pregnancy &lt;br&gt; • Preeclampsia/eclampsia, cesarean delivery, diabetes, low BMI associated with PTD</td>
</tr>
</tbody>
</table>
Table 5. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 3)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total on ARV Drugs</th>
<th>Types of ARV Regimens Compared (Numbers)</th>
<th>Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis, Europe and United States; 1986–2004&lt;sup&gt;12&lt;/sup&gt;</td>
<td>11,224/not given</td>
<td>• Multi-no PI [including dual] or multi-PI (2,556)</td>
<td>• YES (only comparing PI with multi)</td>
<td>• PI versus multi-no PI: 1.35 (1.08–1.70)</td>
</tr>
<tr>
<td>Italy; 2001–2006&lt;sup&gt;7&lt;/sup&gt;</td>
<td>419/366</td>
<td>• Multi-PI second trimester (97) • Multi-PI third trimester (146)</td>
<td>• YES</td>
<td>• Multi-PI second trimester: 2.24 (1.22–4.12) • Multi-PI third trimester: 2.81 (1.46–5.39)</td>
</tr>
<tr>
<td>United States; 1989–2004&lt;sup&gt;6&lt;/sup&gt;</td>
<td>8,793/6,228</td>
<td>• Mono (2,621) • Dual (1,044) • Multi-no PI (1,781) • Multi-PI (782)</td>
<td>• YES (compared with dual) • Multi-PI associated with PTD: 1.21 (1.04–1.40)</td>
<td>• Lack of antepartum ARV also associated with PTD. • PTD and low birthweight decreased over time.</td>
</tr>
<tr>
<td>United Kingdom, Ireland; 1990–2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>5,009/4,445</td>
<td>• Mono/dual (1,061) • Multi-NNRTI or Multi-PI (3,384)</td>
<td>• YES (compared with mono/dual) • Multi: 1.51 (1.19–1.93)</td>
<td>• Similar increased risk with PI or no-PI multi. • No association with duration of use.</td>
</tr>
<tr>
<td>Germany, Austria; 1995–2001&lt;sup&gt;8&lt;/sup&gt;</td>
<td>183/183</td>
<td>• Mono (77) • Dual (31) • Multi-PI (21) • Multi-NNRTI (54)</td>
<td>• YES (compared with mono) • Multi-PI: 3.40 (1.13–10.2)</td>
<td></td>
</tr>
<tr>
<td>United States; 2002–2007&lt;sup&gt;16&lt;/sup&gt;</td>
<td>777/777</td>
<td>• Mono (6) • Dual (11) • Multi-no PI (202) • Multi-PI (558)</td>
<td>• NO (compared PI with all non-PI) • Multi-PI: 1.22 (0.70–2.12)</td>
<td>• All started ARV during pregnancy. • Analyzed only spontaneous PTD.</td>
</tr>
<tr>
<td>Swiss Mother and Child HIV Cohort Study; 1985–2007&lt;sup&gt;13&lt;/sup&gt;</td>
<td>1,180/941</td>
<td>• Mono (94) • Dual (53) • Multi (PI or no PI) (409) • Multi-PI (385)</td>
<td>• YES (compared with no ARV) • Multi: 2.5 (1.4–4.3)</td>
<td>• No association mono/dual with PTD compared with no ARV. • No confounding by duration of ARV or maternal risk factors.</td>
</tr>
</tbody>
</table>
Table 5. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 3 of 3)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total on ARV Drugs</th>
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</tr>
</thead>
</table>
| Botswana; 2006–2008<sup>20</sup> | 530/530 | • Lopinavir/ritonavir plus zidovudine plus lamivudine (267)  
  • Abacavir plus zidovudine plus lamivudine (263) | • YES  
  • Multi-PI versus multi-NRTI: 2.03 (1.26–3.27) | • Secondary analysis of data from randomized, controlled clinical trial of ARV begun at 26–34 weeks for prevention of perinatal transmission.  
  • All CD4-cell counts >200 cells/mm<sup>3</sup> |
| Botswana; 2007–2010<sup>21</sup> | 4,347/3,659 | • ARV, regimen unspecified (70)  
  • Mono (2,473)  
  • Multi, 91% NNRTI (1,116) | • NO  
  • No association between multi-ART and very PTD (<32 weeks gestation) | • Observational multi-ART before conception associated with very small for gestational age and maternal hypertension during pregnancy. |
| Spain; 2000–2008<sup>16</sup> | 803/739 | • Mono/dual (32)  
  • Multi-no PI (281)  
  • Multi-PI (426) | • NO  
  • No association between ARV and PTD | • Greatest PTD risk if no antepartum ARV received. |
| Spain; 1986–2010<sup>17</sup> | 519/371 | • Mono/dual NRTI (73)  
  • All multi (298)  
  • Multi-PI (178) | • NO (compared with no ARV plus mono/dual)  
  • Spontaneous PTD not associated with multi-ART or multi-PI before or during pregnancy | • Iatrogenic PTD associated with multi-ART given in second half of pregnancy and with prior PTD. |
| United States; 2007–2010<sup>18</sup> | 1,869/1,810 | • Mono/dual (138)  
  • Multi-NRTI (193)  
  • Multi-NNRTI (160)  
  • Multi-PI (1,319) | • YES (compared with no ARV in first trimester)  
  • Multi-PI in first trimester vs. none in first trimester  
  • PTD 1.55 (1.16–2.07); spontaneous PTD 1.59 (1.10–2.30) | N/A |

Key to Abbreviations: ARV = antiretroviral; BMI = body mass index; dual = two ARV drugs; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; NNRTI = non-nucleoside analogue reverse transcriptase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; PI = protease inhibitor; PTD = preterm delivery

References


**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States**


Recommendations for Use of Antiretroviral Drugs during Pregnancy (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel's Recommendations

- In general, the same regimens as recommended for treatment of non-pregnant adults should be used in pregnant women unless there are known adverse effects for women, fetuses or infants that outweigh benefits (AII).
- Multiple factors must be considered when choosing a regimen for a pregnant woman including comorbidities, convenience, adverse effects, drug interactions, resistance testing results, pharmacokinetics (PK), and experience with use in pregnancy (AIII).
- PK changes in pregnancy may lead to lower plasma levels of drugs and necessitate increased dosages, more frequent dosing, or boosting, especially of protease inhibitors (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Antiretroviral (ARV) drug recommendations for HIV-infected, pregnant women have been based on the concept that drugs of known benefit to women should not be withheld during pregnancy unless there are known adverse effects to the mother, fetus, or infant and unless these adverse effects outweigh the benefits to the woman.1 Pregnancy should not preclude the use of optimal drug regimens. The decision to use any ARV drug during pregnancy should be made by a woman after discussing with her health care provider the known and potential benefits and risks to her and her fetus.

The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel) reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration review related to treatment of HIV-infected adult women, both pregnant and non-pregnant. The durability, tolerability, and simplicity of a medication regimen are particularly important for ensuring adherence and preserving future treatment options. Regimen selection should be individualized and the following factors should be considered:

- Comorbidities,
- Patient adherence potential,
- Convenience,
- Potential adverse maternal drug effects that may be exacerbated during pregnancy,
- Potential drug interactions with other medications,
- Results of genotypic resistance testing,
- Pharmacokinetic (PK) changes in pregnancy and degree of placental transfer,
- Potential teratogenic effects and other short- and long-term adverse effects on fetuses or newborns including preterm birth, mutagenicity, and carcinogenicity, and
- Experience with use in pregnancy.

Information used by the Panel for recommendations on specific drugs or regimens for pregnant women includes:

- Data from randomized, prospective clinical trials, and cohort studies that demonstrate durable viral suppression as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short- and long-term drug toxicity of ARV regimens, with special attention to maternal toxicity and potential teratogenicity and fetal safety;
- Specific knowledge about drug tolerability and simplified dosing regimens;
Physiologic changes that occur during pregnancy can affect drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering the susceptibility of pregnant women to drug toxicity.\(^2,3\) During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in cellular transporters and drug metabolizing enzymes in the liver and intestine. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug PK in the pregnant woman.

Currently available data on the PKs and dosing of ARV drugs in pregnancy are summarized in Table 7. In general, the PKs of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and non-pregnant women (although data on etravirine and rilpivirine are limited), whereas protease inhibitor (PI) PKs are more variable, particularly in later pregnancy. Current data suggest that with standard adult dosing, plasma concentrations of ritonavir-boosted lopinavir, atazanavir, darunavir, and nelfinavir are reduced during the second and/or third trimesters (see Table 7). The need for a dose adjustment depends on the PI, an individual patient’s treatment experience, and use (if any) of concomitant medications with potential for drug interactions.\(^4-11\) Raltegravir levels in the third trimester were quite variable but not significantly different than postpartum or historical data in non-pregnant individuals.\(^12\) Data on enfuvirtide, maraviroc, and elvitegravir in pregnancy are too limited to allow recommendations on dosing.

Although clinical data are more limited on ARV drugs in pregnant women than in non-pregnant individuals, sufficient data exist on which to base recommendations related to drug choice for many of the available ARV drugs. Drugs and drug regimens for pregnant antiretroviral-naive women are classified as preferred, alternative, insufficient data to recommend use, and not recommended (Table 6).

Categories of ARV regimens include:

- **Preferred:** Drugs or drug combinations are designated as preferred for use in ARV-naive pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific PK data are available to guide dosing; and no established association with teratogenic effects or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported. Drugs in the preferred category may have toxicity concerns based on non-human data that have not been verified or established in humans. Therefore, it is important to read the full discussion of each drug in the Guidelines before using it in your patients (also see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). For example, efavirenz is now listed in the preferred category, but only with initiation after 8 weeks’ gestation because of unresolved questions regarding teratogenicity.

- **Alternative:** Drugs or drug combinations are designated as alternatives for initial therapy in ARV-naive pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: experience in pregnancy is limited; data are lacking on teratogenic effects on the fetus; or the drug or regimen is associated with dosing, formulation, administration, or interaction issues.

- **Insufficient Data to Recommend:** The drugs and drug combinations in this category are approved for use in adults but lack pregnancy-specific PK or safety data or such data are too limited to make a recommendation for use in ARV-naive pregnant women.

- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potentially serious maternal or fetal...
safety concerns, or pharmacologic antagonism or are not recommended for ARV-naive populations regardless of pregnancy status.

In pregnant women, as in non-pregnant adults, a combination ARV treatment (cART) regimen with at least three agents is recommended. Recommendations for choice of ARV drug regimen during pregnancy must be individualized according to a pregnant woman’s specific ARV history and the presence of comorbidities. Some women may become pregnant and present for obstetrical care while receiving cART for their own health. In general, women who are already on a fully suppressive regimen should continue their regimens (see HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy).

Other HIV-infected women may not be receiving cART at the time they present for obstetrical care. Some women have never received ARV drugs, and others may have taken ARV drugs for treatment that was stopped, for prevention of perinatal transmission of HIV in prior pregnancies, or for pre- or post-exposure prophylaxis. The following sections provide detailed discussions of recommendations based on maternal ARV history and current and previous resistance testing.

For ARV-naive women, a cART regimen including two NRTIs and either a PI with low-dose ritonavir or an NNRTI is preferable (Table 6).

While zidovudine/lamivudine remains a preferred dual NRTI combination for ARV-naive pregnant women, based on efficacy studies in preventing perinatal transmission and extensive experience with safe use in pregnancy, additional NRTI combinations are also considered in the preferred category. Tenofovir disoproxil fumarate (tenofovir) with emtricitabine or lamivudine is the preferred NRTI component for non-pregnant adults and, based on increased experience with use in pregnancy, once-daily dosing, enhanced activity against hepatitis B, and less frequent toxicity compared to zidovudine/lamivudine, can now be considered a preferred combination in pregnancy. In addition, abacavir offers the advantage of once-daily dosing in combination with lamivudine and has been well tolerated in pregnancy and can be considered a preferred agent.

Data from the Antiretroviral Pregnancy Registry on 1,612 pregnancies with first-trimester exposure to tenofovir have shown no increase in overall birth defects compared with the general population. Animal studies have shown decreased fetal growth and reduction in fetal bone porosity with tenofovir use in pregnancy, and studies in infected children on chronic tenofovir-based therapy have shown bone demineralization in some children. However, increasing experience with tenofovir use in pregnancy has generally been reassuring. Several large case series as well as an analysis from the Pediatric HIV/AIDS Cohort Study (PHACS) including infants born to 449 women taking tenofovir during pregnancy have not shown differences in weight or other growth parameters at birth compared to infants exposed to other ARV regimens in utero. The PHACS analysis did note slightly lower length and head circumference at 1 year in tenofovir-exposed infants compared to those with other ARV exposures, although this was not reported in other cohorts that had longitudinal follow-up. Additional studies evaluating in utero tenofovir exposure are ongoing; given experience with tenofovir in pregnancy to date as well as once daily dosing and decreased toxicity, a tenofovir-based dual NRTI combination has been added as a preferred NRTI combination in pregnancy.

Data from the Antiretroviral Pregnancy Registry on 848 pregnancies with first-trimester exposure to abacavir have shown no increase in overall birth defects compared with the general population. Abacavir was well-tolerated in pregnancy in a large trial in Botswana. Testing for the HLA-B*5701 allele should be performed and documented as negative before starting abacavir, and women should be educated about symptoms of hypersensitivity reactions.

In addition to the dual NRTIs, either a low-dose ritonavir-boosted PI or an NNRTI would be preferred for cART regimens in ARV-naive pregnant women (Table 6). Ritonavir-boosted lopinavir and ritonavir-boosted atazanavir are the preferred PI drugs for use in ARV-naive pregnant women, based on efficacy studies in pregnant women.
PK data and extensive clinical experience do exist for nelfinavir in pregnancy, but the rate of viral response to nelfinavir-based regimens was lower than ritonavir-boosted lopinavir or efavirenz-based regimens in clinical trials of initial therapy in non-pregnant adults. Because of its lower antiviral activity, nelfinavir use is not recommended. Indinavir may be associated with renal stones and has a higher pill burden than many other PI drugs and thus is also not recommended for use in ARV-naive pregnant women. Both atazanavir and indinavir are associated with increased indirect bilirubin levels, which theoretically may increase the risk of hyperbilirubinemia in neonates although pathologic elevations have not been seen in studies to date. In an analysis from PHACS, in utero exposure to atazanavir compared to other drugs was associated with risk of late language emergence at 12 months, but that was no longer significant at 24 months. Data on use in pregnancy are too limited to recommend routine use of fosamprenavir and ritonavir-boosted tipranavir in pregnant women, although they can be considered for women who are intolerant of other agents or who require tipranavir/ritonavir because of resistance.

Efavirenz is the preferred NNRTI for non-pregnant adults. Although increasing data on use of efavirenz in pregnancy are reassuring, because concerns regarding potential teratogenicity, efavirenz is not recommended for initiation in ARV-naive women in the first 8 weeks of pregnancy (see Teratogenicity). Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens. Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the health of the woman. Because the risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized before 4–6 weeks of pregnancy, and because unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz may be continued in pregnant women presenting for prenatal care in the first trimester who have achieved virologic suppression on the regimen (see HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment). Initiation of efavirenz can be considered in ARV-naive pregnant women after the first 8 weeks of pregnancy with accurate dating parameters, based on clinical indication. Nevirapine would be an alternate NNRTI for ARV-naive pregnant women with CD4 T lymphocyte (CD4) cell counts <250 cells/mm3 and can be continued in ARV-experienced women already receiving a suppressive nevirapine-based regimen, regardless of CD4 cell count. In general, nevirapine should not be initiated in treatment-naive women with CD4 cell counts >250 cells/mm3 because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity. Elevated transaminase levels at baseline also may increase the risk of nevirapine toxicity. Safety and PK data on etravirine and rilpivirine in pregnancy are insufficient to recommend use of these NNRTI drugs in ARV-naive women.

Safety and PK data in pregnancy are insufficient to recommend use of the entry inhibitors enfuvirtide and maraviroc in ARV-naive women during pregnancy. Use of these agents can be considered for women who have failed therapy with several other classes of ARV drugs after consultation with HIV and obstetric specialists.

Data on the integrase inhibitor raltegravir during pregnancy are limited but increasing; cART regimens including raltegravir can be considered as alternate regimens when preferred agents cannot be used in ARV-naive pregnant women. Clinical trial data from non-pregnant adults suggest a more rapid viral decay with the use of raltegravir compared to efavirenz. Case series have reported rapid viral decay with the use of raltegravir initiated late in pregnancy given with the goal of achieving viral suppression and reducing risk of perinatal HIV transmission, but no comparative data are available in pregnancy. The rate of viral decay with raltegravir compared to efavirenz or ritonavir-boosted lopinavir in late-presenting pregnant women is currently under investigation in a trial in the IMPAACT network, P1081. A case report of marked elevation of liver transaminases after initiation of raltegravir in late pregnancy, which resolved rapidly after stopping the drug, suggests that monitoring of transaminases may be indicated with use of this strategy.
There are currently no data on the use of elvitegravir with cobicistat in pregnancy, thus these drugs cannot be recommended for ARV-naive pregnant women at this time.

Although data are insufficient to support or refute the teratogenic risk of ARV drugs when administered during the first trimester, information to date does not support major teratogenic effects for the majority of such agents. (For further data, see www.APRegistry.com.) However, certain drugs are of more concern than others—for example, efavirenz should be avoided during the first 8 weeks of pregnancy when possible (see Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy).

References


Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 1 of 2)

These recommendations are for pregnant women who have never received antiretroviral therapy (ART) previously (i.e., ARV-naive) and are predicated on lack of evidence of resistance to regimen components. See Table 7 for more information on specific drugs and dosing in pregnancy. Within each drug class, regimens are listed alphabetically, and the order does not indicate a ranking of preference. It is recommended that women who become pregnant while on a stable ARV regimen with viral suppression remain on that same regimen.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Regimens with clinical trial data in adults demonstrating optimal efficacy and durability with acceptable toxicity and ease of use, PK data available in pregnancy, and no evidence to date of teratogenic effects or established adverse outcomes for mother/fetus/newborn. To minimize the risk of resistance, a PI regimen is preferred for women who may stop ART during the postpartum period.</td>
<td></td>
</tr>
<tr>
<td><strong>Preferred Two-NRTI Backbone</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>Available as FDC, can be administered once daily, but potential HSR. ABC should not be used in patients who test positive for HLA-B*5701.</td>
</tr>
<tr>
<td>TDF/FTC or 3TC</td>
<td>TDF/FTC available as FDC. Either TDF/FTC or TDF and 3TC can be administered once daily. TDF has potential renal toxicity, thus TDF-based dual NRTI combinations should be used with caution in patients with renal insufficiency.</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>Available as FDC. NRTI combination with most experience for use in pregnancy but has disadvantages of requirement for twice-daily administration and increased potential for hematologic toxicity.</td>
</tr>
<tr>
<td><strong>PI Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>ATV/r + a Preferred Two-NRTI Backbone</td>
<td>Once-daily administration.</td>
</tr>
<tr>
<td>LPV/r + a Preferred Two-NRTI Backbone</td>
<td>Twice-daily administration. Once-daily LPV/r is not recommended for use in pregnant women.</td>
</tr>
<tr>
<td><strong>NNRTI Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>EFV + a Preferred Two-NRTI Backbone</td>
<td>Concern because of birth defects seen in primate study; risk in humans is unclear (see Teratogenicity and Table 7). Postpartum contraception must be ensured. Preferred regimen in women requiring co-administration of drugs with significant interactions with PIs.</td>
</tr>
<tr>
<td><strong>Alternative Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Regimens with clinical trial data demonstrating efficacy in adults but one or more of the following apply: experience in pregnancy is limited, data are lacking or incomplete on teratogenicity, or regimen is associated with dosing, formulation, toxicity, or interaction issues</td>
<td></td>
</tr>
<tr>
<td><strong>PI Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>DRV/r + a Preferred Two-NRTI Backbone</td>
<td>Less experience with use in pregnancy than ATV/r and LPV/r.</td>
</tr>
<tr>
<td>SQV/r + a Preferred Two-NRTI Backbone</td>
<td>Baseline ECG is recommended before initiation of SQV/r because of potential PR and QT prolongation; contraindicated with pre-existing cardiac conduction system disease. Large pill burden.</td>
</tr>
<tr>
<td><strong>NNRTI Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>NVP + a Preferred Two-NRTI Backbone</td>
<td>NVP should be used with caution when initiating ART in women with CD4 T-lymphocyte (CD4) cell count &gt;250 cells/mm³. Use NVP and ABC together with caution; both can cause HSRs within the first few weeks after initiation.</td>
</tr>
<tr>
<td><strong>Integrase Inhibitor Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>RAL + a Preferred Two-NRTI Backbone</td>
<td>Limited data on RAL use in pregnancy, but may be considered when drug interactions with PI regimens are a concern.</td>
</tr>
</tbody>
</table>
### Insufficient Data in Pregnancy to Recommend Routine Use in ART-Naive Women

Drugs that are approved for use in adults but lack adequate pregnancy-specific PK or safety data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>No data on use of DTG in pregnancy</td>
</tr>
<tr>
<td>EVG/COBI/TDF/FTC Fixed Drug Combination</td>
<td>No data on use of EVG/COBI component in pregnancy.</td>
</tr>
<tr>
<td>FPV/r</td>
<td>Limited data on use in pregnancy.</td>
</tr>
<tr>
<td>MVC</td>
<td>MVC requires tropism testing before use. Few case reports of use in pregnancy.</td>
</tr>
<tr>
<td>RPV</td>
<td>RPV not recommended with pretreatment HIV RNA &gt;100,000 copies/mL or CD4 cell count &lt;200 cells/mm³. Do not use with proton pump inhibitor. Limited data on use in pregnancy.</td>
</tr>
</tbody>
</table>

### Not Recommended

Drugs whose use is not recommended because of toxicity, lower rate of viral suppression or because not recommended in ART-naive populations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC/ZDV</td>
<td>Generally not recommended due to inferior virologic efficacy.</td>
</tr>
<tr>
<td>d4T</td>
<td>Not recommended due to toxicity.</td>
</tr>
<tr>
<td>ddl</td>
<td>Not recommended due to toxicity.</td>
</tr>
<tr>
<td>IDV/r</td>
<td>Concerns re: kidney stones, hyperbilirubinemia.</td>
</tr>
<tr>
<td>NFV</td>
<td>Lower rate of viral suppression with NFV compared to LPV/r or EFV in adult trials.</td>
</tr>
<tr>
<td>RTV</td>
<td>RTV as a single PI is not recommended because of inferior efficacy and increased toxicity.</td>
</tr>
<tr>
<td>ETR</td>
<td>Not recommended in ART-naive populations</td>
</tr>
<tr>
<td>T20</td>
<td>Not recommended in ART-naive populations</td>
</tr>
<tr>
<td>TPV</td>
<td>Not recommended in ART-naive populations</td>
</tr>
</tbody>
</table>

### Key to Acronyms:

- 3TC = lamivudine
- ABC = abacavir
- ART = antiretroviral therapy
- ARV = antiretroviral
- ATV/r = atazanavir/ritonavir
- CD4 = CD4 T lymphocyte
- COBI = cobicistat
- d4T = stavudine
- ddl = didanosine
- DTG = dolutegravir
- DRV/r = darunavir/ritonavir
- ECG = electrocardiogram
- EFV = efavirenz
- ETR = etravirine
- EVG = elvitegravir
- FDC = fixed drug combination
- FPV/r = fosamprenavir/ritonavir
- FTC = emtricitabine
- HSR = hypersensitivity reaction
- IDV/r = indinavir/ritonavir
- LPV/r = lopinavir/ritonavir
- MVC = maraviroc
- NFV = nelfinavir
- NRTI = nucleoside reverse transcriptase inhibitor
- NNRTI = non-nucleoside reverse transcriptase inhibitor
- NVP = nevirapine
- PI = protease inhibitor
- PK = pharmacokinetic
- RAL = raltegravir
- RPV = rilpivirine
- RTV = ritonavir
- SQV/r = saquinavir/ritonavir
- T20 = enfuvirtide
- TDF = tenofovir disoproxil fumarate
- TPV = tipranavir
- ZDV = zidovudine
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancya  

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<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
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</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>N/A</td>
<td>N/A</td>
<td>NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection. See text for discussion of potential maternal and infant mitochondrial toxicity.</td>
</tr>
<tr>
<td>Abacavir (ABC) Ziagen (3TC/ABC) Epzicom (ZDV/3TC/ABC) Trizivir</td>
<td>ABC (Ziagen) Tablet: • 300 mg Solution: • 20 mg/mL Epzicom: • ABC 600 mg plus 3TC 300 mg tablet Trizivir: • ABC 600 mg plus 3TC 150 mg plus ZDV 300 mg tablet</td>
<td>Standard Adult Doses ABC (Ziagen): • 300 mg twice daily or 600 mg once daily, without regard to food Epzicom: • 1 tablet once daily without regard to food Trizivir: • 1 tablet twice daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>High placental transfer to fetus. No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Hypersensitivity reactions occur in approximately 5% to 8% of non-pregnant individuals; a much smaller percentage are fatal and are usually associated with re-challenge. Rate in pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of hypersensitivity reaction.</td>
</tr>
<tr>
<td>Didanosine (ddI) Videx Videx EC Generic dd</td>
<td>ddI (Videx) Buffered Tablets (Non-EC): • No longer available Solution: • 10 mg/mL oral solution Videx EC (EC Beadlets) Capsules: • 125 mg • 200 mg • 250 mg • 400 mg Generic Delayed-Release Capsules: • 200 mg • 250 mg • 400 mg</td>
<td>Standard Adult Doses Body Weight ≥60kg: • 400 mg once daily With TDF: • 250 mg once daily; take 1/2 hour before or 2 hours after a meal. Body Weight &lt;60kg: • 250 mg once daily With TDF: • 200 mg once daily; take 1/2 hour before or 2 hours after a meal. Note: Preferred dosing with oral solution is twice daily (total daily dose divided into 2 doses); take 1/2 hour before or 2 hours after a meal. PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>Low-moderate placental transfer to fetus. In the APR, an increased rate of birth defects with ddI compared to general population was noted after both first-trimester (20/413, 4.8%, 95% CI, 3.0–7.4%) and later exposure (20/460, 4.3%, 95% CI 2.7–6.6%). No specific pattern of defects was noted and clinical relevance is uncertain. ddI should not be used with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.</td>
</tr>
</tbody>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Emtricitabine</strong> (FTC)</td>
<td>Emtriva</td>
<td>Capsules: 200 mg</td>
<td>Standard Adult Dose(s) FTC (Emtriva) Capsule: • 200 mg daily without regard to food Oral Solution: • 10 mg/mL Truvada: • FTC 200 mg plus TDF 300 mg tablet Atripla: • FTC 200 mg plus TDF 300 mg plus EFV 600 mg tablet Complera: • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet Stribild: • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet</td>
<td>High placental transfer to fetus. No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). If hepatitis B coinfected, it is possible that a hepatitis B flare may occur if the drug stopped postpartum; see HIV/Hepatitis B Virus Coinfection.</td>
</tr>
<tr>
<td>Emtriva (FTC/TDF)</td>
<td>Truvada</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atripla (FTC/TDF/EFV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complera (FTC/TDF/RPV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(FTC/TDF/EVG/COBI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stribild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamivudine</strong> (3TC)</td>
<td>Epivir</td>
<td>Tablets: 150 mg</td>
<td>Standard Adult Dose(s) 3TC (Lamivudine): • 150 mg twice daily or 300 mg once daily without regard to food Combivir: • 1 tablet twice daily without regard to food Epzicom: • 1 tablet once daily without regard to food Trizivir: • 1 tablet twice daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>High placental transfer to fetus. No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If hepatitis B coinfected, it is possible that a hepatitis B flare may occur if the drug stopped postpartum; see HIV/Hepatitis B Virus Coinfection.</td>
</tr>
<tr>
<td>Epivir (3TC/ZDV)</td>
<td>Combivir</td>
<td>Tablets: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3TC/ABC) Epzicom</td>
<td></td>
<td>10 mg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3TC/ZDV/ABC) Trizivir</td>
<td></td>
<td>Tablets: 150 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trizivir (3TC/ABC)</td>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- FTC (Emtriva) Capsule: 200 mg once daily without regard to food.
- FTC (Emtriva) Oral Solution: 10 mg/mL.
- Truvada: FTC 200 mg plus TDF 300 mg tablet.
- Atripla: FTC 200 mg plus TDF 300 mg plus EFV 600 mg tablet.
- Complera: FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet.
- Stribild: FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet.
- 3TC (Epivir) Tablets: 150 mg, 300 mg.
- Epivir (3TC/ZDV) Tablets: 10 mg/mL.
- Combivir: 3TC 150 mg plus ZDV 300 mg tablet.
- Epzicom: 3TC 300 mg plus ABC 600 mg tablet.
- Trizivir: 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet.
### Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
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<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stavudine</strong>&lt;br&gt;(d4T)&lt;br&gt;Zerit</td>
<td>Capsules:&lt;br&gt;- 15 mg&lt;br&gt;- 20 mg&lt;br&gt;- 30 mg&lt;br&gt;- 40 mg&lt;br&gt;Oral Solution:&lt;br&gt;- 1 mg/mL following reconstitution</td>
<td><strong>Standard Adult Dose(s)</strong>&lt;br&gt;<em>Body Weight ≥60 kg:</em>&lt;br&gt;- 40 mg twice daily without regard to meals&lt;br&gt;<em>Body Weight &lt;60 kg:</em>&lt;br&gt;- 30 mg twice daily without regard to meals</td>
<td>High placental transfer.&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).&lt;br&gt;d4T should not be used with ddI or ZDV. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.</td>
</tr>
<tr>
<td><strong>Tenofovir Disoproxil Fumarate</strong>&lt;br&gt;(TDF)&lt;br&gt;Viread&lt;br&gt;(TDF/FTC)&lt;br&gt;Truvada&lt;br&gt;(TDF/FTC/EFV)&lt;br&gt;Atripla&lt;br&gt;(TDF/FTC/RPV)&lt;br&gt;Complera&lt;br&gt;(TDF/FTC/EVG/COBI)&lt;br&gt;Stribild</td>
<td>TDF (Viread)&lt;br&gt;Tablet:&lt;br&gt;- 300 mg&lt;br&gt;Powder:&lt;br&gt;- 40 mg/1G oral powder&lt;br&gt;Truvada:&lt;br&gt;- TDF 300 mg plus FTC 200 mg tablet&lt;br&gt;Atripla:&lt;br&gt;- TDF 300 mg plus FTC 200 mg plus EFV&lt;sup&gt;c&lt;/sup&gt; 600 mg tablet&lt;br&gt;Complera:&lt;br&gt;- TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet&lt;br&gt;Stribild:&lt;br&gt;- TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet</td>
<td><strong>Standard Adult Dose</strong>&lt;br&gt;<em>TDF (Viread)</em>&lt;br&gt;<strong>Tablet:</strong>&lt;br&gt;- 300 mg once daily without regard to food&lt;br&gt;<em>Powder:</em>&lt;br&gt;- 8 mg/kg (up to maximum 300 mg), take with food&lt;br&gt;<em>Truvada:</em>&lt;br&gt;- 1 tablet once daily without regard to food&lt;br&gt;<em>Atripla:</em>&lt;br&gt;- 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.&lt;br&gt;<em>Complera:</em>&lt;br&gt;- 1 tablet once daily with food&lt;br&gt;<em>Stribild:</em>&lt;br&gt;- 1 tablet once daily with food&lt;br&gt;PK in Pregnancy:&lt;br&gt;- AUC lower in third trimester than postpartum but trough levels adequate.&lt;br&gt;Dosing in Pregnancy:&lt;br&gt;- No change in dose indicated.</td>
<td>High placental transfer to fetus.&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).&lt;br&gt;Studies in monkeys (at doses approximately 2-fold higher than that for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no effect on intrauterine growth, but one study demonstrated lower length and head circumference with exposure.&lt;br&gt;TDF should be used in combination with 3TC or FTC in women with chronic HBV infection. If hepatitis B coinfected, it is possible that a hepatitis B flare may occur if the drug stopped postpartum; see <a href="http://aidsinfo.nih.gov/guidelines">HIV/Hepatitis B Virus Coinfection</a>. Because of potential for renal toxicity, renal function should be monitored.</td>
</tr>
<tr>
<td>Generic Name (Abbreviation) Trade Name</td>
<td>Formulation</td>
<td>Dosing Recommendations</td>
<td>Recommendations for Use in Pregnancy</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td><strong>Zidovudine</strong>&lt;br&gt; (AZT, ZDV)&lt;br&gt; Retrovir&lt;br&gt; (ZDV/3TC)&lt;br&gt; Combivir&lt;br&gt; (ZDV/3TC/ABC)&lt;br&gt; Trizivir</td>
<td>ZDV (Retrovir)&lt;br&gt; Capsule:&lt;br&gt; • 100 mg&lt;br&gt; Tablet:&lt;br&gt; • 300 mg&lt;br&gt; Oral Solution:&lt;br&gt; • 10 mg/mL&lt;br&gt; Intravenous Solution:&lt;br&gt; • 10 mg/mL&lt;br&gt; Combivir:&lt;br&gt; • ZDV 300 mg plus 3TC 150 mg tablet&lt;br&gt; Trizivir:&lt;br&gt; • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet</td>
<td>Standard Adult Dose(s)&lt;br&gt; ZDV (Retrovir):&lt;br&gt; • 300 mg twice daily or 200 mg 3 times daily, without regard to food&lt;br&gt; Active Labor:&lt;br&gt; • 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery&lt;br&gt; Combivir:&lt;br&gt; • 1 tablet twice daily, without regard to food&lt;br&gt; Trizivir:&lt;br&gt; • 1 tablet twice daily, without regard to food&lt;br&gt; PK in Pregnancy:&lt;br&gt; • PK not significantly altered in pregnancy.&lt;br&gt; Dosing in Pregnancy:&lt;br&gt; • No change in dose indicated.</td>
<td>High placental transfer to fetus.&lt;br&gt; No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</td>
</tr>
<tr>
<td><strong>NNRTI Drugs</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.&lt;br&gt; Hypersensitivity reactions, including hepatic toxicity and rash more common in women; unclear if increased in pregnancy.</td>
</tr>
</tbody>
</table>
## Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>(EFV) Sustiva (EFV/TDF/FTC) Atripla</td>
<td>EFV (Sustiva) Capsules: • 50 mg • 200 mg Tablet: • 600 mg Atripla: • EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet</td>
<td>Standard Adult Dose EFV (Sustiva): • 600 mg once daily at or before bedtime, on empty stomach to reduce side effects Atripla: • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. PK in Pregnancy: • AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester participants exceeded target exposure. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>Moderate placental transfer to fetus.&lt;sup&gt;3&lt;/sup&gt; Potential fetal safety concern: FDA Pregnancy Class D. Cynomolgus monkeys receiving EFV during the first trimester at a dose resulting in plasma levels comparable to systemic human therapeutic exposure had 3 of 20 infants with significant CNS or other malformations. In humans, there is no increase in overall birth defects with first-trimester EFV exposure. However, in humans with first-trimester exposure, there have been 6 retrospective case reports and 1 prospective case report of CNS defects and 1 prospective case report of anophthalmia with facial clefts. The relative risk with first-trimester exposure is unclear. Non-pregnant women of childbearing potential should undergo pregnancy testing before EFV initiation and counseling about potential risk to the fetus and desirability of avoiding pregnancy while on EFV-containing regimens. Alternate ARV regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the health of the woman. Because the risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized before 4–6 weeks of pregnancy, and unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV may be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided there is virologic suppression on the regimen (see <a href="http://aidsinfo.nih.gov/guidelines">HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment</a>).</td>
</tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Etravirine</strong> (ETR) Intelence</td>
<td></td>
<td>Tablets: • 25 mg • 100 mg • 200 mg</td>
<td>Standard Adult Dose(s): • 200 mg twice daily with food PK in Pregnancy: • Limited PK data in pregnancy (n = 4) suggest no significant differences from non-pregnant adults. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.</td>
<td>Moderate placental transfer (data from one mother-infant pair). Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</td>
</tr>
<tr>
<td><strong>Nevirapine</strong> (NVP) Viramune Viramune XR (Extended Release)</td>
<td></td>
<td>NVP (Viramune) Tablets: • 200 mg Oral Suspension: • 50 mg/5 mL Viramune XR Tablets: • 100 mg • 400 mg</td>
<td>Standard Adult Dose: • 200 mg once daily Viramune immediate release for 14 days (lead-in period); thereafter, 200 mg twice daily or 400 mg (Viramune XR tablet) once daily, without regard to food. • Repeat lead-in period if therapy is discontinued for &gt;7 days. • In patients who develop mild-to-moderate rash without constitutional symptoms during lead-in, continue lead-in dosing until rash resolves, but ≤28 days total. PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>High placental transfer to fetus. No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of birth defects in more common classes, cardiovascular and genitourinary). Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts ≥250/mm^3 when first initiating therapy; pregnancy does not appear to increase risk. NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm^3 only if benefit clearly outweighs risk because of potential increased risk of life-threatening hepatotoxicity in women with high CD4 cell counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and are tolerating them well can continue therapy, regardless of CD4 cell count.</td>
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<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine (RPV) Endurant (RPV/TDF/FTC) Complera</td>
<td>RPV (Endurant) Tablet: • 25 mg Complera: • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet</td>
<td>Standard Adult Dose RPV (Endurant): • 25 mg once daily with food Complera: • 1 tablet once daily with food PK in Pregnancy: • No PK studies in human pregnancy, no dosing recommendation can be made. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.</td>
<td>Unknown placental transfer to fetus in humans. No evidence of teratogenicity in rats or rabbits. Insufficient data to assess for teratogenicity in humans.</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>N/A</td>
<td>N/A</td>
<td>PIs are recommended for use in combination regimens with 2 NRTI drugs. Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see Combination Antiretroviral Drug Regimens and Pregnancy Outcomes).</td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (ATV) Reyataz</td>
<td>Capsules:</td>
<td>Standard Adult Dose</td>
<td>Low placental transfer to fetus.³</td>
</tr>
<tr>
<td></td>
<td>• 100 mg</td>
<td>ARV-Naive Patients</td>
<td>No evidence of human teratogenicity</td>
</tr>
<tr>
<td></td>
<td>• 150 mg</td>
<td>Without RTV Boosting:</td>
<td>(can rule out 2-fold increase in overall birth defects).</td>
</tr>
<tr>
<td></td>
<td>• 200 mg</td>
<td>• ATV 400 mg once daily</td>
<td>Must be given as low-dose RTV-boosted</td>
</tr>
<tr>
<td></td>
<td>• 300 mg</td>
<td>with food; ATV without</td>
<td>regimen in pregnancy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RTV boosting must not</td>
<td>Effect of in utero ATV exposure on infant indirect bilirubin levels is unclear. Non-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recommended when used</td>
<td>pathologic elevations of neonatal hyperbilirubinemia have been observed in some but not all clinical trials to date.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with TDF, H2-receptor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>antagonist or proton</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pump inhibitor or during</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pregnancy.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>With RTV Boosting:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ATV 300 mg plus RTV 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg once daily with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• When combined with EFV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>in ARV-naive patients:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>ATV 400 mg plus RTV 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg once daily with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARV-Experienced Patients:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ATV 300 mg plus RTV 100</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>mg once daily with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Do not use with proton</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pump inhibitor or EFV.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If combined with an H2-receptor antagonist: ATV 300 mg plus RTV 100 mg once daily with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If combined with an H2-receptor antagonist and TDF: ATV 400 mg plus RTV 100 mg once daily with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ATV concentrations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>reduced during pregnancy,</td>
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<tr>
<td></td>
<td></td>
<td>also reduced when given</td>
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<tr>
<td></td>
<td></td>
<td>concomitantly with TDF or</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>H2-receptor antagonist.</td>
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<tr>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Use of unboosted ATV not</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>recommended during</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pregnancy.</td>
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<tr>
<td></td>
<td></td>
<td>• Use of an increased</td>
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<tr>
<td></td>
<td></td>
<td>dose (400 mg ATV plus 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg RTV once daily with</td>
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<tr>
<td></td>
<td></td>
<td>food) during the second</td>
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<tr>
<td></td>
<td></td>
<td>and third trimesters</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>results in plasma</td>
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<tr>
<td></td>
<td></td>
<td>concentrations equivalent</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>to those in non-pregnant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>adults on standard</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dosing. Although some</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>experts recommend increased</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATV dosing in all women</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>during the second and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>third trimesters, the</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>package insert recommends</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased ATV dosing only</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>for ARV-experienced pregnant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>women in the second and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>third trimesters also</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>receiving either TDF or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>an H2-receptor antagonist.</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
</table>
| Darunavir (DRV) | Tablets: • 75 mg • 150 mg • 400 mg • 600 mg | **Standard Adult Dose:**  
**ARV-Naive Patients:**  
• DRV 800 mg plus RTV 100 mg once daily with food  
**ARV-Experienced Patients**  
If No DRV Resistance Mutations:  
• DRV 800 mg plus RTV 100 mg once daily with food  
If Any DRV Resistance Mutations:  
• DRV 600 mg plus RTV 100 mg twice daily with food  
**PK in Pregnancy:**  
• Decreased exposure in pregnancy.  
**Dosing in Pregnancy:**  
• Once-daily dosing **not** recommended during pregnancy. Twice-daily dosing recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) in pregnancy is being investigated.  | Low placental transfer to fetus. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits. Must be given as low-dose RTV-boosted regimen. |

| Fosamprenavir (FPV) | Tablets: • 700 mg  
**Oral Suspension:** • 50 mg/mL | **Standard Adult Dose**  
**ARV-Naive Patients:**  
• FPV 1400 mg twice daily without food or  
• FPV 1400 mg plus RTV 100 or 200 mg once daily without food or  
• FPV 700 mg plus RTV 100 mg twice daily without food  
**PI-Experienced Patients (Once-Daily Dosing not Recommended):**  
• FPV 700 mg plus RTV 100 mg twice daily without food  
**Co-Administered with EFV:**  
• FPV 700 mg plus RTV 100 mg twice daily without food; or  
• FPV 1400 mg plus RTV 300 mg once daily without food  
**PK in Pregnancy:**  
• With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in non-pregnant adults without boosting, and trough concentrations achieved | Low placental transfer to fetus. Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits but no increase in defects in rats and rabbits. Must be given as low-dose RTV-boosted regimen in pregnancy. |
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamprenavir, continued (FPV)</td>
<td></td>
<td>during the third trimester were adequate for patients without PI resistance mutations. <strong>Dosing in Pregnancy:</strong> • Use of unboosted FPV <strong>not</strong> recommended during pregnancy. No change in standard boosted dose (FPV 700 mg plus RTV 100 mg twice daily without food) indicated.</td>
<td>Minimal placental transfer to fetus. No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Must be given as low-dose RTV-boosted regimen in pregnancy. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates. Minimal placental passage mitigates this concern.</td>
</tr>
<tr>
<td><strong>Note:</strong> Must be combined with low-dose RTV boosting in pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (IDV) Crixivan</td>
<td>Capsules: • 100 mg • 200 mg • 400 mg</td>
<td><strong>Standard Adult Dose Without RTV Boosting:</strong> • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal. <strong>With RTV Boosting:</strong> • IDV 800 mg plus RTV 100 mg twice daily without regard to meals <strong>PK in Pregnancy:</strong> • IDV exposure markedly reduced when administered without RTV boosting during pregnancy. IDV exposure low with IDV 400 mg/RTV 100 mg dosing during pregnancy; no PK data available on alternative boosted dosing regimens in pregnancy. <strong>Dosing in Pregnancy:</strong> • Use of unboosted IDV <strong>not</strong> recommended during pregnancy.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-Boosted Lopinavir</td>
<td>Kaletra</td>
<td>Tablets (Co-Formulated):</td>
<td>Standard Adult Dose:</td>
<td>Low placental transfer to fetus.(^b)</td>
</tr>
<tr>
<td>(LPV/r)</td>
<td></td>
<td>• LPV 200 mg plus RTV 50 mg</td>
<td>• LPV 400 mg plus RTV 100 mg twice daily or</td>
<td>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LPV 100 mg plus RTV 25 mg</td>
<td>• LPV 800 mg plus RTV 100 mg once daily</td>
<td>Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral Solution:</td>
<td>Tablets:</td>
<td>Once-daily LPV/r dosing is not recommended during pregnancy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LPV 400 mg plus RTV 100 mg/5mL</td>
<td>• Take without regard to food. Oral Solution:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Take with food. With EFV or NVP (PI-Naive or PI-Experienced Patients):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LPV 500 mg plus RTV 125 mg tablets twice daily without regard to meals (use a combination of two LPV 200 mg plus RTV 50 mg tablets plus one LPV 100 mg plus RTV 25 mg tablet) without regard to food or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LPV 533 mg plus RTV 133 mg oral solution (6.5 mL) twice daily with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• PK studies suggest increased dose (LPV 600 mg plus RTV 150 mg twice daily without regard to meals) should be used in second and third trimesters, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. No data to address if drug levels are adequate with once-daily dosing in pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Once daily dosing is not recommended during pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Some experts recommend increased dose of LPV 600 mg plus RTV 150 mg twice daily without regard to meals in second and third trimester.</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancya (page 12 of 15)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelfinavir (NFV) Viracept</td>
<td>Tablets:</td>
<td>Standard Adult Dose:</td>
<td>Minimal to low placental transfer to fetus. b</td>
</tr>
<tr>
<td></td>
<td>• 250 mg</td>
<td>• 1250 mg twice daily or 750 mg three times daily with food</td>
<td>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and 2-fold increase in risk of birth defects in more common classes, cardiovascular and genitourinary).</td>
</tr>
<tr>
<td></td>
<td>• 625 mg (Tablets can be dissolved in small amount of water.)</td>
<td>PK in Pregnancy:</td>
<td>Contains aspartame, should not be used in individuals with phenylketonuria.</td>
</tr>
<tr>
<td></td>
<td>Powder for Oral Suspension:</td>
<td>• Lower NFV exposure in third trimester than postpartum in women receiving NFV 1250 mg twice daily; however, generally adequate drug levels are achieved during pregnancy, although levels are variable in late pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 50 mg/G</td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Three-times-daily dosing with 750 mg with food not recommended during pregnancy. No change in standard dose (1250 mg twice daily with food) indicated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lower levels during pregnancy compared with postpartum but no dosage adjustment necessary when used as booster.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Use only as low-dose booster with other PIs.</td>
<td></td>
</tr>
<tr>
<td>Ritonavir (RTV) Norvir</td>
<td>Capsules:</td>
<td>Standard Adult Dose as PK Booster for Other PIs:</td>
<td>Low placental transfer to fetus. b</td>
</tr>
<tr>
<td></td>
<td>• 100 mg</td>
<td>• 100–400 mg per day in 1–2 divided doses (Refer to other PIs for specific dosing recommendations.)</td>
<td>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</td>
</tr>
<tr>
<td>Note: Should be only be used as a low-dose booster with other PIs</td>
<td>Tablets:</td>
<td>Tablet:</td>
<td>Oral solution contains 43% alcohol and is not recommended for use in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• 100 mg</td>
<td>• Take with food.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral Solution:</td>
<td>Capsule or Oral Solution:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 80 mg/mL</td>
<td>• To improve tolerability, recommended to take with food if possible.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lower levels during pregnancy compared with postpartum but no dosage adjustment necessary when used as booster.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Use only as low-dose booster with other PIs.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saquinavir</strong> (SQV)</td>
<td>Invirase</td>
<td>Tablets:</td>
<td>Standard Adult Dose:</td>
<td>Low placental transfer to fetus.(^b)</td>
</tr>
<tr>
<td>Note: Must be combined with low-dose RTV boosting</td>
<td></td>
<td>• 500 mg</td>
<td>• SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal</td>
<td>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsules:</td>
<td>PK in Pregnancy:</td>
<td>Must be given as low-dose RTV-boosted regimen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 200 mg</td>
<td>• Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No change in dose indicated.</td>
<td></td>
</tr>
<tr>
<td><strong>Tipranavir</strong> (TPV)</td>
<td>Aptivus</td>
<td>Capsules:</td>
<td>Standard Adult Dose:</td>
<td>Moderate placental transfer to fetus reported in one patient.(^b)</td>
</tr>
<tr>
<td>Note: must be combined with low-dose RTV boosting</td>
<td></td>
<td>• 250 mg</td>
<td>• TPV 500 mg plus RTV 200 mg twice daily</td>
<td>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral Solution:</td>
<td>With RTV Tablets:</td>
<td>Must be given as low-dose RTV-boosted regimen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 100 mg/mL</td>
<td>• Take with food.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With RTV Capsules or Solution:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Take without regard to food.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Limited PK data in human pregnancy.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Insufficient data to make dosing recommendation.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
<tr>
<td><strong>Entry Inhibitors</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Enfuvirtide</strong> (T20)</td>
<td>Fuzeon</td>
<td>Injectable:</td>
<td>Standard Adult Dose:</td>
<td>Minimal to low placental transfer to fetus.(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Supplied as lyophilized powder. Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.</td>
<td>• 90 mg (1 mL) twice daily without regard to meals</td>
<td>No data on human teratogenicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No PK data in human pregnancy.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Insufficient data to make dosing recommendation.</td>
<td>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc (MVC) Selzentry</td>
<td>Tablets:</td>
<td>Standard Adult Dose:</td>
<td>Minimal to low placental transfer to fetus.</td>
</tr>
<tr>
<td></td>
<td>• 150 mg</td>
<td>• 300 mg twice daily without regard to meals</td>
<td>No data on human teratogenicity.</td>
</tr>
<tr>
<td></td>
<td>• 300 mg</td>
<td>Dosing Affected by Concomitant Use of Drugs Metabolized by CYP450 3A4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Co-Administration with CYP 3A4 Inhibitors:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 150 mg twice daily without regard to meals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Co-Administration with CYP 3A4 Inducers:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 600 mg twice daily without regard to meals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limited PK data in human pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insufficient data to make dosing recommendation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PK in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No PK data in human pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing in Pregnancy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insufficient data to make dosing recommendation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown placental transfer to fetus.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits.</td>
<td></td>
</tr>
</tbody>
</table>

Integrase Inhibitors

Dolutegravir (DTG) Tivicay

Tablets: • 50 mg

Standard Adult Dose
ARV-Naive or ARV-Experienced but Integrase Inhibitor-Naive Patients: • DTG 50 mg once daily
ARV-Naive or ARV-Experienced but Integrase Inhibitor-Naive if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced: • DTG 50 mg twice daily
PK in Pregnancy: • No PK data in human pregnancy.
Dosing in Pregnancy: • Insufficient data to make dosing recommendation.

Elvitegravir plus cobicistat (EVG/COBI) Stribild

Tablet (Co-Formulated): • EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg

Standard Adult Dose: • One tablet once daily with food.
PK in Pregnancy: • No PK studies in human pregnancy.
Dosing in Pregnancy: • Insufficient data to make dosing recommendation.

No data on placental transfer of EVG/COBI are available.
Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.
Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Recommendations for Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir (RAL) Isentress</td>
<td></td>
<td>Film-Coated Tablets:</td>
<td>Standard Adult Dose:</td>
<td>High placental transfer to fetus. b Insufficient data to assess for teratogenicity in humans. Increased skeletal variants in rats, no increase in defects in rabbits. Case report of markedly elevated liver transaminases with use in late pregnancy. Severe, potentially life-threatening and fatal skin and hypersensitivity reactions have been reported in non-pregnant adults. Chewable tablets contain phenylalanine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 400 mg Chewable Tablets:</td>
<td>• 400 mg twice daily without regard to food With Rifampin:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 25 mg • 100 mg PK in Pregnancy:</td>
<td>• 800 mg twice daily without regard to food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Limited data suggest PK not significantly altered in pregnancy. Dosing in Pregnancy:</td>
<td>• No change in dose indicated.</td>
</tr>
</tbody>
</table>

a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult Guidelines, Appendix B, Table 7).

b Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6  
Moderate: 0.3–0.6  
Low: 0.1–0.3  
Minimal: <0.1

c See Teratogenicity for discussion of EFV and risks in pregnancy.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; APR = Antiretroviral Pregnancy Registry; ARV = antiretroviral; ATV = atazanavir; AUC = area under the curve; CD4 = CD4 T lymphocyte; CI = confidence interval; CNS = central nervous system; COBI = cobicistat; d4T = stavudine; ddi = didanosine; DTG = dolutegravir; DRV = darunavir; EC = enteric coated; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; IDV = indinavir; IV = intravenous; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = ritipiravir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = ritonavir-boosted tipranavir; T20 = enfuvirtide; ZDV = zidovudine
HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel's Recommendations

- All HIV-infected pregnant women should receive a potent combination antiretroviral (ARV) regimen to reduce the risk of perinatal transmission of HIV (AI). The choice of regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy, and the risk of teratogenicity (see Table 6 and Table 7).

- The decision as to whether to start the regimen in the first trimester or delay until 12 weeks' gestation will depend on CD4 T lymphocyte count, HIV RNA levels, and maternal conditions (e.g., nausea and vomiting) (AIII). Earlier initiation of a combination ARV regimen may be more effective in reducing transmission, but benefits must be weighed against potential fetal effects of first-trimester drug exposure.

- ARV drug-resistance studies should be performed before starting the ARV regimen if HIV RNA is above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) unless drug-resistance studies have already been performed (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) (AI). If HIV is diagnosed later in pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing (BIII).

- If there is no evidence of resistance, combination ARV regimens that are preferred for the treatment of antiretroviral-naive HIV-infected pregnant women include: a dual nucleoside reverse transcriptase inhibitor combination (abacavir/lamivudine, tenofovir/emtricitabine or lamivudine, or zidovudine/lamivudine) and either a ritonavir-boosted protease inhibitor (ritonavir-boosted atazanavir or ritonavir-boosted lopinavir) or a non-nucleoside reverse transcriptase inhibitor (efavirenz initiated after 8 weeks of pregnancy) (see Table 6) (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation. They should be counseled about and offered combination antiretroviral therapy (cART) containing at least 3 drugs for their own health and for prevention of perinatal transmission of HIV, consistent with the principles of treatment for non-pregnant adults. Use of a cART regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal transmission of HIV, lessens the need for consideration of elective cesarean delivery as an intervention to reduce risk of transmission, and reduces risk of ARV drug resistance in the mother. In an analysis of perinatal transmission in 5,151 HIV-infected women between 2000 and 2006 in the United Kingdom and Ireland, the overall perinatal transmission rate was 1.2%. A transmission rate of 0.8% was seen in women on ARV drugs for at least the last 14 days of pregnancy, regardless of the type of ARV regimen or mode of delivery. After adjustment for viral load, mode of delivery, and sex of the infant, longer duration of use of ARV drugs was associated with reduced transmission rates. Similar data from Canada in 1,707 HIV-infected pregnant women followed between 1997 and 2010 showed perinatal transmission was 1% in mothers receiving cART, and 0.4% if more than 4 weeks of cART was received.

ARV drug-resistance testing should be performed before starting an ARV regimen if plasma HIV RNA levels are above the threshold for resistance testing (that is, >500 to 1,000 copies/mL) unless drug-resistance testing has already been performed. For details regarding genotypic and phenotypic resistance testing, see Adult and Adolescent Antiretroviral Guidelines. Given the association of earlier viral suppression with lower risk of transmission as discussed above, if HIV is diagnosed in the second half of pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing, with modification of the regimen, if required, when test results return. Because clinically significant resistance to protease inhibitors (PI) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in ARV-naive individuals, a PI-based cART regimen generally should be considered in this situation.

Table 6 outlines the ARV regimens that are preferred for treatment of HIV-infected pregnant women who have never received ARV drugs, based on available data indicating acceptable toxicity profiles, ease of use, pharmacokinetic data in pregnancy, and lack of evidence of teratogenic effects or established adverse
Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

outcomes for mother, fetus or newborn in addition to optimal ARV efficacy and durability. Preferred dual nucleoside reverse transcriptase inhibitor (NRTI) combinations include abacavir/lamivudine, tenofovir/emtricitabine or lamivudine, or zidovudine/lamivudine in combination with either a ritonavir-boosted PI (ritonavir-boosted atazanavir or ritonavir-boosted lopinavir) or an NNRTI (efavirenz initiated after 8 weeks of pregnancy). Alternative regimens include those demonstrated to be effective in adults but with more limited data on use in pregnancy, lack of or incomplete data on teratogenicity, and dosing, formulation, toxicity or interaction issues. Selection of these regimens should be based on individual patient characteristics and needs (see Table 7).

Fetuses are most susceptible to the potential teratogenic effects of drugs during the first trimester and the risks of ARV drug exposure during that period are not fully known. Therefore, women in the first trimester who do not require immediate initiation of therapy for symptomatic HIV infection can consider delaying initiation of ARV drugs until after 12 weeks’ gestation. This decision should be carefully considered by health care providers and their patients. The discussion should include an assessment of a woman’s health status and the benefits and risks to her health of delaying initiation of ARV drugs for several weeks.

Although most perinatal transmission events occur late in pregnancy or during delivery, recent analyses suggest that early control of viral replication may be important in preventing transmission. In a French study, lack of early and sustained control of maternal viral load appeared strongly associated with residual perinatal transmission of HIV. That study evaluated risk factors for perinatal transmission in women with HIV RNA <500 copies/mL at the time of delivery; overall HIV transmission was 0.5%. Women who transmitted were less likely to have received ARV drugs at the time of conception than were nontransmitters and were less likely to have HIV RNA <500 copies/mL at 14, 28, and 32 weeks’ gestation. By multivariate analysis, plasma viral load at 30 weeks’ gestation was significantly associated with transmission. Among women starting ARV drugs during pregnancy, the gestational age at initiation of therapy did not differ between groups (30 weeks), but viral load tended to decrease earlier in the nontransmitters, although this was not statistically significant. The number of patients initiating therapy during pregnancy was too small to assess whether initiation of ARV drugs in the first trimester was associated with lower rates of transmission. These data suggest that early and sustained control of HIV viral replication is associated with decreasing residual risk of transmission and favor initiating cART sufficiently early in ARV-naive women to suppress viral replication by the third trimester. Other studies have demonstrated that baseline viral load is significantly associated with the likelihood of viral suppression by delivery, and thus, prompt initiation of cART would be particularly important in HIV-infected pregnant women who have high baseline viral loads. However, the potential benefits of earlier initiation of cART must be balanced against the unknown long-term outcome of first-trimester ARV exposure to the fetus.

A cART regimen is recommended for all HIV-infected pregnant women, regardless of viral load. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, there is no threshold below which lack of transmission can be ensured. The mechanism by which ARV drugs reduce perinatal transmission of HIV is multifactorial. Although lowering maternal antenatal viral load is an important component of prevention in women with higher viral load, ARV prophylaxis is effective even in women with low viral load. Additional mechanisms of protection include pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis of the infant. With PrEP, passage of the ARV drug across the placenta results in presence of drug levels sufficient for inhibition of viral replication in the fetus, particularly during the birth process when there is intensive viral exposure. Therefore, whenever possible, cART regimens initiated during pregnancy should include zidovudine or another NRTI with high transplacental passage, such as lamivudine, emtricitabine, tenofovir, or abacavir (see Table 7). With post-exposure prophylaxis, ARV drugs are administered to the infant after birth.

Some women may wish to restrict fetal exposure to ARV drugs while reducing the risk of HIV transmission to their infants. Use of zidovudine alone during pregnancy for prophylaxis of perinatal transmission is not optimal, but it could be an option for women with low viral loads (i.e., <1,000 copies/mL) on no ARV drugs. In the U.K. study discussed above, transmission rates were 0.7% for women receiving a triple-ARV drug regimen combined with planned cesarean delivery or with planned vaginal delivery and 0.5% in 464 women with HIV RNA levels
<10,000 copies/mL who received single-drug prophylaxis with zidovudine combined with planned cesarean delivery, not significantly different between groups. Zidovudine single-drug prophylaxis is recommended in the British HIV Association guidelines for women with CD4 T lymphocyte counts >350 cells/mm³ and HIV RNA levels <10,000 copies/mL and wild-type virus who do not require treatment for their own health.¹⁹ Time-limited administration of zidovudine during the second and third trimesters is less likely to induce development of resistance in women with low viral loads than in those with higher viral loads. This lower rate of resistance is likely because of the low level of viral replication and the short duration of exposure.²⁰,²¹ Women’s choices after counseling to use or not use ARV drugs during pregnancy should be respected.

Raltegravir has been suggested for use in late pregnancy in women who have high viral loads because of its ability to rapidly suppress viral load (approximately 2-log copies/mL decrease by Week 2 of therapy).²²-²⁵ A recent publication reported the effect of adding raltegravir to a standard ARV regimen in 4 women diagnosed with HIV infection in the third trimester.²⁶ The median viral load at presentation was 271,000 copies/mL and the mean viral load decline per week was 1.12 log (usually not seen until after 1–2 months of standard cART). Although no raltegravir-related side effects were noted in these reports, marked elevations in hepatic transaminases were reported in a single HIV-infected pregnant woman when raltegravir was added to an ARV regimen.²⁷ Because the efficacy and safety of this approach has only been described in anecdotal reports, it cannot be routinely recommended at this time for women who are ARV-naive.

The cART regimen initiated during pregnancy can be modified after delivery to include simplified regimens that were not used in pregnancy because pregnancy safety data were insufficient. Decisions regarding continuation of an ARV regimen or which specific ARV agents to use should be made by women in consultation with their HIV care providers, taking into account current recommendations and life circumstances (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy).

References


Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

C-50

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In general, women who have been receiving combination antiretroviral therapy (cART) for their HIV infection should continue that treatment during pregnancy, assuming it is tolerated and effective in suppressing viral replication. Discontinuation of therapy could lead to an increase in viral load with possible decline in immune status and disease progression as well as adverse consequences for the fetus, including increased risk of HIV transmission. Continuation of therapy, therefore, is recommended when pregnancy is identified in HIV-infected women receiving cART.

HIV-infected women receiving cART who present for care during the first trimester should be counseled regarding the benefits and potential risks of administration of antiretroviral (ARV) drugs during this period and that continuation of cART is recommended. There are concerns regarding efavirenz use in the first trimester and potential for neural tube defects, based on preclinical primate data and retrospective case reports (for more details see Teratogenicity). A recent meta-analysis including data on 1,437 women with first-trimester efavirenz exposure from 19 prospective studies did not find an increased relative risk (RR) of overall birth defects in infants born to women receiving efavirenz-based versus non-efavirenz-based regimens (RR 0.85, 95% confidence interval [CI], 0.6–1.2) and identified 1 neural tube defect, resulting in an incidence of 0.07% (95% CI, 0.002–0.39%).

Although a 2- to 3-fold increased incidence of a rare outcome (e.g., neural tube defects [0.02%–0.2% incidence in the United States]) cannot be ruled out given the limited data on first-trimester efavirenz exposure, the available data suggest that first-trimester exposure is not associated with a large (i.e., 10-fold or more) increase in risk of neural tube defects. Analyses from the Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy found that treatment changes during pregnancy significantly increased the risk of incomplete viral suppression at the end of pregnancy. The risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after last menstrual period), pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs in pregnancy may be associated with loss of viral control and, thus, increased risk of transmission to the infant. Therefore, the Panel recommends that efavirenz be continued in pregnant women receiving efavirenz-based cART who present for antenatal care in the first trimester, provided that the regimen is resulting in virologic suppression. In such situations, additional fetal monitoring (such as with second-trimester ultrasound) should be considered to evaluate fetal anatomy.

Resistance testing should be performed in women who are on therapy but in whom viral replication is not fully suppressed (i.e., patient has detectable viremia). The results can be used to select a new regimen with a greater likelihood of suppressing viral replication to undetectable levels. Drug resistance testing is generally done in individuals with HIV RNA levels >1,000 copies/mL; however, in individuals with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered.

**Panel’s Recommendations**

- In general, HIV-infected pregnant women receiving combination antiretroviral therapy (cART) who present for care during the first trimester should continue treatment during pregnancy, assuming the regimen is tolerated and effective in suppressing viral replication (HIV-1 viral load less than lower limits of detection of the assay) (AII).
- The Panel recommends that efavirenz be continued in pregnant women receiving efavirenz-based cART who present for antenatal care in the first trimester provided the regimen is achieving virologic suppression (see text below) (CIII).
- HIV antiretroviral drug-resistance testing is recommended for pregnant women who have detectable viremia (i.e., >500 to 1,000 copies/mL) on therapy (see Failure of Viral Suppression) (AI).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
Pregnant women for whom nevirapine-containing regimens are achieving virologic suppression and who are tolerating therapy may be continued on that regimen, regardless of current CD4 T lymphocyte (CD4) cell count. Although hepatic toxicity is a concern in women starting a nevirapine-containing regimen who have CD4 cell counts >250 cells/mm³, an increased risk of hepatic toxicity has not been seen in women receiving nevirapine-based therapy in whom the therapy has produced immune reconstitution.

References


During a previous pregnancy, HIV-infected women may have received antiretroviral (ARV) drugs solely for prevention of perinatal transmission. At any time in the past, they also may have discontinued ARV drugs given to them for treatment of their own disease. A small number of clinical trials or observational studies have generated information about how effective combination antiretroviral therapy (cART) is in individuals who previously received ARV prophylaxis. The data are limited to outcomes with therapy containing nevirapine initiated after the use of peripartum single-dose nevirapine.1-5 Diminished viral and clinical response to nevirapine-based cART has been observed if cART was initiated within 12 to 24 months after single-dose nevirapine exposure. Adding other ARV drugs to single-dose nevirapine (such as use of an ARV tail) decreases rates of nevirapine resistance6,7 (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

There is concern that time-limited use of ARV drugs during pregnancy for prophylaxis of perinatal transmission may lead to genotypic resistance and, thus, reduced efficacy of these ARV drugs when used either for indicated HIV therapy in a woman or during a subsequent pregnancy for prevention of perinatal transmission. Rates of resistance appear to be low, based on standard genotyping, after prophylaxis for prevention of perinatal transmission with cART consisting of zidovudine, lamivudine, and nevirapine.8,9 However, minority populations of virus with resistance to nevirapine or lamivudine have been detected using sensitive allele-specific polymerase chain reaction (PCR) techniques, particularly in women whose virus was inadequately suppressed during prophylaxis.9-11 Rates of minor, drug-resistant variants may be lower in women given longer or more complex ARV tails after stopping pregnancy-limited nevirapine-based cART.12-16 Only limited data are available on the impact of these resistance-conferring minority variants on prediction of virologic or clinical failure of subsequent cART, and the PCR-based assays are not widely available. However, in the OCTANE/A5208 study, while the presence of low-frequency minority viral variants with nevirapine resistance was associated with higher rates of viral failure in women starting nevirapine-based cART after receiving single-dose nevirapine for prevention of perinatal transmission, low-frequency minority variants were not associated with higher rates of nevirapine-cART failure in women who had not had prior single-dose nevirapine exposure.17 Both standard and sensitive genotyping techniques appear to show a low rate of
resistance to protease inhibitors (PIs) after pregnancy-limited use of PI-based combination ARV regimens for prophylaxis, but these results reflect assessments in only small numbers of women.\textsuperscript{11,18}

To date, treatment failure has not been demonstrated with reinitiation of combination ARV regimens following prophylactic use in pregnancy for prevention of transmission. In ACTG 5227, 52 women who had previously received combination ARV regimens for prevention of perinatal transmission, had no evidence of HIV drug resistance, and had an indication for restarting cART were prescribed a fixed-dose combination of efavirenz plus tenofovir/emtricitabine once daily. After 6 months of therapy, 81% achieved plasma viral loads below the limit of detection; the virologic suppression rate was similar regardless of the drug class of the prior combination ARV regimen and whether women had received such ARV regimens in 1 or more than 1 previous pregnancy.\textsuperscript{19} Data from the French Perinatal Cohort assessed virologic suppression with a PI-based combination ARV regimen administered for prevention of perinatal transmission to women who had received ARV prophylaxis during a previous pregnancy. No differences in rates of undetectable viral load at delivery were noted among ARV-naive women when compared with those with previous prophylaxis or according to type of previous prophylaxis regimens received.\textsuperscript{20} In addition, the United Kingdom- and Ireland-based National Study of HIV in Pregnancy and Childhood found no increased risk of perinatal transmission in sequential pregnancies compared with 1 pregnancy at a time when most women received interventions for prevention of perinatal HIV transmission.\textsuperscript{21} However, in a subsequent comparison between 5,372 ARV-naive pregnant women and 605 women who had previously received ARV but were on no ARV prior to the current pregnancy, there was a slight increase in the risk of detectable viral load among the ARV-experienced women at delivery after receiving antenatal cART (aOR 1.27; 95% CI, 1.01,1.60). This risk was confined to those ARV-experienced women who received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based as opposed to PI-based therapy.\textsuperscript{22} Sufficiently large, prospective, observational studies and clinical trials are lacking by which we can definitively assess the effect of pregnancy-limited ARV prophylaxis on virologic outcomes of subsequent ARV therapy.

Given the lack of substantive data, it is reasonable to use results of initial resistance testing, if available, to make preliminary decisions about ARV regimens in women whose only previous exposure to ARV drugs was during pregnancy for prophylaxis of perinatal transmission. However, interpretation of resistance testing after discontinuation of ARV drugs can be complex because drug-resistance testing is most accurate if performed while an individual is taking the ARV regimen or within 4 weeks of treatment discontinuation. In the absence of selective drug pressure, resistant virus may revert to wild-type virus, and although detection of drug-resistance mutations is informative for choosing a regimen, a negative finding does not rule out the presence of archived drug-resistant virus that could re-emerge once drugs are reinitiated. Therefore, when selecting a new regimen for use during the current pregnancy, all information from the previous pregnancy—including regimens received, viral response, laboratory testing (including HLA-B*5701 results), and any tolerance or adherence issues—and the results of resistance testing should be taken into consideration. In women who present late in pregnancy, ARVs should be started pending results of resistance testing. Careful monitoring of virologic response to the chosen ARV regimen is important.

If the chosen regimen produces an insufficient viral response, decisions about switching regimens should be guided by repeat resistance testing and assessment of medication adherence. These measures should be undertaken in consultation with an HIV treatment specialist.

Some women who receive cART for their own health choose to discontinue the drugs for a variety of reasons, and the length of time between treatment termination and pregnancy may vary. In these cases, careful clinical and laboratory assessments are necessary before therapy is reinitiated during pregnancy. The evaluations should include a review of a woman’s prior history of virologic response and medication toxicity and her adherence to therapy. The appropriate choice of ARV regimen to be initiated during pregnancy will vary according to a woman’s history of cART; the indication for stopping therapy; the effect of prior therapy on clinical, virologic, and immunologic status; and the results of past and current testing for resistance and for HLA-B*5701. It may be possible, for example, to restart the same regimen in women with a history of...
prior cART associated with successful suppression of viral load who then stopped all drugs simultaneously (or staggered discontinuation, if therapy was NNRTI-based) and who have no evidence of resistance. On the other hand, the selection of an appropriate ARV regimen may be challenging even for health care providers experienced in HIV care in women with advanced HIV disease, a history of extensive prior cART, or previous significant toxicity or nonadherence to ARV drugs. In such cases, restarting the prior regimen for a week or two before performing a resistance assay may yield more accurate results. In addition to obtaining genotypic resistance testing, it is strongly recommended that specialists in the treatment of HIV infection be consulted early during the pregnancy about the choice of a suitable combination ARV regimen.

References


### Monitoring of the Woman and Fetus During Pregnancy

**Panel's Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Rating of Recommendations</th>
<th>Rating of Evidence</th>
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<tbody>
<tr>
<td>Plasma HIV RNA levels should be monitored at the initial visit (AI); 2 to 4 weeks after initiating (or changing) antiretroviral (ARV) drug regimens (BI); monthly until RNA levels are undetectable (BIII); and then at least every 3 months during pregnancy (BIII). HIV RNA levels also should be assessed at approximately 34 to 36 weeks’ gestation to inform decisions about mode of delivery (see Transmission and Mode of Delivery) (AIII).</td>
<td>A = Strong; B = Moderate; C = Optional</td>
<td>I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion</td>
</tr>
<tr>
<td>CD4 T lymphocyte (CD4) cell count should be monitored at the initial antenatal visit (AI) and at least every 3 months during pregnancy (BIII). Monitoring of CD4 cell count can be performed every 6 months in patients on combination ARV therapy (cART) with consistently suppressed viral load who have immune reconstitution (CD4 count increase well above threshold for opportunistic infection risk) related to use of the regimen (CIII).</td>
<td>A = Strong; B = Moderate; C = Optional</td>
<td>I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion</td>
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<tr>
<td>Genotypic ARV drug-resistance testing should be performed at baseline in all HIV-infected pregnant women with HIV RNA levels above the threshold for resistance testing (that is, &gt;500 to 1,000 copies/mL), whether they are ARV-naive or currently on therapy (AIII). However, it is not necessary to repeat a genotype in pregnancy if the woman already had a genotype prior to pregnancy and was ARV-naive. Repeat testing is indicated following initiation of an ARV regimen in women who have suboptimal viral suppression or who have persistent viral rebound to detectable levels after prior viral suppression on an ARV regimen (AII).</td>
<td>A = Strong; B = Moderate; C = Optional</td>
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<tr>
<td>Monitoring for complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs a woman is receiving (AIII).</td>
<td>A = Strong; B = Moderate; C = Optional</td>
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<tr>
<td>HIV-infected women taking cART during pregnancy should undergo standard glucose screening at 24 to 28 weeks’ gestation (AIII). Some experts would perform earlier glucose screening in women receiving ongoing protease inhibitor-based regimens initiated before pregnancy, similar to recommendations for women with high risk factors for glucose intolerance (BIII).</td>
<td>A = Strong; B = Moderate; C = Optional</td>
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<tr>
<td>Early ultrasound is recommended to confirm gestational age and, if scheduled cesarean delivery is necessary, to guide timing of the procedure (see Transmission and Mode of Delivery) (AII).</td>
<td>A = Strong; B = Moderate; C = Optional</td>
<td>I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion</td>
</tr>
<tr>
<td>In women on effective cART, no perinatal transmissions have been reported after amniocentesis, but a small risk of transmission cannot be ruled out. If amniocentesis is indicated in HIV-infected women, it should be done only after initiation of an effective cART regimen and, if possible, when HIV RNA levels are undetectable (BIII). In women with detectable HIV RNA levels in whom amniocentesis is deemed necessary, consultation with an expert should be considered.</td>
<td>A = Strong; B = Moderate; C = Optional</td>
<td>I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion</td>
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Viral load should be monitored in HIV-infected pregnant women at the initial visit, 2 to 4 weeks after initiating or changing antiretroviral (ARV) regimens, monthly until undetectable, and at least every 3 months thereafter. If adherence is a concern, more frequent monitoring is recommended because of the potential increased risk of perinatal HIV infection associated with detectable HIV viremia during pregnancy. More frequent viral load monitoring is recommended in pregnant versus non-pregnant individuals because of the urgency to lower viral load as rapidly as possible to reduce the risk of perinatal transmission. Therefore, there is a need to identify pregnant women in whom the decline in viral load is slower than expected. Adult ARV guidelines note that for most individuals who are adherent to their ARV regimen and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 12 to 24 weeks, although it may take longer in some patients. Viral load also should be assessed at approximately 34 to 36 weeks’ gestation to inform decisions about mode of delivery (see Transmission and Mode of Delivery).

In HIV-infected pregnant women, CD4 T lymphocyte (CD4) cell count should be monitored at the initial visit and at least every 3 months during pregnancy. CD4 cell counts can be performed every 6 months in patients who are clinically stable with consistently suppressed viral load who have ARV regimen-related immune reconstitution (CD4 count increase well above threshold for opportunistic infection risk).

Whenever feasible, ARV drug-resistance testing should be performed in HIV-infected pregnant women before initiation of ARV drugs, if HIV RNA levels are above the threshold for resistance testing, unless a
delay in getting results back would lead to a delay in starting ARV for prevention of perinatal transmission. Testing also should be performed on women taking an ARV regimen who have suboptimal viral suppression or who have persistant viral rebound to detectable levels after prior viral suppression on an ARV regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Drug-resistance testing in the setting of virologic failure should be performed while patients are receiving ARV drugs or within 4 weeks after discontinuation of drugs. Genotypic testing is preferable to phenotypic testing because it costs less, has a faster turnaround time, and is more sensitive for detection of mixtures of wild-type and resistant virus.

Monitoring for potential complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs a woman is receiving. For example, routine hematologic monitoring is recommended for women receiving zidovudine-containing regimens and routine renal monitoring should be recommended for women on tenofovir. Liver function should be monitored in all women receiving ARV drugs. Hepatic dysfunction has been observed in pregnant women on protease inhibitors (PI), and hepatic steatosis and lactic acidosis in pregnancy have been related to nucleoside reverse transcriptase inhibitor use. Women with CD4 cell counts >250 cells/mm³ are thought to be at particular risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity within the first 18 weeks after initiation of therapy. However, recent data either do not show the same association between nevirapine toxicity and CD4 cell counts among pregnant women, or found only weak evidence of an association. Additional data from a 2010 study suggest that abnormal liver transaminase levels at baseline may be more predictive of risk than CD4 cell count. Transaminase levels should be monitored more frequently and carefully in pregnant women initiating therapy with nevirapine, and they should also be watched for clinical symptoms of potential hepatotoxicity (see Nevirapine and Hepatic/Rash Toxicity). The drug can be used cautiously with careful monitoring in women with mildly abnormal liver function tests at the time of ARV drug initiation.

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported in HIV-infected patients taking PIs. In addition, pregnancy is itself a risk factor for hyperglycemia. To date, however, the majority of studies have not shown an increased risk of glucose intolerance with PI-based regimens during pregnancy. A prospective study including detailed evaluations for glucose intolerance and insulin resistance among HIV-infected pregnant women did not find differences between women on PI-containing and non-PI-containing regimens. In both groups, however, the rate of impaired glucose tolerance was high (38%); this is likely related to high body mass index and race/ethnicity among trial subjects. HIV-infected women receiving ARV regimens during pregnancy should receive standard glucose screening at 24 to 28 weeks’ gestation. Some experts would perform earlier glucose screening in women with ongoing PI-based ARV regimens initiated before pregnancy (particularly those of minority race/ethnicity), similar to recommendations for women with high risk factors for glucose intolerance, such as maternal obesity, advanced maternal age, and family history of type II diabetes mellitus.

First-trimester ultrasound is recommended to confirm gestational age and, if scheduled cesarean delivery is necessary, to guide potential timing because such deliveries for prevention of perinatal transmission of HIV should be performed at 38 weeks’ gestation (see Transmission and Mode of Delivery). In patients who are not seen until later in gestation, second-trimester ultrasound can be used for both anatomical scanning and determination of gestational age.

Although data are still somewhat limited, the risk of transmission does not appear to be increased with amniocentesis or other invasive diagnostic procedures in women receiving effective combination ARV therapy (cART) resulting in viral suppression. This is in contrast to the era before effective cART, during which invasive procedures such as amniocentesis and chorionic villus sampling (CVS) were associated with a two- to four-fold increased risk of perinatal transmission of HIV. Although no transmissions have occurred among 159 cases reported to date of amniocentesis or other invasive diagnostic procedures among women on effective cART, a small increase in risk of transmission cannot be ruled out. HIV-infected women who have indications for invasive testing in pregnancy (e.g., abnormal ultrasound or aneuploidy screening) should be counseled about the potential risk of transmission of HIV along with other risks of the
procedure and allowed to make an informed decision about testing. Some experts consider CVS and cordocentesis too risky to offer to HIV-infected women and they recommend limiting invasive procedures to amniocentesis, but existing data on transmission risk associated with these procedures are limited. At a minimum, HIV-infected pregnant women should receive effective cART before undergoing any invasive prenatal testing and, ideally, have an undetectable HIV RNA level at the time of the procedure. Consideration can also be given to non-invasive testing using cell-free, fetal DNA to reduce the need for amniocentesis. In women with detectable HIV RNA levels for whom amniocentesis is deemed necessary, consultation with an expert should be considered. These procedures should be done under continuous ultrasound guidance and, if possible, the placenta should be avoided.

References


<table>
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<tbody>
<tr>
<td>• HIV drug-resistance studies should be performed before starting antiretroviral (ARV) regimens in all ARV-naive pregnant women whose HIV RNA levels are above the threshold for resistance testing (i.e., &gt;500 to 1,000 copies/mL) unless they have already been tested for ARV resistance (AIII).</td>
</tr>
<tr>
<td>• HIV drug-resistance studies should be performed before modifying ARV regimens for those entering pregnancy with detectable HIV RNA levels that are above the threshold for resistance testing (i.e., &gt;500 to 1,000 copies/mL) while receiving ARV drugs or who have suboptimal viral suppression after starting ARV drugs during pregnancy (AII).</td>
</tr>
<tr>
<td>• In women who present late in pregnancy, an empiric ARV regimen should be initiated promptly without waiting for the results of resistance testing, with adjustment as needed after test results are available, for optimal prevention of perinatal transmission and maternal health (BII).</td>
</tr>
<tr>
<td>• Women who have documented zidovudine resistance and are on regimens that do not include zidovudine for their own health should still receive intravenous zidovudine during labor along with their established ARV regimens if they have HIV RNA levels &gt;1,000 copies/mL near delivery (see Intrapartum Antiretroviral Therapy/Prophylaxis), unless a history of hypersensitivity is documented (AII).</td>
</tr>
<tr>
<td>• The optimal prophylactic regimen for newborns of women with ARV resistance is unknown. Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery (see Infant Antiretroviral Prophylaxis) (AII).</td>
</tr>
<tr>
<td>• HIV-infected pregnant women should be given combination ARV therapy (cART) to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission (AII).</td>
</tr>
<tr>
<td>• All pregnant and postpartum women should be counseled about the importance of adherence to prescribed ARV medications to reduce the potential for development of resistance (AII).</td>
</tr>
<tr>
<td>• To minimize development of resistance, pregnant women who receive a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination ARV regimen that is discontinued after delivery should receive either dual nucleoside analogue reverse transcriptase inhibitor agents alone (AI) or with a protease inhibitor (BII) for 7 to 30 days (AII) after stopping the NNRTI drug. The optimal interval between stopping an NNRTI and the other ARV drugs is unknown (see Stopping Antiretroviral Drugs During Pregnancy and Postpartum Follow-Up of HIV-Infected Women).</td>
</tr>
</tbody>
</table>

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

*Indications for Antiretroviral Drug-Resistance Testing in HIV-Infected Pregnant Women*

Because identification of baseline resistance mutations allows selection of more effective and durable ARV regimens, in addition to a comprehensive history of antiretroviral (ARV) drug use, genotypic resistance testing is recommended:

• Before initiating combination antiretroviral therapy (cART) in ARV-naive HIV-infected pregnant women with HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) who have not been previously tested for ARV resistance;

• Before initiating cART in HIV-infected pregnant women who have received ARVs for prevention of perinatal transmission in prior pregnancies and who are restarting ARVs for prevention of perinatal transmission if HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL);

• Before modifying ARV regimens in HIV-infected pregnant women entering pregnancy with detectable HIV RNA levels that are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) while receiving cART or who have suboptimal viral suppression after starting cART during pregnancy.
In most settings, the results of resistance testing guide selection of the initial ARV regimen. In some situations in pregnant women, however, the clinician may choose to initiate an empiric ARV drug regimen before resistance-testing results are available to optimize prevention of perinatal transmission of HIV. Most experts believe that for women in the third trimester, the benefits of immediate initiation of ARV drugs for prevention of perinatal transmission, pending results of resistance testing, outweigh the possible risks of short-term use of a regimen that could be suboptimal because of pre-existing resistance. Once resistance-test results are obtained, the ARV drug regimen can be modified as needed.

**Incidence and Significance of Antiretroviral Drug Resistance in Pregnancy**

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in HIV-infected individuals. Additionally, pre-existing resistance to a drug in a cART regimen may diminish the regimen’s efficacy in preventing perinatal transmission. The development of resistance to drugs used during pregnancy for prophylaxis of perinatal transmission may limit future maternal treatment options or decrease the effectiveness of prophylactic regimens in the current pregnancy or during future pregnancies. Infant treatment options also may be limited if maternal drug resistance is present or develops and resistant virus is transmitted to the fetus.

Several factors unique to pregnancy may increase the risk of development of resistance. If drugs with significant differences in half-life and a low genetic barrier to resistance (e.g., non-nucleoside reverse transcriptase inhibitors combined with two nucleoside analogue drugs) are included in the ARV regimen, simultaneous postpartum discontinuation of all regimen components may result in persistent sub-therapeutic drug levels and increase the risk of development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (see **Stopping Antiretroviral Drugs During Pregnancy**). Issues relating to discontinuation of NNRTI-based combination therapy are discussed in **Prevention of Antiretroviral Drug Resistance**. Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to sub-therapeutic drug levels, increasing the risk that resistance will develop.

**The Impact of Resistance on the Risk of Perinatal Transmission of HIV and Maternal Response to Subsequent Therapy**

**Perinatal Transmission**

Perinatal transmission of resistant virus has been reported, but appears to be unusual. There is little evidence that presence of resistance mutations increases risk of transmission when current recommendations for ARV management in pregnancy are followed. A sub-study of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV infection in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count; however, women in this cohort had characteristics that would indicate a need for cART under the current Department of Health and Human Services recommendations for maternal health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild-type and virus with low-level zidovudine resistance, only wild-type virus was detected in their infants; and other studies have suggested that drug-resistance mutations may diminish viral fitness, possibly leading to a decrease in transmissibility. In another study, prevalence of ARV drug resistance among HIV-infected newborns in New York State was examined. Eleven (12.1%) of 91 infants born between 1989 and 1999 and 8 (19%) of 42 infants born between 2001 and 2002 had mutations associated with decreased drug susceptibility. However, perinatal exposure to ARVs was not found to be a significant risk factor for the presence of resistance during either time period. Neither resistance to NNRTI drugs that develops as a result of exposure to single-dose nevirapine nor exposure to single-dose nevirapine in a prior pregnancy has been shown to affect perinatal transmission rates.
Maternal Response to Subsequent Treatment Regimens

Few studies have evaluated response to subsequent therapy in women who receive current combination ARV regimens for prophylaxis and discontinue the drugs postpartum. In theory, however, resistance should not occur if the regimen that was discontinued had fully suppressed viral replication. The French Perinatal Cohort evaluated the association between exposure to ARV drugs for perinatal transmission during a previous pregnancy and presence of a detectable viral load with exposure to ARV drugs during the current pregnancy in women followed between 2005 and 2009. In 1,166 women not receiving ARVs at the time of conception, 869 were ARV-naive and 247 had received ARV drugs for perinatal transmission during a previous pregnancy. Previous ARV prophylaxis was protease inhibitor (PI) based in 48%, non-PI based in 4%, nucleoside reverse transcriptase inhibitor (NRTI) dual ARVs in 19%, and zidovudine as a single ARV in 29%. A PI-based ARV regimen was initiated in 90% of the women during the current pregnancy; in multivariate analysis, previous ARV exposure in a prior pregnancy was not associated with detectable viral load in the current pregnancy. A separate study reported in abstract form—ACTG A5227—evaluated viral suppression in 52 women with prior combination ARV exposure for perinatal transmission who had stopped ARV at least 24 weeks before study entry and were now initiating cART (efavirenz, tenofovir, and emtricitabine) for treatment. None of the women had prior or recent resistance detected on standard bulk genotyping. Viral suppression was observed in 81% of women after 24 weeks of follow-up, with no difference in response by number of prior ARV exposures for perinatal transmission or the drug class of prior exposure.

Management of Antiretroviral Drug Resistance during Pregnancy

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, the drug still should be given intravenously (IV) during labor when indicated (i.e., HIV RNA > 1,000 copies/mL near delivery; see Intrapartum Antiretroviral Drug Therapy/Prophylaxis). Other ARVs should be continued orally during labor to the extent possible. The rationale for including zidovudine intrapartum when a woman is known to harbor virus with zidovudine resistance is based on several factors. Data thus far have suggested that only wild-type virus appears to be transmitted to infants by mothers who have mixed populations of wild-type virus and virus with low-level zidovudine resistance. The efficacy of the zidovudine prophylaxis appears to be based not only on a reduction in maternal HIV viral load but also on pre- and post-exposure prophylaxis in the infant. Zidovudine crosses the placenta readily and has a high maternal-to-cord blood ratio. In addition, zidovudine is metabolized to the active triphosphate within the placenta, which may provide additional protection against transmission. Metabolism to the active triphosphate, which is required for activity of all nucleoside analogue agents, has not been observed within the placenta with other nucleoside analogues that have been evaluated (didanosine and zalcitabine). Zidovudine penetrates the central nervous system (CNS) better than do other nucleoside analogues except stavudine, which has similar CNS penetration; this may help to eliminate a potential reservoir for transmitted HIV in the infant. Thus, intrapartum IV administration of zidovudine when indicated currently is recommended even in the presence of known resistance because of the drug’s unique characteristics and its proven record in reducing perinatal transmission.

The optimal prophylactic regimen for newborns of women with ARV drug-resistant virus is unknown. Therefore, ARV prophylaxis for infants born to women with known or suspected drug-resistant virus should be determined with a pediatric HIV specialist, preferably before delivery (see Infant Antiretroviral Prophylaxis).

Prevention of Antiretroviral Drug Resistance

The most effective way to prevent development of ARV drug resistance in pregnancy is to use and adhere to an effective cART regimen to achieve maximal viral suppression. More frequent monitoring of viral load in pregnant women than in non-pregnant individuals is recommended because of the potential increased risk of perinatal HIV infection associated with detectable HIV viremia during pregnancy (see Monitoring of the...
Several studies have demonstrated that women’s adherence to cART may worsen in the postpartum period. Clinicians caring for postpartum women receiving ART should specifically address adherence, including evaluating specific factors that facilitate or impede adherence.

Because of the prolonged half-life of NNRTI drugs, if an NNRTI-based ARV regimen is stopped postpartum, there is a risk of development of NNRTI-resistance mutations if all drugs in the regimen are stopped simultaneously. This has been demonstrated for nevirapine and efavirenz but may also be a problem with newer NNRTI drugs with long half-lives, such as etravirine and rilpivirine. Several studies have shown that development of NNRTI resistance is significantly decreased (but not eliminated) when zidovudine/lamivudine is given intrapartum and administered for 3 to 7 days postpartum in women who have received single-dose intrapartum nevirapine. A variety of other regimens (e.g., tenofovir/emtricitabine, zidovudine/didanosine, zidovudine/didanosine/lipinavir/ritonavir) given for 7 to 30 days postpartum following maternal single-dose nevirapine have also been shown to be very effective in reducing the development of NNRTI resistance. These data suggest that the NRTI components of an NNRTI-based regimen should be continued for 7 to 30 days after discontinuation of the NNRTI to minimize the risk of resistance. An alternative equally effective strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time. The optimal duration for continuation of either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is unknown. NNRTI drugs have long half-lives, and drug levels can persist for up to 1 to 3 weeks after stopping the drugs; efavirenz levels persist longer than nevirapine levels. Despite the use of various multiple drug regimens, ARV drug resistance may still develop in some women. More research is needed on the optimal duration of time and regimen to cover this period of prolonged NNRTI exposure to prevent the emergence of resistance after discontinuation of an NNRTI-based ARV regimen.

References


A three-pronged approach is indicated for management of women on antiretroviral (ARV) regimens who have suboptimal suppression of HIV RNA (that is, detectable virus at any time during pregnancy using ultrasensitive assays). They should be:

- Evaluated for resistant virus (if plasma HIV RNA is >500 to 1,000 copies/mL);
- Assessed for adherence, tolerability, incorrect dosing, or potential problems with absorption (e.g., nausea/vomiting, lack of attention to food requirements); and
- Considered for ARV regimen modification.

Experts in the care of ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary. Hospitalization can be considered for directly observed drug administration, adherence education, and treatment of comorbidities such as nausea and vomiting.

Among 662 pregnancies followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with an HIV-1 RNA level >400 copies/mL in late pregnancy (adjusted odds ratio, 1.66; 95% confidence interval, 1.07–2.57; \( P = 0.024 \)), highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize need to modify treatment.\(^1\)

HIV RNA levels should be assessed 2 to 4 weeks after an ARV drug regimen is initiated or changed to provide an initial assessment of effectiveness.\(^2\) Baseline HIV RNA levels have been shown to affect the time to response in both pregnant and non-pregnant individuals, with no difference in response between pregnant and non-pregnant women.\(^3,4\) Most patients with an adequate viral response at 24 weeks have had at least a 1 log copies/mL HIV RNA decrease within 1 to 4 weeks after starting therapy.\(^2\) In a retrospective multicenter cohort of 378 pregnant women, 77.2% achieved HIV RNA <50 copies/mL by delivery, with success of viral suppression varying by baseline HIV RNA level. With baseline <10,000 copies/mL, gestational age at initiation did not affect success up to 26.3 weeks. With baseline >10,000 copies/mL, however, delaying initiation past 20.4 weeks significantly reduced ability for achieving maximal suppression at delivery.\(^3\) In data on 1,070 HIV-infected treatment-naive pregnant women participating in IMPAACT P1025, a prospective cohort study, later initiation of combination antiretroviral therapy (cART) at >32 weeks’ gestation also was associated with a significantly higher risk of having viral load >400 copies/mL at delivery.\(^5\) The role of therapeutic drug monitoring in reducing the risk of virologic failure is still undefined.\(^6,7\)

A recent systematic review and meta-analysis of adherence to cART during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the United States) found that a pooled estimate of 73.5% of pregnant women had adequate (>80%) adherence to cART.\(^8\) Evaluation of and support
for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

Because maternal antenatal viral load correlates with risk of perinatal transmission of HIV, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible. The addition of raltegravir in late pregnancy has been suggested for women who have high viral loads and/or in whom multiple drug-resistant mutations have resulted in incomplete suppression of viremia because of the ability of raltegravir to rapidly suppress viral load (approximately 2 log copies/mL decrease by Week 2 of therapy).<ref>9-12</ref> However, the efficacy and safety of this approach have not been evaluated and only anecdotal reports are available. In the setting of a failing regimen related to non-adherence and/or resistance, there are concerns that the addition of a single agent may further increase risk of resistance and potential loss of future effectiveness with raltegravir. A recent report found a 10- to 23-fold increase in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with return to normal levels after raltegravir discontinuation.<ref>13</ref> Therefore, at the current time, this approach cannot be routinely recommended. Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL.

References


Discontinuation of antiretroviral (ARV) drug regimens during pregnancy may be indicated in some situations, including serious drug-related toxicity, pregnancy-induced hyperemesis unresponsive to antiemetics, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or at patients’ request.

HIV-infected women receiving combination antiretroviral therapy (cART) who present for care during the first trimester should continue treatment during pregnancy [AII]. If an antiretroviral (ARV) drug regimen is stopped acutely for severe or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to antiemetics, or other acute illnesses that preclude oral intake, all ARV drugs should be stopped and reinitiated at the same time [AII].

If an ARV drug regimen is being stopped for non-life-threatening reasons and the patient is receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI), consideration should be given to either:

- Stopping the NNRTI first and continuing the other ARV drugs for a period of time; or
- Switching from an NNRTI to a protease inhibitor (PI) before interruption and continuing the PI with the other ARV drugs for a period of time before electively stopping.

The optimal interval between stopping an NNRTI and the other ARV drugs is unknown; at least 7 days is recommended. Given the potential for prolonged detectable efavirenz concentrations for >3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other ARV agents or substituting a PI plus 2 other agents for up to 30 days after stopping the NNRTI drug [CIII].

If nevirapine is stopped and more than 7 days have passed before restarting therapy, nevirapine should be restarted with the 2-week half-dose escalation period [AII].

Continuation of all drugs during the intrapartum period generally is recommended. Women who are having elective cesarean delivery can take oral medications before the procedure and restart drugs following surgery. Because most drugs are given once or twice daily, it is likely that no doses would be missed or that at most the postpartum dose would be given a few hours late.

When short-term drug interruption is indicated, in most cases, all ARV drugs should be stopped and reintroduced at the same time. This can be problematic with drugs that have a long half-life. However, in...
conditions such as serious or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to antiemetics, or other acute illnesses precluding oral intake, the clinician has no choice but to stop all therapy at the same time. In the rare case in which a woman has limited oral intake that does not meet food requirements for certain ARV agents, decisions about the ARV regimen administered during the antepartum or intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert.

Non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs (e.g., nevirapine, efavirenz) have very long half-lives and can be detected for 21 days or longer after discontinuation; efavirenz has a longer half-life than nevirapine.2-6 Because other drugs in the ARV regimen have shorter half-lives and are cleared more rapidly, only detectable NNRTI drug levels persist, resulting in subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, certain genetic polymorphisms, which may be more common among ethnic groups such as African Americans and Hispanics, may have the potential to result in a slower rate of clearance.4,6 To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other ARV drugs for a period of time.3 Detectable levels of NNRTIs may be present from <1 week to >3 weeks after discontinuation, with the longer duration primarily observed with efavirenz.6 An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI and to continue the PI with dual nucleoside reverse transcriptase inhibitors (NRTIs) for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI- to a PI-based regimen before interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of HIV RNA re-suppression after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual NRTIs.7

The optimal duration for continuing either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI has not been definitively established, but a minimum of 7 days is recommended based on past studies to reduce resistance following single-dose nevirapine.8,9 More recently, among 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or ritonavir-boosted lopinavir for either 7 or 21 days, there was an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific polymerase chain reaction emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019).10

A pharmacokinetic study of nevirapine elimination in African adults following cessation of steady-state nevirapine-containing regimens found that nevirapine concentrations were estimated to have fallen below 20 ng/mL in 3 of 19 (16%) and 14 of 19 (74%) subjects by 7 and 14 days, respectively, after the cessation of dosing.11 Elimination half-life was 39 hours in these subjects, considerably shorter than that observed after peripartum exposure to single doses of nevirapine (average 55–60 hours), likely related to induction of nevirapine metabolism with chronic nevirapine exposure.2,12,13 Because efavirenz concentrations have the potential to be detectable for more than 3 weeks, some experts suggest that if efavirenz-based therapy is stopped, the dual NRTIs or PI may need to be continued for up to 30 days. Further research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens.

Another consideration is reintroduction of nevirapine if it is temporarily stopped and subsequently restarted. A 2-week, half-dose escalation currently is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing cytochrome P450 3A4 liver metabolic enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. In cases where nevirapine has been discontinued for more than 7 days, another 2-week dose escalation is recommended when it is reintroduced.

References


Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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## HIV/Hepatitis B Virus Coinfection

### Panel's Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All HIV-infected pregnant women should be screened during pregnancy for hepatitis B virus (HBV) and hepatitis C virus (HCV), unless they are known to be coinfected or have already been screened during the current pregnancy (see HIV/Hepatitis C Virus Coinfection) (AIII).</td>
<td>AII</td>
</tr>
<tr>
<td>• All pregnant women who screen negative for HBV (i.e., HBV surface antigen [HBsAg]-negative, HBV core antibody-negative, and HBV surface antibody [anti-HBs]-negative) should receive the HBV vaccine series (AII).</td>
<td>AII</td>
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<tr>
<td>• Women with chronic HBV infection should also be screened for hepatitis A virus (HAV) because they are at increased risk of complications from coinfection with other viral hepatitis infections (AII).</td>
<td>AII</td>
</tr>
<tr>
<td>• Women with chronic HBV infection who are negative for hepatitis A immunoglobulin G should receive the HAV vaccine series (AII).</td>
<td>AII</td>
</tr>
<tr>
<td>• The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV is strongly recommended (AIII).</td>
<td>AIII</td>
</tr>
<tr>
<td>• Interferon alfa and pegylated interferon alfa are not recommended during pregnancy (AII).</td>
<td>AII</td>
</tr>
<tr>
<td>• All pregnant women with HIV/HBV coinfection should receive combination antiretroviral therapy (cART), including a dual nucleoside reverse transcriptase inhibitor (NRTI)/nucleotide analogue reverse transcriptase inhibitor (NtRTI) backbone with two drugs active against both HIV and HBV (AII). Tenofovir plus lamivudine or emtricitabine is the preferred dual NtRTI/NRTI backbone of antepartum cART in HIV/HBV-coinfected pregnant women (AII).</td>
<td>AII</td>
</tr>
<tr>
<td>• Pregnant women with HIV/HBV coinfection receiving antiretroviral (ARV) drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter during pregnancy (BIII).</td>
<td>BIII</td>
</tr>
<tr>
<td>• If ARV drugs are discontinued postpartum in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected (BIII).</td>
<td>BIII</td>
</tr>
<tr>
<td>• Decisions concerning mode of delivery in HIV/HBV-coinfected pregnant women should be based on standard obstetric and HIV-related indications alone (see Intrapartum Care) (BIII).</td>
<td>BIII</td>
</tr>
<tr>
<td>• Within 12 hours of birth, infants born to women with HBV infection should receive hepatitis B immune globulin and the first dose of the HBV vaccine series. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively (AI).</td>
<td>AI</td>
</tr>
<tr>
<td>Post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 9 months to 18 months.</td>
<td></td>
</tr>
</tbody>
</table>

### Rating of Recommendations:

- **A** = Strong
- **B** = Moderate
- **C** = Optional

### Rating of Evidence:

- **I** = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
- **II** = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
- **III** = Expert opinion

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For additional information on hepatitis B virus (HBV) and HIV, see [HIV/Hepatitis B (HBV) Coinfection](http://AIDSInfo.nih.gov) in the Adult and Adolescent Antiretroviral Guidelines and [Hepatitis B Virus Infection](http://AIDSInfo.nih.gov) in the Adult Opportunistic Infections Guidelines. The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended.

All HIV-infected women should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. Pregnant HIV-infected women should be rescreened for HBV and HCV unless they are known to be coinfected or have already been screened during the current pregnancy. Women who screen negative for HBV (i.e., hepatitis B surface antigen [HBsAg]-negative, hepatitis B core antibody [anti-HBc]-negative, and hepatitis B surface antibody [anti-HBs]-negative) should receive the HBV vaccine series. Data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg and should cause no risk to fetuses. A positive test for anti-HBc alone can be false-positive, or it may signify past exposure with subsequent loss of anti-HBs or “occult” HBV infection, which can be confirmed by detection of HBV DNA. The clinical significance of isolated anti-HBc is unknown.
Some experts recommend that HIV-infected individuals with anti-HBc alone be tested for HBV DNA before vaccination for HBV or before treatment or prophylaxis with antiretroviral (ARV) drugs is initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS).2 HIV-infected pregnant women with isolated anti-HBc and occult HBV infection have very low levels of HBV DNA and are thought to be at extremely low risk of transmitting HBV to their infants.8

Because of the added risk of acute infection with hepatitis A virus (HAV) in individuals with chronic HBV, women who are found to have chronic HBV infection should also be screened for HAV. Women with chronic HBV infection who are hepatitis A immunoglobulin G-negative should receive the HAV vaccine series. Although the safety of HAV vaccination during pregnancy has not been determined, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.3

An ARV regimen that includes drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection who require HBV treatment or who are starting ARV drugs, including pregnant women. Initiation of an ARV regimen that does not include anti-HBV drugs may be associated with reactivation of HBV and development of IRIS; IRIS-related flare of HBV activity during pregnancy can occur even in women with relatively high CD4 T lymphocyte (CD4) cell counts at the time of ARV initiation. In addition, use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia, potentially increasing the efficacy of neonatal hepatitis B immune globulin (HBIG) and hepatitis B vaccine in prevention of perinatal transmission of HBV. High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.8-11 Several small studies and a recent meta-analysis suggest that lamivudine or tenofovir may reduce the risk of perinatal transmission of HBV if given during the third trimester to HBV-infected, HIV-seronegative women with high HBV DNA viremia.12 Although a high HBV viral load clearly is important, it is not the only factor predisposing to failure of prophylaxis.19

Because lamivudine, tenofovir, and emtricitabine have activity against both HIV and HBV, the recommended dual-nucleoside reverse transcriptase/nucleotide analogue reverse transcriptase inhibitor (NRTI) backbone for HIV/HBV-coinfected individuals, including pregnant women, is tenofovir/emtricitabine or tenofovir/lamivudine. Lamivudine has been extensively studied and is recommended for use in pregnancy (see Table 6). The Antiretroviral Pregnancy Registry includes reports on the outcomes of 4,273 pregnancies that involved administration of lamivudine in the first trimester and there is no indication that the exposure was associated with an increased risk of birth defects.20 Similarly, no increase in birth defects has been noted in 1,230 cases of first-trimester exposure to emtricitabine, which, like lamivudine, is recommended for use in pregnancy (see Table 6). Tenofovir is not teratogenic in animals, but reversible bone changes at high doses have been seen in multiple animal species. A total of 1,800 cases of first-trimester exposure have been reported to the Antiretroviral Pregnancy Registry, with no increase in birth defects noted.20 Tenofovir with emtricitabine or lamivudine is a preferred dual NRTI backbone in women who are HIV-infected or HIV/HBV-coinfected (see Table 6).

Several other antivirals with activity against HBV, including entecavir, adefovir, and telbivudine, have not been well evaluated in pregnancy. Entecavir is associated with skeletal anomalies in rats and rabbits but only at doses high enough to cause toxicity to the mother. Fewer than 52 cases of exposure to each of these drugs during pregnancy have been reported to the Antiretroviral Pregnancy Registry prospectively, with no increased risk of birth defects.20 Telbivudine was given to 135 HBV-positive, HIV-seronegative women during the third trimester and was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers (0% vs. 8%; P = 0.002).15,21 In a larger meta-analysis of the effects of telbivudine in late pregnancy in women infected with HBV alone, telbivudine was effective in interrupting intrauterine HBV infection without significant adverse effects or complications.16 Each of these anti-HBV drugs should be administered only in addition to a fully suppressive regimen for HIV. Because these other anti-HBV drugs also have weak activity against HIV, they may select for anti-HIV drug resistance in the absence of fully suppressive cART regimen as well as confer the potential for developing cross-resistance to other ARV
drugs. (Entecavir, for example, can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine.) Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com).

Interferon alfa and pegylated interferon alfa are not recommended for use in pregnancy and should be used only if the potential benefits outweigh the potential risks. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents.22

Following initiation of ARV drugs, an elevation in hepatic enzymes can occur in HIV/HBV-coinfected women—particularly those with low CD-cell counts at the time of treatment initiation—as a result of an immune-mediated flare in HBV disease triggered by immune reconstitution with effective HIV therapy. HBV infection also can increase hepatotoxic risk of certain ARV drugs, specifically protease inhibitors and nevirapine. Pregnant women with HIV/HBV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter. If hepatic toxicity occurs, it may be necessary to consider substituting a less hepatotoxic regimen or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between a flare in HBV disease due to immune reconstitution and drug toxicity often can be difficult, and consultation with an expert in HIV and HBV coinfection is strongly recommended. Because tenofovir has potential to cause renal toxicity, kidney function also should be monitored regularly in women receiving this drug, based on toxicity seen in non-pregnant adults.

Following delivery, considerations regarding continuation of the ARV drug regimen are the same as for other non-pregnant individuals (see General Principles Regarding Use of Antiretroviral Drugs During Pregnancy). Discontinuing agents with anti-HBV activity may be associated with hepatocellular damage resulting from reactivation of HBV. Frequent monitoring of liver function tests for potential HBV flare is recommended in women with HIV/HBV coinfection whose ARV drugs are discontinued postpartum, with prompt re-initiation of treatment for both HIV and HBV if a flare is suspected.

Within 12 hours of birth, all infants who weigh >2,000 g born to mothers with chronic HBV infection should receive HBIG and the first dose of the HBV vaccination series. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively. This regimen is >95% effective in preventing HBV infection in these infants. Consult the CDC Morbidity and Mortality Weekly Report recommendations for similar infants with birth weights <2,000 g at birth.21

Post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 9 months to 18 months. Testing should not be performed before age 9 months to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti-HBc testing of infants is not recommended because passively acquired maternal anti-HBc might be detected in infants born to HBV-infected mothers up to age 24 months. HBsAg-negative infants with anti-HBs levels >10 mIU/mL are protected and need no further medical management. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1–2 months after the final dose of vaccine.

References


### HIV/Hepatitis C Virus Coinfection

For additional information on hepatitis C virus (HCV) and HIV, see [HIV/Hepatitis C Coinfection](#) in the Adult and Adolescent Antiretroviral Guidelines[^1] and [Hepatitis C Virus Infection](#) in the Adult Opportunistic Infections Guidelines[^2]. The management of HIV/HCV coinfection in pregnancy is complex and consultation with an expert in HIV and HCV is strongly recommended.

All HIV-infected women should be screened for hepatitis B virus (HBV) and HCV at entry into general HIV care. Pregnant HIV-infected women should be re-screened for HBV and HCV unless they are known to be coinfected or have already been screened during the current pregnancy. HCV coinfection is not uncommon in HIV-infected women, particularly those infected via parenteral use of drugs; among HIV-infected pregnant women, the HCV seroprevalence rate ranges from 17% to 54%^[^3]. Screening for chronic HCV infection using a sensitive immunoassay for HCV antibody is recommended for all HIV-infected individuals, including pregnant women. False-negative anti-HCV immunoassay results can occur in HIV-infected individuals, particularly those with very low CD4 T lymphocyte (CD4) cell counts, but it is uncommon with the most

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[^1]: Adult and Adolescent Antiretroviral Guidelines
[^2]: Adult Opportunistic Infections Guidelines
[^3]: HCV seroprevalence rate ranges from 17% to 54%.
sensitive immunoassays. Individuals who have a positive HCV antibody test should undergo confirmatory testing for plasma HCV RNA using a commercially available quantitative diagnostic assay. Testing for HCV RNA also should be performed on individuals whose serologic test results are indeterminate or negative but in whom HCV infection is suspected because of elevated aminotransaminase levels or risk factors such as a history of intravenous drug use.

Women who screen negative for HBV (i.e., hepatitis B surface antigen (HBsAg)-negative, hepatitis B core antibody-negative, and hepatitis B surface antibody-negative) should receive the HBV vaccine series. Data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg and should cause no risk to fetuses.4

Because of the added risk of acute infection with hepatitis A virus (HAV) in individuals with chronic HCV, women who are found to have chronic HCV infection should also be screened for HAV. Women with chronic HCV infection who are hepatitis A immunoglobulin G-negative should receive the HAV vaccine series. Although the safety of HAV vaccination during pregnancy has not been determined, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.4 Few data exist on the optimal management of HIV-infected pregnant women with HCV coinfection.

Recommendations for antiretroviral (ARV) drug use during pregnancy for treatment of HIV and/or prevention of perinatal transmission are the same for women who have HCV coinfection as for those with HIV alone (see HIV/Hepatitis C Coinfection in the Adult and Adolescent Antiretroviral Guidelines). However, currently available anti-HCV treatments are not recommended during pregnancy. Interferons are not recommended for use in pregnancy because they are abortifacient at high doses in monkeys and have direct antigrowth and antiproliferative effects,2 and ribavirin is contraindicated (Food and Drug Administration [FDA] Pregnancy Category X) because of teratogenicity at low doses in multiple animal species. Ribavirin-associated defects in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Concerns have been raised about potential mutagenic effects of ribavirin in the offspring of men taking ribavirin before conception because of possible accumulation of ribavirin in spermatozoa. However, in a small number of inadvertent pregnancies occurring in partners of men receiving ribavirin therapy, no adverse outcomes were reported.6

Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or http://www.ribavirinpregnancyregistry.com). There are no data in pregnancy on telaprevir or boceprevir, both approved in 2011 by the FDA for treatment of HCV, or simeprevir or sofosbuvir, also approved for HCV treatment by the FDA in 2013. Telaprevir, boceprevir, and sofosbuvir are Pregnancy Category B agents and simeprevir is a Pregnancy Category C agent; however, these agents currently must be used in combination with pegylated interferon and ribavirin, which should not be used in pregnancy. In addition, potential drug interactions between these newer anti-HCV drugs and ARV drugs, particularly certain ritonavir-boosted protease inhibitor (PI) regimens, may reduce the effectiveness of these medications if used together (for more detailed information see Adult and Adolescent Antiretroviral Guidelines).7 Pregnancy does not appear to influence the course of HCV infection and women with chronic HCV generally do quite well during pregnancy, provided that their infections have not progressed to decompensated cirrhosis.8

In a majority of studies, the incidence of perinatal HCV transmission increases if the mother is coinfected with HIV, with transmission rates between 10% and 20%.9,12 These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impact on HCV disease activity.13 A European study of perinatal transmission of HCV found that use of effective combination antiretroviral therapy (cART) for HIV was associated with a strong trend toward reduction in HCV transmission (odds ratio 0.26, 95% confidence interval, 0.07–1.01).14 Maternal HIV/HCV coinfection also may increase the risk of perinatal transmission of HIV.15 Therefore, potent cART with at least three drugs is recommended for all HIV/HCV-coinfected pregnant women, regardless of CD4 cell count or HIV viral load.

As with chronic HBV infection, an elevation in hepatic enzymes following initiation of cART can occur in HIV/HCV-coinfected women—particularly in those with low CD4 cell counts at treatment initiation—as a result of an immune-mediated flare in HCV disease triggered by immune reconstitution with effective cART.
Like HBV, HCV infection may increase the hepatotoxic risk of certain ARV agents, specifically PIs and nevirapine. Pregnant women with HIV/HCV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiation of ARV drugs and then every 3 months thereafter. If hepatic toxicity occurs, consideration may need to be given to substituting a less hepatotoxic drug regimen, and if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between a flare in HCV disease associated with immune reconstitution and drug toxicity often can be difficult; therefore, consultation with an expert in HIV and HCV coinfection is strongly recommended.

As with transmission of HIV, risk of perinatal transmission of HCV may be increased by use of internal fetal monitoring, amniocentesis, and rupture of membranes for more than 6 hours. The majority of studies of elective cesarean delivery that have included HIV-infected women have found that the procedure does not reduce the risk of perinatal transmission of HCV. Thus, the general recommendations for intrapartum management are the same in women with HIV/HCV coinfection as in those with HIV infection alone (see Intrapartum Care).

Infants born to women with HIV/HCV coinfection should be assessed for HCV infection with anti-HCV antibody testing after age 18 months. Infants who screen positive should undergo confirmatory HCV RNA testing. HCV RNA virologic testing can be done after age 2 months, if earlier diagnosis is indicated or desirable. Because HCV viremia can be intermittent, 2 negative HCV RNA tests at or after age 2 months, including 1 at or after age 12 months, are needed to definitively exclude HCV infection. Children are considered to be HCV-infected if they have 2 or more positive HCV RNA polymerase chain reaction results or are HCV antibody-positive beyond age 18 months.

References


HIV-2 Infection and Pregnancy  (Last updated March 28, 2014; last reviewed March 28, 2014)

HIV-2 infection is endemic in West African countries including Ivory Coast, Ghana, Cape Verde, Gambia, Mali, Senegal, Liberia, Guinea, Burkina Faso, Nigeria, Mauritania, Sierra Leone, Guinea Bissau, Niger, Sao Tome, and Togo; Angola; Mozambique; and in parts of India. It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions. HIV-2 remains rare in the United States. Between 1998 and 2010, a total of 242 HIV-2 cases were reported to the Centers for Disease Control and Prevention (CDC), with 166 cases meeting criteria for HIV-2 diagnosis. These 166 cases constituted only 0.01% of the more than 1.4 million U.S. cases of HIV infection. Of the 50 women aged 15 to 44 years at diagnosis, 24 (48%) were pregnant at or after HIV-2 diagnosis. HIV-2 infection should be suspected in pregnant women who are from—or have partners from—countries in which the disease is endemic, who are HIV antibody-positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot along with HIV-1 RNA viral loads at or below the limit of detection.

A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted protease inhibitor (PI) currently is recommended for HIV-2-infected pregnant women who require treatment for their own health because they have significant clinical disease or CD4 T-lymphocyte (CD4-cell) counts <500 cells/mm³.

Lopinavir/ritonavir plus zidovudine/lamivudine or abacavir/lamivudine or tenofovir/emtricitabine is the preferred ART regimen for HIV-2-infected pregnant women who require treatment, based on safety data on use of these drugs in HIV-1-infected pregnant women.

Optimal prophylactic regimens have not been defined for HIV-2-infected pregnant women who do not require treatment for their own health (i.e., CD4 cell counts >500 cells/mm³ and no significant clinical disease). Experts have recommended the following approaches:

- A boosted PI-based regimen (two NRTIs plus ritonavir-boosted lopinavir) for prophylaxis, with the drugs stopped postpartum;
- Zidovudine prophylaxis alone during pregnancy and intrapartum.

Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.

All infants born to HIV-2-infected mothers should receive the standard 6-week zidovudine prophylactic regimen regardless of maternal treatment choice.

Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.

In the United States, safe infant formula is readily available. Breastfeeding is not recommended for infants of HIV-2-infected mothers.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

The FDA has approved the first rapid diagnostic test that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen, the Alere Determine HIV-1/2 Ag/Ab Combo, which can be used on human serum, plasma, and venous or fingerstick whole-blood specimens. However, this test does not distinguish between antibodies to HIV-1 and HIV-2. Specimens which are reactive on the rapid test must be tested with an FDA-approved 2nd generation antibody assay to distinguish HIV-1 from HIV-2 antibodies. The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is FDA-approved for differentiating HIV-1 from HIV-2 infections. In some commercial and public health laboratories, HIV-2 supplemental tests, such as HIV-2 immunoblot or HIV-2-specific Western...
blot, are available. However, none of these tests has been FDA approved for diagnosis or clinical management of HIV-2. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2 and no HIV-2 commercial viral load assays are currently available. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by the CDC. No validated HIV-2 genotype or phenotype resistance assays are available in the United States. Recently, European experts developed a rule set and an automated tool for HIV-2 drug resistance analyses that is freely available on the Internet (see http://www.hiv-grade.de).

HIV-2 has a longer asymptomatic phase than HIV-1, with a slower progression to AIDS. The most common mode of HIV-2 transmission is through heterosexual sex. HIV-2 is less infectious than HIV-1, with a 5-fold lower rate of sexual transmission and 20- to 30-fold lower rate of vertical transmission. Several studies confirm that rates of perinatal transmission of HIV-2 are low with and without interventions (0%–4%), which may be a result of reduced plasma viral loads and less cervical viral shedding, compared with that seen in HIV-1-infected women. HIV-2 also can be transmitted through breastfeeding. HIV-2 infection does not protect against HIV-1 and dual infection, which carries the same prognosis as HIV-1 mono-infection, can occur.

Few data exist on which to base treatment decisions or strategies for prevention of perinatal transmission in patients infected with HIV-2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis. HIV-2 has variable sensitivity to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity against the virus. The integrase inhibitors raltegravir and elvitegravir also appear to be effective against HIV-2. The CCR5 antagonist maraviroc appears active against some strains of HIV-2, although there are no approved assays to determine HIV-2 co-receptor tropism.

The care of HIV-2-infected pregnant women has been based on expert opinion. A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted PI currently is recommended for HIV-2-infected pregnant women who require treatment for their own health because they have significant clinical disease or CD4 T lymphocyte (CD4) cell counts <500 cells/mm³. Based on efficacy and available data on safety in HIV-1-infected pregnant women, ritonavir-boosted lopinavir plus zidovudine/lamivudine or abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine would be preferred. NNRTIs should not be used because they are not active against HIV-2. All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen.

For HIV-2-infected pregnant women with CD4 cell counts >500 cells/mm³ and no significant clinical disease, who do not require treatment for their own health, some experts would use a boosted PI-based regimen for prophylaxis and stop the drugs postpartum. Other experts would consider zidovudine prophylaxis alone during pregnancy and intrapartum. Because HIV-2 has a significantly lower risk of perinatal transmission than does HIV-1, single-drug prophylaxis with zidovudine alone can be considered for prevention of perinatal transmission. All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen. The possible risks and benefits of antiretroviral (ART) prophylaxis should be discussed with the mothers.

Pregnant women who have HIV-1/HIV-2 coinfection should be treated according to the guidelines for HIV-1-monoinfected patients, making sure that the ART regimen chosen is also appropriate for HIV-2.

Other than the standard obstetrical indications, no data exist regarding the role of elective cesarean delivery in women who are infected with HIV-2. The risk to infants from breastfeeding is lower for HIV-2 than for HIV-1, but breastfeeding should be avoided in the United States and other resource-rich countries where safe infant formula is readily available.

Infants born to HIV-2-infected mothers should be tested for HIV-2 infection with HIV-2-specific virologic assays at time points similar to those used for HIV-1 testing. HIV-2 virologic assays are not commercially available, but the National Perinatal HIV Hotline (888-448-8765) can provide a list of sites that perform this testing.
Testing of infants at age 18 months (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) also is recommended to confirm clearance of HIV-2 antibodies.29

References


Primary or acute HIV infection in pregnancy or during breastfeeding is associated with an increased risk of perinatal transmission of HIV and may represent a significant proportion of residual perinatal transmission in the United States.

In North Carolina, from 2002 to 2005, 5 of 15 women found to have acute HIV infection on nucleic acid amplification testing of pooled HIV antibody-negative specimens were pregnant at the time of testing. All 5 women received antiretroviral (ARV) drugs and delivered HIV-uninfected infants.

From 2002 to 2006, 3,396 HIV-exposed neonates were born in New York State—22% (9 of 41) of infants born to mothers who acquired HIV during pregnancy became infected with HIV, compared with 1.8% of those born to mothers who did not acquire HIV during pregnancy (odds ratio 15.19; 95% confidence interval, 3.98–56.30). Maternal acquisition of HIV during pregnancy was documented in only 1.3% of perinatal HIV exposures, but it was associated with 9 (13.8%) of the 65 perinatal transmission cases. A case series from China reported a perinatal transmission rate of 35.8% in 106 breastfeeding infants of mothers who acquired HIV postnatally through blood transfusion. The high rate of transmission associated with acute infection likely is related to the combination of the high viral load in plasma, breast milk, and the genital tract associated with acute infection and the fact that the diagnosis is easy to miss, which results in lost opportunities for implementation of prevention interventions.

Health care providers should maintain a high level of suspicion of acute HIV infection in women who are pregnant or breastfeeding and have a compatible clinical syndrome, even when they do not report high-risk behaviors, because it is possible that their sexual partners are practicing high-risk behaviors of which the women are unaware.

An estimated 40% to 90% of patients with acute HIV infection will experience symptoms of acute retroviral syndrome, characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms. Providers often do not recognize acute HIV infection, however, because the symptoms are similar to those of other common illnesses and individuals with the condition also can be asymptomatic. When acute retroviral syndrome is suspected, a plasma HIV RNA test typically is used in conjunction with an HIV antibody test to diagnose acute infection. A low-positive HIV RNA level (<10,000 copies/mL) may
represent a false-positive test because values in acute infection generally are very high (>100,000 copies/mL).4,10 In individuals infected with non-B HIV-1 subtypes, however, HIV RNA levels may be lower, even with acute infection, because those subtypes may not amplify as well as subtype B. In that situation, consultation with an HIV treatment specialist is recommended. Confirmatory serologic testing should be performed within 3 months on patients whose acute HIV infection is diagnosed with virologic testing but who are antibody-negative or whose antibody levels cannot be determined.

Recent HIV infection also can be detected by repeat HIV antibody testing later in pregnancy in women whose initial HIV antibody testing earlier in pregnancy was negative.13 A report from the Mother-Infant Rapid Intervention at Delivery study found that 6 (11%) of 54 women whose HIV was identified with rapid HIV testing during labor had primary infection.12,13 In the United States, of 10,308 HIV-infected pregnant women who delivered live infants from 2005 to 2010 in 15 areas conducting Enhanced Perinatal Surveillance (EPS), 124 (1.2%) were identified as seroconverting during pregnancy. The rate of perinatal transmission was 8 times higher among women who seroconverted during pregnancy (12.9%) than in those who became infected prior to pregnancy (1.6%) (P < 0.0001).14 Repeat HIV testing in the third trimester is recommended for pregnant women known to be at risk of HIV who receive care in facilities with an HIV incidence of at least 1 case per 1,000 pregnant women per year, who are incarcerated, or who reside in jurisdictions with elevated HIV incidence (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings).15

Whether treatment of acute or recent HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown, and in non-pregnant adults, therapy currently is considered optional.16 In pregnant or breastfeeding women, however, acute or recent HIV infection is associated with a high risk of perinatal transmission of HIV. All HIV-infected pregnant women with acute or recent infection should start a combination ARV regimen as soon as possible, with the goal of preventing perinatal transmission by optimal suppression of plasma HIV RNA below detectable levels. Data from the United States and Europe demonstrate that in 6% to 16% of patients, transmitted virus may be resistant to at least one ARV drug.17,18 Therefore, baseline genotypic resistance testing should be performed to guide selection or adjustment of an optimal ARV drug regimen. If results of resistance testing or the source virus’s resistance pattern are known, that information should be used to guide selection of the drug regimen, but initiation of the combination ARV regimen should not be delayed. Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors in ARV-naive persons, a PI-based ARV drug regimen generally should be initiated. Choice of regimen should be based on recommendations for use of ARV drugs in pregnancy (see Table 6 and Table 7). Following delivery, considerations regarding continuation of the ARV regimen for treatment are the same for mothers as for other non-pregnant individuals.

When acute HIV infection is diagnosed during pregnancy, and particularly if it is documented in late pregnancy, cesarean delivery is likely to be necessary because there may be insufficient time to fully suppress a patient’s viral load. In nursing mothers in whom seroconversion is suspected, breastfeeding should be interrupted and it should not resume if infection is definitively confirmed (see Breastfeeding Infants of Mothers Diagnosed with HIV Infection in Infant Antiretroviral Prophylaxis). In such a situation, consultation with a pediatric HIV specialist regarding appropriate infant management is recommended.

All women who are pregnant or breastfeeding should be counseled about prevention of acquisition of HIV (see Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis and Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States). Several studies suggest that pregnancy may be a time of increased risk of transmission of HIV.19,20 even when controlling for sexual risk behaviors.19 It is hypothesized that the heightened risk may be attributable to hormonal changes that affect the genital tract mucosa or immune responses.19 Although no reliable data on HIV serodiscordance rates in the United States exist, data on women from sub-Saharan Africa show that women in serodiscordant relationships may be particularly vulnerable to acquisition of HIV.24,25 HIV testing
of the sexual partners of pregnant women should be encouraged. The importance of using condoms should be reinforced in pregnant and breastfeeding women who may be at risk of acquisition of HIV, including those whose partners are HIV-infected, and the potential use of pre- or post-exposure antiretroviral prophylaxis also should be emphasized (see Reproductive Options for HIV-Concordant and Serodiscordant Couples).

References


Panel’s Recommendations

- Women should continue their antepartum combination antiretroviral (ARV) drug regimen on schedule as much as possible during labor and before scheduled cesarean delivery (AIII).
- **Intravenous (IV) zidovudine should be administered to HIV-infected women with HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery (AI), but is not required for HIV-infected women receiving combination ARV regimens who have HIV RNA ≤1,000 copies/mL consistently during late pregnancy and near delivery and no concerns regarding adherence to the regimen (BII).**
- For women who have suboptimal viral suppression near delivery (i.e., HIV RNA >1,000 copies/mL), scheduled cesarean delivery is recommended (see Transmission and Mode of Delivery) (AI).
- Women whose HIV status is unknown who present in labor should undergo rapid HIV antibody testing (AII). If the results are positive, a confirmatory HIV test should be done as soon as possible and maternal (IV zidovudine)/infant (combination ARV prophylaxis) ARV drugs should be initiated pending results of the confirmatory test (AII). If the confirmatory HIV test is positive, infant ARV drugs should be continued for 6 weeks (see Infant Antiretroviral Prophylaxis) (AI); if the confirmatory HIV test is negative, the infant ARV drugs should be stopped.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Women Who Have Received Antepartum Antiretroviral Drugs

Use of Intravenous Zidovudine During Labor

The PACTG 076 zidovudine regimen included a continuous intravenous (IV) infusion of zidovudine during labor for all women. Combination antiretroviral (ARV) regimens are now recommended for treatment and prevention of perinatal transmission of HIV; the additional benefit of IV zidovudine in women receiving combination regimens has not been evaluated in randomized clinical trials.

The French Perinatal Cohort evaluated transmission in >11,000 HIV-infected pregnant women receiving ARV drugs (10% zidovudine alone, 18% dual ARV, and 72% triple ARV) who delivered between 1997 and 2010, stratified by viral load at delivery; 95% received IV intrapartum zidovudine. The overall rate of perinatal transmission was 0.9% (95/10,239) with IV zidovudine and 1.8% (9/514, P = 0.06) without IV zidovudine. Among women with HIV RNA <1,000 copies/mL at delivery, no transmission occurred among 369 who did not receive IV zidovudine compared to a rate of 0.6% (47/8,132, P > 0.20) among those receiving IV zidovudine. Among women with HIV RNA >1,000 copies/mL, the risk of transmission was increased without IV zidovudine (10.2%) compared to 2.5% with IV zidovudine (P < 0.01) if neonates received only zidovudine for prophylaxis, but was not different (4.8% versus 4.1%, P = 0.83) without or with intrapartum zidovudine if the neonate received intensified prophylaxis with two or more ARV drugs. In a cohort of 717 women delivering between 1996 and 2008 in Miami, the majority of whom were on a combination ARV regimen and had HIV RNA <1,000 copies/mL at delivery, lack of receipt of IV zidovudine during labor was not associated with an increased risk of transmission. Among a European cohort of infants considered at high risk of transmission, lack of IV zidovudine in labor was associated with transmission on univariate analysis but was not significantly associated once adjusted for maternal HIV RNA and other factors (adjusted odds ratio with IV zidovudine 0.79, 95% confidence interval 0.55-1.15, P = 0.23). In a cohort of Irish women on a combination ARV regimen for at least 4 weeks before delivery with HIV RNA <1,000 copies/mL, no transmission occurred among 61 who received either no zidovudine in labor or <4 hours of IV zidovudine.

Based on these studies, IV zidovudine is not required for HIV-infected women receiving combination ARV regimens with HIV RNA ≤1,000 copies/mL consistently in late pregnancy and/or near delivery and with no...
indication of concerns about adherence to or tolerance of their ARV regimens; IV zidovudine should continue to be administered to HIV-infected women with HIV RNA >1,000 copies/mL near delivery (or unknown HIV RNA levels), regardless of antepartum regimen.

Previously, these guidelines specified that the threshold for not requiring intrapartum IV zidovudine was <400 copies/mL. However, based on more recent studies that have used a threshold of 1,000 copies/mL, a threshold of ≤1,000 copies/mL is now recommended for consideration of eliminating the requirement for IV zidovudine. This recommendation is now consistent with the mode of delivery recommendations that specify that a scheduled cesarean delivery is not recommended for women receiving combination ARV drugs with plasma HIV RNA levels ≤1,000 copies/mL. In addition, the previous guidelines did not specify that viral suppression had to be sustained. This guidance has been clarified to state that the viral loads should be consistently suppressed when intrapartum IV zidovudine is not used. However, regardless of viral load, the clinician may elect to use intrapartum IV zidovudine based on clinical judgement.

In women with HIV RNA >1,000 copies/mL receiving a scheduled cesarean delivery for prevention of transmission, IV zidovudine administration should begin 3 hours before the scheduled operative delivery. This recommendation is based on a pharmacokinetic (PK) study of zidovudine given orally during pregnancy and as a continuous infusion during labor. Maternal zidovudine levels were measured at baseline, after the initial IV loading dose and then every 3 to 4 hours until delivery, and in cord blood. Systemic and intracellular zidovudine levels increased from baseline but appeared to stabilize after 3 hours of infusion; cord blood zidovudine levels were associated with maternal levels and maternal infusion duration. If cesarean section is being performed for other indications and maternal viral load is ≤1,000 copies/mL near the time of delivery, administration of IV zidovudine is not required.

If antenatal use of zidovudine was precluded by known or suspected zidovudine resistance, intrapartum use of the drug still should be recommended in women with HIV RNA >1,000 copies/mL near delivery, except in women with documented histories of hypersensitivity. This intrapartum use of the drug is recommended because of the unique characteristics of zidovudine and its proven record in reducing perinatal transmission, even in the presence of maternal resistance to the drug (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

In some international studies, oral rather than IV zidovudine has been administered during labor. Data are limited on the PKs of oral compared with IV zidovudine during labor. Additionally, the drug levels needed for prophylaxis are unknown, although extrapolations have been made using therapeutic drug level targets. In a study of oral intrapartum zidovudine 300 mg every 3 hours in Thailand, most cord blood zidovudine levels were at therapeutic levels but were lower than those reported after continuous IV administration; 17% of infants had subtherapeutic levels at birth. In another study, the PKs of two dosing regimens of oral zidovudine during labor were evaluated in 10 HIV-infected pregnant women. The oral regimen was well tolerated; plasma zidovudine concentrations were substantially lower with 300 mg every 3 hours given orally during labor than previously reported with continuous IV therapy. A revised regimen with a 600 mg oral loading dose, followed by 400 mg every 3 hours, resulted in increased zidovudine concentrations but inter-patient variance was significant. In both cohorts, PK parameters suggested erratic absorption during labor. Therefore, in women with HIV RNA >1,000 copies/mL near delivery for whom zidovudine is recommended, IV would be preferred to oral administration in the United States; in situations where IV administration is not possible, oral administration can be considered.

**Continuation of Antenatal Antiretroviral Drugs during Labor**

Women who are receiving an antepartum combination ARV drug regimen should continue that regimen on schedule as much as possible during the intrapartum period to provide maximal virologic effect and to minimize the chance of development of drug resistance. If the woman’s HIV-1 RNA level is >1,000 copies/mL and oral zidovudine is part of the antepartum regimen, the oral zidovudine component of the regimen can be held while she receives IV zidovudine. When cesarean delivery is planned, oral medications can be
continued preoperatively with sips of water. Medications requiring food ingestion for absorption can be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist in the preoperative period. If the maternal ARV regimen must be interrupted temporarily (meaning for less than 24 hours) during the peripartum period, all drugs should be stopped and reinstituted simultaneously to minimize the chance that resistance will develop.

**Women Who Have Received Antepartum Antiretroviral Drugs But Have Suboptimal Viral Suppression Near Delivery**

Women who have received combination ARV drug regimens may not achieve complete viral suppression by the time of delivery because of factors such as poor adherence, viral resistance, or late entry into care. Regardless of the reason, all women who have HIV RNA levels >1,000 copies/mL near the time of delivery should be offered a scheduled cesarean delivery at 38 weeks, which may significantly reduce risk of transmission (see [Transmission and Mode of Delivery](#)).

Women with incomplete viral suppression at the time of delivery should receive IV zidovudine along with their other ARVs orally, as described above. In certain high-risk situations, additional medications for prophylaxis in infants may be warranted, such as in cases where maternal HIV RNA levels are high at or near the time of delivery, especially if delivery is not a scheduled cesarean delivery (see [Infant Antiretroviral Prophylaxis](#) and [Table 8](#)).

**Women Who Have Not Received Antepartum Antiretroviral Drugs**

**Women Who Present in Labor without Documentation of HIV Status**

All women without documentation of HIV status at the time of labor should be screened with rapid HIV testing unless they decline (opt-out screening). Rapid HIV testing is also recommended for women presenting in labor who tested negative for HIV in early pregnancy but are at increased risk of HIV infection and were not retested in the third trimester. Factors that may increase risk of infection include diagnosis of a sexually transmitted disease, illicit drug use or exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of HIV infection, signs/symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age and not undergoing repeat HIV testing in the third trimester.

Rapid HIV antibody testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit. Statutes and regulations regarding rapid testing vary from state to state (see [http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws](http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws) for a review of state HIV testing laws). Current information on rapid testing also should be available at all facilities with a maternity service and/or neonatal intensive care unit.

Women with positive rapid HIV antibody tests should be presumed to be infected until standard HIV antibody confirmatory testing clarifies their infection status. IV zidovudine should be started immediately in all women with positive rapid HIV tests in labor to prevent perinatal transmission of HIV, as discussed below.

In the postpartum period, along with confirmatory HIV antibody testing, these women should receive appropriate assessments as soon as possible to determine their health status, including CD4 T lymphocyte count and HIV-1 RNA viral load. Arrangements also should be made for establishing HIV care and providing ongoing psychosocial support after discharge.

**Choice of Intrapartum/Postpartum Antiretroviral Regimen for Women without Antepartum Antiretroviral Therapy**

All HIV-infected women who have not received antepartum ARV drugs should have IV zidovudine started immediately to prevent perinatal transmission of HIV. Although intrapartum/neonatal ARV medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to or during labor.
and delivery. Pre-exposure prophylaxis for the fetus can be provided by giving mothers a drug that rapidly crosses the placenta, producing fetal systemic ARV drug levels during intensive exposure to HIV in maternal genital secretions and in blood during birth. In general, zidovudine and other nucleoside reverse transcriptase inhibitor drugs and non-nucleoside reverse transcriptase inhibitors cross the placenta well, whereas protease inhibitors do not (see Table 7).

A large international trial (NICHD-HPTN 040/PACTG 1043) demonstrated that adding ARV agents to the neonatal portion of the intrapartum/neonatal zidovudine regimen can further reduce perinatal transmission of HIV for mothers who have received no antepartum ARV drugs (see Infant Antiretroviral Prophylaxis). In this study, women who had not received antepartum ARV drugs received IV zidovudine if they were identified in labor or no zidovudine when diagnosed immediately postpartum; their infants received either 6 weeks of zidovudine alone or zidovudine in combination with other agents. The combination infant regimens resulted in a 50% reduction in transmission compared with zidovudine alone. Therefore, no additional intrapartum drugs, including intrapartum maternal single-dose nevirapine, are indicated for a woman in this situation. Women diagnosed with HIV infection during labor or the early postpartum period should be counseled against breastfeeding in the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe.

References


### Basis for Current Recommendations

Scheduled cesarean delivery, defined as cesarean delivery performed before the onset of labor and before rupture of membranes, is recommended for prevention of perinatal transmission of HIV in women with HIV RNA levels >1000 copies/mL near delivery and for women with unknown HIV RNA levels.

This recommendation is based on findings from a multicenter, randomized clinical trial and from a large individual patient data meta-analysis. These two studies were conducted at a time when the majority of HIV-infected women received no antiretroviral (ARV) medications or zidovudine as a single drug and before the availability of viral load information. Study results have since been extrapolated to make current recommendations about the mode of delivery in an era when combination ARV regimens during pregnancy are recommended and viral load information is readily available.

In the randomized clinical trial, 1.8% of infants born to women randomized to undergo cesarean delivery were HIV-infected compared with 10.5% of infants born to women randomized to vaginal delivery ($P < .001$). When adjusted for ARV use in pregnancy (zidovudine alone), scheduled cesarean delivery lowered risk of HIV transmission by 80%, although the results were no longer statistically significant (odds ratio [OR] 0.2; 95% confidence interval [CI], 0–1.7). The protective effect still remained for scheduled delivery (adjusted OR [AOR] 0.3; 95% CI, 0.1–0.8) but not for emergency cesarean delivery (AOR 1.0; 95% CI, 0.3–3.7) when the data were analyzed by actual mode of delivery rather than by the group to which women were allocated. Results from a large meta-analysis of individual patient data from 15 prospective cohort studies also demonstrated the benefit of scheduled cesarean delivery, with a 50% reduction in risk.

### HIV RNA Level of >1000 copies/mL as a Threshold for Recommendation of Scheduled Cesarean Delivery

The American College of Obstetricians and Gynecologists (ACOG) recommends that women with HIV RNA >1000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery. Initially, the threshold of 1000 copies/mL was based largely on data from the Women and Infants Transmission Study, a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels less than 1000 copies/mL. Studies reported since then have demonstrated that HIV transmission can occur in infants born to women with low viral loads.

#### Panel's Recommendations

- Scheduled cesarean delivery at 38 weeks’ gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral drugs (AII). Data are insufficient to evaluate the potential benefit of cesarean delivery used solely for prevention of perinatal transmission in women receiving combination antiretroviral therapy with HIV RNA levels ≤1000 copies/mL, and given the low rate of transmission in these patients, it is unclear whether scheduled cesarean delivery would confer additional benefit in reducing transmission (BIII). In women with HIV RNA levels ≤1000 copies/mL, cesarean delivery performed for standard obstetrical indications should be scheduled at 39 weeks’ gestation.

- It is not clear whether cesarean delivery after rupture of membranes or onset of labor provides benefit in preventing perinatal transmission. Management of women originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized at the time of presentation based on duration of rupture and/or labor, plasma HIV RNA level, and current antiretroviral regimen (BII).

- Women should be informed of the risks associated with cesarean delivery. If the indication for cesarean delivery is prevention of perinatal transmission of HIV, the risks to a woman should be balanced with potential benefits expected for the neonate (AII).

#### Rating of Recommendations: A = Strong; B = Moderate; C = Optional

#### Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
In an analysis of 957 women with plasma viral loads ≤1000 copies/mL, cesarean delivery (scheduled or urgent) reduced risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications; however, zidovudine alone was the regimen primarily used as prophylaxis (AOR 0.30; \( P = 0.022 \)). Among infants born to 834 women with HIV RNA ≤1000 copies/mL receiving ARV medications, 8 (1%) were HIV-infected. In a more recent report from a comprehensive national surveillance system in the United Kingdom and Ireland, 3 (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA levels <50 copies/mL and 50 to 999 copies/mL, respectively, were HIV infected.

The recent studies demonstrate that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission in this group, it is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. Although decisions about mode of delivery for women receiving combination ARV therapy (cART) with HIV RNA levels ≤1000 copies/mL should be individualized based on discussion between the obstetrician and the mother, women should be informed that there is no evidence of benefit for scheduled cesarean delivery performed solely for prevention of perinatal transmission in women receiving cART with HIV RNA ≤1000 copies/mL and that it is not routinely recommended in this group.

Scheduled Cesarean Delivery in the Combination Antiretroviral Therapy Era

In surveillance data from the United Kingdom and Ireland, pregnant women receiving cART (i.e., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery. Given the low transmission rates achievable with use of maternal cART, the benefit of scheduled cesarean delivery is difficult to evaluate. Both the randomized clinical trial and meta-analysis documenting the benefits of cesarean delivery included mostly women who were receiving either no ARVs or zidovudine alone. However, other data partially address this issue.

In a report from the European Collaborative Study that included data from 4,525 women, the overall transmission rate in the subset of women on cART was 1.2% (11 of 918). In the subset of 560 women with undetectable HIV RNA levels (≤50 to ≤200 copies/mL, depending on site), scheduled cesarean delivery was associated with a significant reduction in perinatal transmission in univariate analysis (OR 0.07; 95% CI, 0.02–0.31; \( P = .0004 \)). However, after adjustment for ARV drug use (none vs. any), the effect was no longer significant (AOR 0.52; 95% CI, 0.14–2.03; \( P = .359 \)). Similarly, data from a European surveillance study did not demonstrate a statistically significant difference in transmission rates between scheduled cesarean delivery and planned vaginal delivery (AOR 1.24; 95% CI, 0.34–4.5) in women on cART. The transmission rate in all women who received at least 14 days of ARV medications was 0.8% (40 of 4,864), regardless of mode of delivery. Therefore, no evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving cART for several weeks and who have achieved virologic suppression.

When the delivery method selected is scheduled cesarean delivery and the maternal viral load is >1000 copies/mL, administer a 1-hour loading dose and continuous intravenous (IV) zidovudine for 2 hours (3 hours total) before scheduled cesarean delivery. In a study of the pharmacokinetics of IV zidovudine in 28 pregnant women, the ratio of cord blood to maternal zidovudine levels increased significantly in women who received IV zidovudine for 3 to 6 hours compared with <3 hours before delivery (1.0 vs 0.55, respectively)\(^8\). This suggests that an interval of at least 3 hours may provide adequate time to reach equilibrium across the placenta, although the relationship between specific cord blood zidovudine levels or cord blood-to-maternal-zidovudine levels and efficacy in preventing perinatal transmission of HIV is unknown.

Because unscheduled cesarean delivery is performed for both maternal and fetal indications, when an unscheduled cesarean delivery is indicated in a woman who has a viral load >1000 copies/mL, consideration can be given to shortening the interval between initiation of IV zidovudine administration and delivery. For example, some experts recommend administering the 1-hour loading dose of IV zidovudine and not waiting to complete additional administration before proceeding with delivery.
Women Presenting Late in Pregnancy
HIV-infected women who present late in pregnancy and are not receiving ARV drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be \( \leq 1000 \) copies/mL at baseline. Even if cART was begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the kinetics of viral decay for a particular drug regimen.\(^9,10\) In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing the risk of perinatal transmission of HIV for women, unless viral suppression can be documented before 38 weeks’ gestation.

Timing of Scheduled Cesarean Delivery
For the general obstetric population, ACOG recommends that scheduled cesarean delivery not be performed before 39 weeks’ gestation because of the risk of iatrogenic prematurity.\(^11,12\) However, in cases of cesarean delivery performed to prevent transmission of HIV, ACOG recommends scheduling cesarean delivery at 38 weeks’ gestation in order to decrease the likelihood of onset of labor or rupture of membranes before delivery.\(^3\) In all women undergoing repeat cesarean delivery, the risk of any neonatal adverse event—including neonatal death, respiratory complications, hypoglycemia, newborn sepsis, or admission to the neonatal intensive care unit—is 15.3% at 37 weeks, 11.0% at 38 weeks, and 8.0% at 39 weeks.\(^12\) Gestational age should be determined by best obstetrical dating criteria, including last menstrual period and early ultrasound for dating purposes. Amniocentesis to document lung maturity should be avoided when possible in HIV-infected women and is rarely indicated before scheduled cesarean section for prevention of HIV transmission.

Among 1,194 infants born to HIV-infected mothers, 9 (1.6%) infants born vaginally had respiratory distress syndrome (RDS) compared with 18 (4.4%) infants born by scheduled cesarean delivery (\( P <0.001 \)). There was no statistically significant association between mode of delivery and infant RDS in an adjusted model that included infant gestational age and birth weight.\(^13\) Although newborn complications may be increased in planned births <39 weeks’ gestation, the benefits of planned cesarean delivery at 38 weeks are generally thought to outweigh the risks if the procedure is performed for prevention of HIV transmission. When cesarean delivery is performed in HIV-infected women for an indication other than decreasing HIV transmission, cesarean delivery should be scheduled at 39 weeks, based on ACOG guidelines.

Risk of Maternal Complications
Administration of perioperative antimicrobial prophylaxis is recommended for all women to decrease maternal infectious morbidity associated with cesarean delivery. Most studies have demonstrated that HIV-infected women have increased rates of postoperative complications, mostly infectious, compared with HIV-uninfected women and that risk of complications is related to degree of immunosuppression and the receipt of suppressive cART.\(^14-19\) Furthermore, a Cochrane review of six studies of HIV-infected women concluded that urgent cesarean delivery was associated with the highest risk of postpartum morbidity, scheduled cesarean delivery was intermediate in risk, and vaginal delivery had the lowest risk of morbidity.\(^20\) Complication rates in most studies\(^1,21-25\) were within the range reported in populations of HIV-uninfected women with similar risk factors and not of sufficient frequency or severity to outweigh the potential benefit of reduced perinatal HIV transmission. Therefore, HIV-infected women should be counseled regarding the risks associated with undergoing cesarean delivery and the potential benefits in decreasing perinatal transmission of HIV if HIV RNA levels at term are >1000 copies/mL.

Management of Women Who Present in Early Labor or With Ruptured Membranes
Few data are available to address the question of whether performing cesarean delivery after the onset of labor or membrane rupture decreases risk of perinatal transmission of HIV. Most studies have shown a similar risk of transmission for cesarean delivery performed for obstetric indications after labor and membrane rupture and for vaginal delivery. In one study, the HIV transmission rate was similar in women undergoing emergency cesarean delivery and those delivering vaginally (1.6% vs. 1.9%, respectively).\(^6\) A meta-analysis of HIV-infected women, most of whom were on zidovudine as a single drug or receiving no
ARV medications, demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes.26 However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.27 Therefore, the decision about whether to deliver by expeditious cesarean section for prevention of perinatal transmission in women originally scheduled for cesarean delivery who then present with ruptured membranes or in labor must be individualized, taking into account duration of rupture or labor upon presentation, plasma RNA level, and current ARV drug regimen status. The ARV drug regimen should be continued and IV zidovudine initiated, if previously planned.

When membrane rupture occurs before 37 weeks’ gestation, decisions about timing of delivery should be based on best obstetrical practices, taking into account risks to the infant of prematurity and of HIV transmission. Steroids should be given, if appropriate, to accelerate fetal lung maturity because no data exist to suggest that these recommendations need to be altered for HIV-infected women. When the decision is made to deliver, route of delivery should be according to obstetrical indications.

References


Other Intrapartum Management Considerations  (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel's Recommendations

- The following should generally be avoided because of a potential increased risk of transmission, unless there are clear obstetric indications:
  - Artificial rupture of membranes (BIII)
  - Routine use of fetal scalp electrodes for fetal monitoring (BIII)
  - Operative delivery with forceps or a vacuum extractor and/or episiotomy (BIII)

- The antiretroviral drug regimen a woman is receiving should be taken into consideration when treating excessive postpartum bleeding resulting from uterine atony:
  - In women who are receiving a cytochrome P (CYP) 3A4 enzyme inhibitor such as a protease inhibitor, methergine should be used only if no alternative treatments for postpartum hemorrhage are available and the need for pharmacologic treatment outweighs the risks. If methergine is used, it should be administered in the lowest effective dose for the shortest possible duration (BIII).
  - In women who are receiving a CYP3A4 enzyme inducer such as nevirapine, efavirenz, or etravirine, additional uterotonic agents may be needed because of the potential for decreased methergine levels and inadequate treatment effect.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

If spontaneous rupture of membranes occurs before or early during the course of labor, interventions to decrease the interval to delivery (e.g., administration of oxytocin) can be considered in HIV-infected women with viral suppression and no indications for cesarean delivery. Artificial rupture of membranes should be avoided and used only for a clear obstetric indication in women with intact membranes and detectable viral loads who present in labor and will be allowed to proceed to vaginal delivery. Data are limited on artificial rupture of membranes in women with undetectable viral loads and planned vaginal delivery. Data on the association of duration of membrane rupture and perinatal transmission in the era of effective combination antiretroviral therapy (cART) are more reassuring on this issue. A recent prospective cohort study of 707 HIV-infected pregnant women on cART included 493 women with delivery HIV-RNA <1000 copies/mL with no cases of perinatal transmission with up to 25 hours of membrane rupture; logistic regression found that HIV viral load >10,000 copies/mL was the only independent risk factor for transmission. In general, the procedure should be performed only for clear obstetrical indications because of the potential, albeit small, of an increased risk of HIV transmission.

Obstetric procedures that increase the risk of fetal exposure to maternal blood, such as invasive fetal monitoring, have been implicated in increasing vertical transmission rates by some, but not all, investigators, primarily in studies performed in the pre-ART era. Data are limited on use of fetal scalp electrodes in labor in women receiving suppressive antiretroviral (ARV) regimens who have undetectable viral loads; routine use of fetal scalp electrodes for fetal monitoring should be avoided in the setting of maternal HIV infection unless there are clear obstetric indications.

Similarly, data are limited to those obtained in the pre-cART era regarding the potential risk of perinatal transmission of HIV associated with operative vaginal delivery with forceps or the vacuum extractor and/or use of episiotomy. These procedures should be performed only if there are clear obstetric indications. Delayed cord clamping has been associated with improved iron status in both term and preterm infants and benefits such as decreased risk of intraventricular hemorrhage in preterm births to HIV-uninfected mothers. Even though HIV-specific data on the practice are lacking, there is no reason to modify it in HIV-infected mothers.
Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use

Oral or parenteral methergine or other ergot alkaloids are often used as first-line treatment for postpartum hemorrhage resulting from uterine atony. However, methergine should not be coadministered with drugs that are potent cytochrome P (CYP) 3A4 enzyme inhibitors, including protease inhibitors (PIs). Concomitant use of ergotamines and PIs has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving PIs, methergine should be used only if alternative treatments such as prostaglandin F2-alpha, misoprostol, or oxytocin are unavailable. If no alternative medications are available and the need for pharmacologic treatment outweighs the risks, methergine should be used in as low a dose and for as short a period as possible. In contrast, additional uterotonic agents may be needed when other ARV drugs that are CYP3A4 inducers (e.g., nevirapine, efavirenz, etravirine) are used because of the potential for decreased methergine levels and inadequate treatment effect.

References


Postpartum Care  (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel’s Recommendations

- Decisions regarding continuing combination antiretroviral therapy (cART) after delivery should be made in consultation with the woman and her HIV provider, ideally before delivery (AIII). cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission, although the strength and evidence for this recommendation varies by pre-treatment CD4 T lymphocyte (CD4) count. Decisions should take into account current recommendations for initiation of cART in adults, pre-treatment CD4 cell counts and trajectory, HIV RNA levels, adherence issues, whether a woman has an HIV-uninfected sexual partner, and patient preference.
- For women continuing cART postpartum, arrangements for new or continued supportive services should be made before hospital discharge because the immediate postpartum period poses unique challenges to adherence (AII).
- Contraceptive counseling should be a critical aspect of postpartum care (AII).
- Women with a positive rapid HIV antibody test during labor require immediate linkage to HIV care and comprehensive follow-up, including confirmation of HIV infection. If infection is confirmed, a full health assessment is warranted, including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of need for cART and opportunistic infection prophylaxis (AII).
- Breastfeeding is not recommended for HIV-infected women in the United States, including those receiving cART (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Postpartum Follow-Up of HIV-Infected Women

The postpartum period provides an opportunity to review and optimize women’s health care. Comprehensive medical care and supportive services are particularly important for HIV-infected women and their families, who often face multiple medical and social challenges. Components of comprehensive care include the following services as needed:
- Primary, gynecologic/obstetric, and HIV specialty care for the HIV-infected woman;
- Pediatric care for her infant;
- Family planning services;
- Mental health services;
- Substance abuse treatment;
- Support services; and
- Coordination of care through case management for a woman, her child(ren), and other family members.

Support services should be tailored to the individual woman’s needs and can include case management; child care; respite care; assistance with basic life needs, such as housing, food, and transportation; peer counseling; and legal and advocacy services. Ideally, this care should begin before pregnancy and continue throughout pregnancy and the postpartum period.

During the postpartum period, maternal medical services must be coordinated between obstetric care providers and HIV specialists. Decisions about continuing combination antiretroviral therapy (cART) after delivery should be made in consultation with the woman and her HIV provider, ideally prior to delivery. It is especially critical to ensure continuity of cART between the antepartum and postpartum periods.

cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission; the strength and evidence for this recommendation varies by...
pretreatment CD4 T lymphocyte (CD4) cell count. Randomized clinical trials have demonstrated clear evidence of individual clinical benefit for starting cART in persons with CD4 <350 cells/mm³. Data from observational studies support initiation of cART in individuals with CD4 cell counts of 350 to 500 cells/mm³. Data from observational studies are conflicting regarding individual clinical benefit for starting cART in individuals with CD4 cell counts >500 cells/mm³. The HPTN 052 clinical trial, which evaluated immediate versus delayed initiation of cART to HIV-infected individuals with CD4 cell counts between 350 and 550 cells/mm³, showed that earlier initiation of antiretroviral (ARV) drugs led to a significant reduction in sexual transmission of HIV to uninfected partners in serodiscordant couples (see Preconception Counseling). The Adult and Adolescent Guidelines note that when discussing initiation of cART at high CD4 cell counts, clinicians should inform patients that the data on clinical benefit of starting treatment at study levels are not conclusive, but that viral suppression can reduce the risk of sexual transmission to others. It is important to counsel the woman that no single method (including treatment of the infected partner) is fully protective against HIV transmission and safer sexual practices must be continued.

In a study of postpartum women in Haiti, women who stopped ARVs after delivery with antepartum CD4 cell counts between 350 and 499 cells/mm³ near delivery progressed to CD4 cell counts <350 cells/mm³ by 19 months post-delivery, whereas women with CD4 cell counts ≥500 cells/mm³ took significantly longer (5 to 7 years) to progress to CD4 cell counts <350 cells/mm³; mortality was confined to women with CD4 cell counts <350 cells/mm³. Similar data were reported in the HPTN 046 study in Africa, in which 37% of women with CD4 cell counts 400 to 549 cells /mm³ near delivery had CD4 cell counts decline to <350 cells/mm³ by 12 months post-delivery, whereas only 7% of women with CD4 cell counts ≥550 cells/mm³ had a similar decline. Factors to be taken into consideration regarding continuation of postpartum cART should include current recommendations for initiation of cART in adults, pretreatment CD4 cell counts and trajectory, HIV RNA levels, adherence issues, partner HIV status, and patient preference. The risks versus benefits of stopping cART postpartum in women with high CD4 cell counts are being evaluated in the ongoing PROMISE study (clinical trial number NCT00955968). Unplanned changes in ARV regimes and discontinuations of cART in the postpartum period have led to viral load rebound, although no change in viral setpoint has been observed. In contrast to results from treatment interruption studies in adults, in a study of biomarkers in postpartum HIV-infected women with pre-cART CD4 cell counts >350 cells/mm³ who received cART during pregnancy, significant decreases in the levels of D-dimer, highly sensitive C-reactive protein, and interleukin-6 in the postpartum period were seen in both women who stopped as well as those who continued cART postpartum.

Systematic monitoring of retention in HIV care is recommended for all HIV-infected individuals but special attention is warranted during the postpartum period. Retention in care is associated with improved individual health outcomes, including HIV biomarker and clinical variables, and may reduce community-level viral burden. Because the postpartum period is a particularly vulnerable period for a new mother with HIV, interventions to improve adherence to medical care—to ensure follow-up medical appointments and cART adherence—can include medication management services, community outreach, one-on-one adherence support, group education and support, peer support, reminder devices, and home visits by medical HIV case managers. A number of studies have suggested that postpartum depression may be common among HIV-infected women. Health care providers should be vigilant for signs of depression and illicit drug or alcohol use that may require intervention assessment to avoid problems with adherence. Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of cART. Simplification of a cART regimen (e.g., to once-daily medications) can be considered. For women who are unable to adhere to their regimens postpartum, it may be preferable to temporarily interrupt cART while they work with their health care provider on strategies to improve adherence. Efforts to maintain adequate adherence during the postpartum period may prolong the effectiveness of therapy (see the section on Adherence in the Adult and Adolescent Antiretroviral Guidelines).

The postpartum period also is a critical time for addressing the issue of safer sex practices, secondary transmission prevention, and contraception. It is important that comprehensive family planning and
preconception care be integrated into routine health visits. Women who receive family planning counseling during prenatal care are more likely to use effective contraception postpartum. Lack of breastfeeding is associated with earlier return of fertility; ovulation returns as early as 6 weeks postpartum, and earlier in some women—even before resumption of menses—putting them at risk of pregnancy shortly after delivery. Interpregnancy intervals of less than 18 months have been associated with increased risk of poor perinatal and maternal outcomes in HIV-uninfected women. Because of the stresses and demands of a new baby, women may be more receptive to use of effective contraception, yet simultaneously at higher risk of nonadherence to contraceptive use and, thus, unintended pregnancy. This is an important concern in women who are on an efavirenz-containing regimen because of the potential risk of teratogenicity in the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after the last menstrual period). A dual-protection strategy (e.g., use of condoms plus a second highly effective contraceptive) is ideal for HIV-infected women because it provides simultaneous protection against unintended pregnancy, transmission of HIV, and acquisition or transmission of sexually transmitted disease. Longer-term reversible contraceptive methods, such as injectables, implants, and intrauterine devices (IUDs) should be included as options.

Drug interactions have been documented between oral contraceptives and many ARV drugs; however, data primarily come from pharmacokinetic studies and the clinical implications have not been well studied. The magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy or increase contraceptive-associated adverse effects is unknown. Hormonal contraceptives can be used with cART in women who have no other contraindications. Additional or alternative methods of contraception can be recommended where drug interactions are known. ARV-contraceptive interactions are discussed in Preconception Counseling and Care for HIV-Infected Women of Childbearing Age and Table 3. A systematic review conducted for the World Health Organization has summarized the research on hormonal contraception, IUD use, and risk of HIV infection. Permanent sterilization is appropriate only for women who are certain they do not desire future childbearing.

Concerns have been raised about adherence to ARV regimens during the postpartum period, because a number of studies have found significant decreases in adherence postpartum. Women should be counseled that postpartum physical and psychological changes and the stresses and demands of caring for a new baby may make adherence more difficult and that additional support may be needed during this period. For women whose antepartum regimen included a non-nucleoside reverse transcriptase inhibitor (NNRTI) and who plan to stop ART after delivery, consideration should be given to stopping the NNRTI and continuing the other ARV drugs for a period of time before stopping electively. The optimal interval between stopping an NNRTI and the other ARV drugs is unknown; a minimum of 7 days is recommended. Because efavirenz-based therapy has potential to result in prolonged, detectable NNRTI concentrations for more than 3 weeks, some experts recommend that patients receiving efavirenz continue their other ARV drugs or substitute a protease inhibitor (PI) for the NNRTI drug in combination with their other ARV drugs for up to 30 days after stopping efavirenz (see Stopping Antiretroviral Drugs during Pregnancy and Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Women whose antepartum regimen did not include an NNRTI and who plan to stop cART after delivery should stop all ARV drugs at the same time. Doses of some PIs may be increased during pregnancy. For women continuing cART, available data suggest that standard doses can be used again, beginning immediately after delivery.

Immediate linking to care, comprehensive medical assessment, counseling, and follow-up are required for women who test positive on rapid HIV antibody assay during labor or at delivery. To minimize the delay in definitive diagnosis, confirmatory HIV antibody testing should be performed as soon as possible after an initial positive rapid test. Women who test positive on rapid HIV antibody assay should not breastfeed unless a confirmatory HIV test is negative. Women with a new HIV diagnosis postpartum should receive the same thorough evaluation as other newly identified infected patients, including consideration of cART and prophylaxis for opportunistic infections, as indicated. Other children and partner(s) should be referred for HIV testing.


Infant Antiretroviral Prophylaxis (Last Updated March 28, 2014; last reviewed March 28, 2014)

Panel’s Recommendations

- The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is generally recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV (AI). However, a 4-week neonatal chemoprophylaxis regimen can be considered when the mother has received standard combination antiretroviral therapy (cART) during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence (BII).

- Zidovudine, at gestational age-appropriate doses, should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (AI).

- Infants born to HIV-infected women who have not received cART should receive prophylaxis with zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (i.e., at birth, 48 hours later, and 96 hours after the second dose), begun as soon after birth as possible (AI).

- In other scenarios, the decision to combine other drugs with the 6-week zidovudine regimen should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by maternal counseling on the potential risks and benefits of this approach (BIII).

- For infants born to mothers with unknown HIV status, expedited (rapid) HIV testing of mothers and/or infants is recommended as soon as possible, either during labor or after birth, with immediate initiation of infant antiretroviral (ARV) prophylaxis if the initial expedited test is positive (AI). If supplemental testing is negative, ARV prophylaxis can be discontinued.

- In the United States, the use of ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants as prophylaxis to prevent transmission because of lack of dosing and safety data (BIII).

- The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV, including infant care.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

General Considerations for Choice of Infant Prophylaxis

All HIV-exposed infants should receive postpartum antiretroviral (ARV) drugs to reduce perinatal transmission of HIV. The 6-week neonatal zidovudine chemoprophylaxis regimen is generally recommended for all HIV-exposed infants.1,2 However, a 4-week neonatal chemoprophylaxis regimen can be considered when the mother has received standard combination antiretroviral therapy (cART) during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence (see Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression below).3,4 Table 8 shows recommended zidovudine dosing based on gestational age, birth weight and the status of maternal antepartum ARV regimens.

The risk of transmission is increased when maternal viral load at delivery is high or maternal antepartum and/or intrapartum prophylaxis was incomplete or not received. In these situations, the potential benefit of combining zidovudine infant prophylaxis with additional ARV drugs must be weighed against the potential risks to infants of multiple drug exposure. In the following sections, we present available data and recommendations for management of infants born to mothers:

- Who received antepartum/intrapartum ARV drugs with effective viral suppression;
- Who received antepartum and intrapartum ARV drugs but who had suboptimal viral suppression at delivery, particularly if delivery was vaginal;
- Who received only intrapartum ARV drugs;
- Who received neither antepartum nor intrapartum ARV drugs;
- With unknown HIV status; and
- With known ARV drug-resistant virus.
In each of these situations, there is a spectrum of transmission risk that depends on a number of maternal and infant factors, including maternal viral load, mode of delivery, and gestational age at delivery. The risks and benefits of infant exposure to ARV drugs in addition to zidovudine will differ depending on where the mother/child falls in the risk spectrum. Thus, a generic recommendation cannot be made regarding use of combination drug regimens for infant prophylaxis. Each situation needs to be considered individually, balancing potential benefits (in terms of preventing perinatal transmission of HIV) with risks (in terms of toxicity to the infant). In addition, appropriate drug formulations and dosing regimens for neonates are incompletely defined and data are minimal on the safety of combination drugs in the neonate (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis and the Pediatric Antiretroviral Guidelines).

Data from the NICHD-HPTN 040/PACTG 1043 study have provided guidance for management of infants born to women who received no ARV prophylaxis during pregnancy. In this study, 1,746 formula-fed infants born to HIV-infected women who did not receive any ARV drugs during pregnancy were randomized to one of three infant prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. The risk of intrapartum transmission was significantly lower in the two- and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone; \( P = .046 \) for each experimental arm vs. zidovudine alone).5 Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or zidovudine-alone regimen (27.5% vs. 15%, \( P < .0001 \)). In other studies, significantly higher rates of neutropenia and anemia have been reported with co-administration of zidovudine and lamivudine to infants.6 Thus, based on comparable efficacy and reduced toxicity, the Panel recommends 6 weeks of zidovudine plus three doses of nevirapine for infants whose mothers have not received antepartum ARVs (Table 8).

Despite the paucity of available data, the use of combination ARV prophylaxis for infants in high-risk situations is increasing. Surveillance of obstetric and pediatric HIV infection in the United Kingdom and Ireland through the National Study of HIV in Pregnancy and Childhood noted that between 2001 and 2004, 9% of HIV-exposed infants received triple-drug prophylaxis compared with 13% between 2005 and 2008.7 Similarly, in an Internet-based poll of 134 U.S.-based perinatal HIV service providers, 62% reported using combination postnatal prophylaxis in high-risk situations in the past year. Zidovudine, lamivudine, and nevirapine was the combination regimen used most often.8 The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) has pooled data from 5,285 mother-infant pairs included in eight European cohorts and evaluated the use of combination prophylaxis. Among the 1,105 infants receiving combination prophylaxis, 13.5% received zidovudine plus lamivudine, 22.7% received zidovudine plus single-dose nevirapine, 55.8% received zidovudine plus single-dose nevirapine plus lamivudine, and 4.4% received a regimen including a protease inhibitor (PI). In these observational cohorts, there was no difference in infant infection rates between one drug and combination prophylactic regimens.9 The authors concluded that the lack of difference may be related to residual confounding or the fact that combination prophylaxis may only be effective in a subset of infants.

A case of a “functional cure” of HIV in an infant was recently reported.10 The infant was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and was diagnosed as HIV-infected by rapid testing during labor; delivery occurred before maternal intrapartum ARV prophylaxis could be given. At age 30 hours, the infant initiated a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher therapeutic dose rather than standard prophylactic dosing). The infant was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these tests, the infant was continued on treatment for HIV infection, thought to be acquired in utero. Nevirapine was replaced by ritonavir-boosted lopinavir at day 7 of life (Note: This decision preceded warnings from the Food and Drug Administration (FDA) against use of ritonavir-boosted lopinavir in infants younger than age 14 days). At age 18 months, therapy was discontinued by the mother; levels of plasma RNA, proviral DNA, and HIV antibodies have remained undetectable in the child through age 30 months on...
no therapy. Further investigation is ongoing, and clinical trials are planned to address whether administration of a therapeutic combination ARV regimen to HIV-exposed high-risk infants could alter the establishment and long-term persistence of HIV infection and assess the safety of such an approach for the infant.

There are two key safety issues related to the choice of ARV drugs in this infant. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birth-weight infants (see Antiretroviral Drug Dosing for Premature Infants), these prophylaxis-dose regimens target trough drug levels of 100 ng/mL, with peak levels averaging 1,000 to 1,500 ng/mL. However, there have been no studies in neonates under age 2 weeks or preterm infants to determine the appropriate dosing or safety of nevirapine administered at therapeutic doses, designed to maintain trough drug concentrations above 3,000 ng/mL and peak levels below 10,000 ng/mL for treatment of HIV-infected individuals. Second, ritonavir-boosted lopinavir is not recommended for neonates younger than age 14 days because of the potential for significant toxicity (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis). Therefore, the risks of this approach in terms of infant toxicity (particularly in preterm infants), as well as whether the functional cure can be replicated in additional infants, require further study before a general recommendation can be made.

In this and all other scenarios, decisions about use of combination ARV prophylaxis in infants should be made in consultation with a pediatric HIV specialist before delivery, if possible, and should be accompanied by a discussion with the mothers about potential risks and benefits of this approach.

The National Perinatal HIV Hotline
The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for HIV-infected pregnant women and their infants, and can provide referral to local or regional pediatric HIV specialists.

**Recommendations for Infant Antiretroviral Prophylaxis in Specific Clinical Situations**

**Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression**

The risk of HIV acquisition is small in infants born to women who received standard ARV prophylaxis regimens during pregnancy and labor and had undetectable viral loads at delivery or by scheduled cesarean section to mothers with low viral loads at delivery. The optimal minimum duration of neonatal zidovudine chemoprophylaxis has not been established in clinical trials. In the United States, the standard 6-week infant zidovudine regimen has been recommended, based on data from PACTG studies 076 and 316 (both performed during an era when a greater proportion of women did not receive antenatal cART). In the United Kingdom and many other European countries, a 4-week neonatal chemoprophylaxis regimen is now recommended for infants born to mothers who have received cART regimens and have viral suppression, with no apparent increase in the overall HIV perinatal transmission rate. Additionally, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy infants compared with the 6-week zidovudine regimen. Therefore, a 4-week zidovudine neonatal chemoprophylaxis regimen can be considered when a mother has received standard cART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence.

In infants born to women with effective viral suppression, combining zidovudine with additional ARV drugs to reduce transmission risk is not recommended because the risk of transmission is low and any potential benefit would be very limited. Any potential benefits must be balanced by the known toxicities of ARV drugs in infants.

**Infants Born to Mothers Who Have Received Antepartum/Intrapartum Antiretroviral Drugs But Have Suboptimal Viral Suppression Near Delivery**

All infants born to women who have received antepartum/intrapartum ARVs but with suboptimal viral suppression near delivery should receive zidovudine for 6 weeks. No specific data address whether a more

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/8/2014
intensive combination infant prophylaxis regimen (two or three drugs) provides additional protection against transmission when maternal antepartum/intrapartum prophylaxis is received but viral replication near delivery is significant. Extrapolation of findings from the previously discussed NICHD-HPTN 040/PACTG 1043 study suggests that combination infant prophylaxis should be considered, depending on assessment of risk based on maternal viral load and mode of delivery. That decision should be made in consultation with a pediatric HIV specialist before delivery and accompanied by maternal counseling on the potential risks and benefits of this approach.

Many data support the observation that the risk of perinatal transmission is related to maternal antepartum viral load in women on no ARV drugs as well as women receiving ARVs. Scheduled cesarean delivery is recommended for prevention of perinatal transmission in women who have received antepartum ARV drugs but have detectable viremia (HIV RNA >1,000 copies/mL) near the time of delivery (see Intrapartum Care and Transmission and Mode of Delivery). In PACTG 316, transmission occurred in 0% of 17 infants when maternal HIV RNA levels at delivery were >10,000 copies/mL and delivery was by scheduled cesarean delivery. However, not all women with detectable viremia near delivery will undergo cesarean delivery. The risk of acquisition of HIV will be higher in infants born to mothers with higher viral loads near delivery, particularly if delivery is vaginal. The gradient of transmission risk is based on HIV RNA levels. In the Women and Infants Transmission Study (WITS), the risk of transmission of HIV was ≤1.8% in women who received cART and had HIV RNA levels <30,000 copies/mL at delivery; it increased to 4.8% in women with HIV RNA levels ≥30,000 copies/mL.

Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs

All infants whose mothers have received only intrapartum ARV drugs should receive the two-drug regimen of 6 weeks of zidovudine plus three doses of nevirapine in the first week of life (first dose at birth to 48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose), based on the results of the NICHD-HPTN 040/PACTG 1043 study. Infant prophylaxis should be initiated as soon after delivery as possible. Infant prophylaxis is a critical component of prevention when no maternal antepartum ARV drugs have been received. The PETRA study demonstrated that intrapartum prophylaxis alone, without infant prophylaxis, is ineffective in reducing perinatal transmission. A study in Thailand indicated that longer infant prophylaxis with zidovudine (6 weeks versus 3 days) is required for optimal efficacy when maternal antenatal exposure to zidovudine is <4 weeks. In the NICHD-HPTN 040/PACTG 043 trial, 41% of women received zidovudine during labor. Administration of intrapartum zidovudine did not affect transmission rates.

Infants Born to Mothers Who Did Not Receive Antepartum or Intrapartum Antiretroviral Drugs

The two-drug regimen of 6 weeks of zidovudine plus three doses of nevirapine in the first week of life (first dose at birth to 48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose) is recommended for infants born to mothers who did not receive antepartum or intrapartum ARVs based on the results of the NICHD-HPTN 040/PACTG 1043 study, which demonstrated increased efficacy of combination regimens in reducing intrapartum transmission compared with use of zidovudine alone in infants. Prophylaxis should be initiated as soon after delivery as possible.

The interval during which infant prophylaxis can be initiated and still be of benefit is undefined. In the New York State study, when prophylaxis was delayed beyond 48 hours after birth, no efficacy could be demonstrated. Data from animal studies indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, ARV prophylaxis initiated 24 to 36 hours after exposure usually has been ineffective in preventing infection, although a delay in administration has been associated with decreased viremia. In the NICHD-HPTN 040/PACTG 1043 study, infant regimens were initiated within 48 hours of life and usually within 12 hours of life. Initiation of infant prophylaxis after age 2 days is not likely to be efficacious in preventing transmission and, by age 14 days, infection already would be established in most infants. Initiating prophylaxis as soon after delivery as possible increases its potential efficacy and minimizes potential harm, such as development of resistant virus, if infection has occurred.
Infants Born to Mothers with Unknown HIV Infection Status

Expedited (previously referred to as “rapid”) HIV testing of mothers is recommended during labor for women with unknown HIV status and for mothers and/or infants as soon as possible after birth if expedited HIV testing was not performed during labor. Expedited test results should be available within 60 minutes. Commercially available antigen/antibody tests are preferred to those that test only for antibody. Oral fluid-based tests are not recommended for infant testing; blood or serum testing has notably better sensitivity in infants than does oral fluid testing. If expedited testing is positive, infant ARV prophylaxis should be initiated immediately, without waiting for the results of supplemental tests (see scenario: Infants Born to Mothers Who Did Not Receive Antepartum or Intrapartum Antiretroviral Drugs). Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care, special care or newborn nursery. A positive initial test result in mothers or infants should be presumed to indicate maternal HIV infection until standard supplemental testing clarifies maternal status. A positive HIV antibody test in an infant indicates maternal but not necessarily infant HIV infection; diagnosis of HIV infection in infants younger than age 18 months requires virologic testing using a viral nucleic amplification test (NAT; includes DNA and RNA PCR and related assays). Initial positive HIV antibody tests can be confirmed using a recommended HIV-1/2 diagnostic testing algorithm. Supplemental tests should be performed on mothers (or their infants) as soon as possible after the initial positive test. If the supplemental test results are negative, ARV prophylaxis can be discontinued. If the supplemental test results are positive, an HIV NAT should be obtained urgently from the newborn to determine the infant’s HIV infection status. If the HIV NAT is positive, ARV prophylaxis should be promptly discontinued and the infant should receive treatment for HIV infection with standard cART according to the Pediatric Antiretroviral Guidelines.

Breastfeeding should be stopped until HIV infection is confirmed or ruled out in a woman who is suspected of being HIV-infected based on an initial positive antibody test result. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV infection is ruled out, breastfeeding can resume. If HIV infection is confirmed, breastfeeding should be discontinued permanently.

Infants Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal prophylactic regimen for newborns delivered by women with ARV drug-resistant virus is unknown. ARV prophylaxis for infants born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery.

Data from WITS suggest that in women who have mixed zidovudine-resistant and -sensitive viral populations, the zidovudine-sensitive rather than -resistant virus may be preferentially transmitted. Thus, the 6-week infant zidovudine prophylaxis (along with maternal intravenous [IV] intrapartum zidovudine prophylaxis) continues to be recommended, even when maternal zidovudine-resistant virus with thymidine-associated mutations is identified.

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility. However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and international settings.

For these newborns, use of zidovudine in combination with other ARV drugs, selected on the basis of maternal virus resistance testing, should be considered. The efficacy of this approach for prevention of transmission, however, has not been proven in clinical trials, and for many drugs, appropriate dosing regimens for neonates have not been established. Decisions regarding use of additional drugs should be made in consultation with a pediatric HIV specialist and will depend on maternal history of past and current ARV drug exposure, HIV RNA levels at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant.
Infant prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management). Data are limited on the toxicity to infants of exposure to multiple ARV drugs.

The latest information on neonatal dosing for ARV drugs can be found in the Pediatric Antiretroviral Guidelines. Other than zidovudine, lamivudine is the nucleoside reverse transcriptase inhibitor (NRTI) with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1,31,32 or 2 weeks.5 Six weeks of infant zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the infants also had in utero exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in infants exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and infant zidovudine. Anemia was reported in 15% and neutropenia in 18% of infants exposed to zidovudine/lamivudine, with 2% of infants requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.6 Similarly, in a Brazilian study of maternal antepartum and 6-week infant zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of infants.33

Tenovir with and without emtricitabine has been investigated in several small studies to define the safety and pharmacokinetics (PKs) of the agents in newborns.34,35,36 However, at this time, tenofovir and emtricitabine are not generally recommended for use in infant prophylaxis by the Panel because data on appropriate dosing are limited and the safety of these agents in the neonate is not well defined.

Experience with other NRTI drugs for neonatal prophylaxis is more limited.37,38 Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.6,39-42

Nevirapine is the only non-nucleoside reverse transcriptase inhibitor drug with a pediatric drug formulation and neonatal prophylactic (but not therapeutic) dosing information (see the Adult and Adolescent Antiretroviral Guidelines).43 In rare cases, chronic multiple-dose therapeutic nevirapine therapy has been associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving prophylactic dosing with single-dose nevirapine, the 2-drug zidovudine regimen plus 3 doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding infants receiving nevirapine prophylaxis daily for 6 weeks to 6 months to prevent transmission of HIV via breast milk.5,44-47 Resistance to nevirapine can occur, however, with exposure to nevirapine in infants who become infected despite prophylaxis.58,49 ARV drug-resistance testing is recommended for all HIV-infected infants before initiation of cART (see the Adult and Adolescent Antiretroviral Guidelines).

Of the PIs, pediatric drug formulations are available for ritonavir-boosted lopinavir, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended due to lack of dosing and safety information. No PK data are available for any PIs in the first 2 weeks of life. PK data are available for treatment of HIV-infected infants aged 2 to 6 weeks with ritonavir-boosted lopinavir. Although the lopinavir area under the curve (AUC) was significantly lower with dosing 300 mg lopinavir/75 mg ritonavir/m² body surface area twice daily than observed for infants >6 weeks of age, treatment was well tolerated and 80% of 10 infants had viral control at 6 months.50 Studies are ongoing but data are not yet available for infants aged <2 weeks. However, in 4 premature infants (2 sets of twins) started on ritonavir-boosted lopinavir from birth, heart block developed that resolved after drug discontinuation.51,52 In studies of adults, both ritonavir and ritonavir-boosted lopinavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of ritonavir-boosted lopinavir compared with zidovudine in the neonatal period. Levels of 17-hydroxyprogesterone were greater in infants who were also exposed to ritonavir-boosted lopinavir in utero compared with those exposed only in the neonatal period.
period. Term infants were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock. Based on these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity, predominantly in preterm neonates, the Food and Drug Administration now recommends that ritonavir-boosted lopinavir not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

Raltegravir is the only integrase inhibitor with an available pediatric drug formulation. However, it is not FDA-approved for use in infants aged <2 years and there are no PK and safety data on its use during the first weeks of life. Raltegravir competes with bilirubin for albumin binding sites, which could increase unconjugated bilirubin levels in the neonate. An in vitro study has demonstrated that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant unless raltegravir concentrations 50- to 100-fold higher than typical peak concentrations with usual dosing are reached. Use of raltegravir in neonates is not recommended until adequate PK and safety data are available.

### Neonatal Antiretroviral Drug Dosing

**Table 8. Recommended Neonatal Dosing for Prevention of Perinatal Transmission of HIV**

<table>
<thead>
<tr>
<th>Zidovudine (ZDV)</th>
<th>Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>≥35 weeks’ gestation at birth: 4 mg/kg/dose PO twice daily, started as soon after birth as possible and preferably within 6–12 hours of delivery (or, if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 hours of delivery, then every 12 hours)</td>
<td>Birth through 4-6 weeks*</td>
</tr>
<tr>
<td>ZDV</td>
<td>≥30 to &lt;35 weeks’ gestation at birth: 2 mg/kg/dose PO (or 1.5 mg/kg/dose IV), started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours at age 15 days</td>
<td>Birth through 6 weeks</td>
</tr>
<tr>
<td>ZDV</td>
<td>&lt;30 weeks’ gestation at birth: 2 mg/kg body weight/dose PO (or 1.5 mg/kg/dose IV) started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours after age 4 weeks</td>
<td>Birth through 6 weeks</td>
</tr>
</tbody>
</table>

**Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants of Women who Received No Antepartum Antiretroviral Prophylaxis (initiated as soon after delivery as possible)**

<table>
<thead>
<tr>
<th>In addition to ZDV as shown above, administer NVP</th>
<th>Birth weight 1.5–2 kg: 8 mg/dose PO</th>
<th>Birth weight &gt;2 kg: 12 mg/dose PO</th>
<th>3 doses in the first week of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st dose within 48 hrs of birth (birth–48 hrs)</td>
<td>2nd dose 48 hrs after 1st</td>
<td>3rd dose 96 hrs after 2nd</td>
</tr>
</tbody>
</table>

* A 6-week course of neonatal zidovudine is generally recommended. A 4-week neonatal zidovudine chemoprophylaxis regimen may be considered when the mother has received standard ART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence.

**Key to Abbreviations:** IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine

The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 4 mg/kg body weight orally (PO) twice daily, beginning as soon after birth as possible and preferably within 6 to 12 hours of delivery (see Table 8). If an infant is unable to tolerate oral medications, the zidovudine prophylaxis regimen can be administered intravenously (IV). The zidovudine dosing requirements differ for...
premature infants and term infants (see Table 8 and Antiretroviral Drug Dosing for Premature Infants).

PKs and safety of the single-dose nevirapine regimen to mother and infant\textsuperscript{64} and chronic prophylactic nevirapine administration to infants to prevent HIV transmission during breastfeeding have been studied.\textsuperscript{65} The 3-dose extended nevirapine regimen that was used in NICHD-HPTN 040/PACTG1043 and is recommended for HIV-exposed infants whose mothers did not receive ARV during the antepartum period has also been studied.\textsuperscript{43} Nevirapine concentrations were measured in 14 newborns participating in a PK substudy during the second week of life and in single samples from 30 more newborns on Days 10 to 14. The median nevirapine elimination half-life was 30.2 hours (range: 17.8–50.3 hours) and the concentration remained greater than the target of 100 ng/mL in all infants through Day 10 of life.

**Antiretroviral Drug Dosing for Premature Infants**

Dosing recommendations for premature infants are available for only zidovudine (prophylaxis and therapy) and nevirapine (prophylaxis only) (see Table 8). Zidovudine is primarily cleared through hepatic glucuronidation to an inactive metabolite; this metabolic pathway is immature in neonates, leading to prolonged zidovudine half-life and decreased clearance compared with older infants. Clearance is further decreased in premature infants because their hepatic metabolic function is less mature than in term infants.\textsuperscript{66,67} The recommended zidovudine dosage for preterm infants is shown in Table 8.

Nevirapine PKs have been described in low-birth-weight neonates receiving a single postnatal prophylaxis dose of the drug. In a study of 81 infants <37 weeks' gestation, of which 29.6% were small for gestational age, half-lives were very long—median 59 hours in infants whose mothers received single-dose nevirapine and 69 hours in infants whose mothers did not receive single-dose nevirapine. AUC of nevirapine was higher and clearance lower (\(P < .0001\)) in small-for-gestational-age infants.\textsuperscript{68}

Use of ARV drugs other than zidovudine and nevirapine cannot be recommended at this time in premature infants because data on dosing and safety are lacking. Immature renal and hepatic metabolism can increase the risk of overdosing and toxicity. However, in situations where there is a high risk of infant HIV infection, consultation with a pediatric HIV specialist is recommended to determine if the benefits of combination ARV prophylaxis with drugs in addition to or other than zidovudine and nevirapine outweigh the potential risks.

**Breastfeeding Infants of Mothers Diagnosed with HIV Infection Postpartum**

Breastfeeding should be stopped until infection is confirmed or ruled out in women who are breastfeeding and suspected to have become HIV infected. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of being HIV infected but whose infection is not yet confirmed and who want to continue to breastfeed. If HIV infection is ruled out, breastfeeding can resume. Breastfeeding is not recommended for women with documented HIV infection in the United States, including those receiving cART (see Infant Feeding Practices and Risk of HIV Transmission).\textsuperscript{69}

The risk of acquisition of HIV associated with breastfeeding depends on multiple infant and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.\textsuperscript{70} Infants of women who develop acute HIV infection while breastfeeding are at greater risk of becoming infected than are those of women with chronic HIV infection\textsuperscript{71} because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.\textsuperscript{72}

Other than discontinuing breastfeeding, optimal strategies for managing infants born to HIV-infected mothers who breastfed their infants prior to HIV diagnosis have yet to be defined. Some experts would consider the use of post-exposure prophylaxis in infants for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance compared with other non-occupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure.\textsuperscript{73}

Several studies of infants breastfed by women with chronic HIV infection have shown that daily infant nevirapine or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.\textsuperscript{44-46}
The NICHD-HPTN 040/PACTG 1043 study demonstrated that combination ARV prophylaxis was more effective than zidovudine prophylaxis alone for preventing intrapartum transmission in mothers who have not received antepartum ARV drugs. However, whether the combination regimens in this trial are effective for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection is unknown.

Because of the high risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some experts would be to offer a combination ARV regimen that would be effective for treatment of HIV, should an infant become infected. If this route is chosen, current recommendations for treatment should guide selection of an appropriate combination ARV regimen (see the Pediatric Antiretroviral Guidelines). Regardless of whether post-exposure prophylaxis or “pre-emptive therapy” is chosen, the optimal duration of the intervention is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure. As in other situations, decisions regarding administration of a prophylactic or preemptive treatment regimen should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach.

Infants should be tested for HIV infection at baseline and 4 to 6 weeks, 3 months, and 6 months after recognition of maternal infection to determine HIV status. In infants younger than age 18 months, HIV NAT should be used for diagnosis. HIV DNA PCR testing may be preferable for infants who are receiving combination ARV prophylaxis or preemptive treatment, because HIV RNA assays may be less sensitive in the presence of combination ARVs, which might lower infant plasma viral RNA to undetectable levels. However, HIV DNA PCR assays available in the United States may not detect non-subtype B or group O HIV as well as many HIV RNA assays. Therefore, if non-subtype B or group O HIV infection in an infant is considered possible, both HIV DNA and RNA assays should be obtained from the infant. HIV antibody assays can be used in infants older than age 18 months.

If an infant is already receiving post-exposure ARV prophylaxis and is found to be HIV-infected, prophylaxis should be discontinued and treatment for HIV infection initiated with standard cART according to the Pediatric Antiretroviral Guidelines. Resistance testing should be performed and the cART regimen modified if needed (see the Pediatric Antiretroviral Guidelines).

References


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### Initial Postnatal Management of the HIV-Exposed Neonate

**Panel’s Recommendations**

- A complete blood count and differential should be performed on newborns as a baseline evaluation (BIII).
- If hematologic abnormalities are identified in infants receiving prophylaxis, decisions on whether to continue infant antiretroviral (ARV) prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered (CIII).
- Decisions about the timing of subsequent monitoring of hematologic parameters in infants depend on baseline hematologic values, gestational age at birth, clinical condition of the infants, the zidovudine dose being administered, receipt of other ARV drugs and concomitant medications, and maternal antepartum therapy (CIII).
- Some experts recommend more intensive monitoring of hematologic and serum chemistry and liver function assays at birth and when diagnostic HIV polymerase chain reaction tests are obtained in infants exposed to combination ARV drug regimens in utero or during the neonatal period (CIII).
- A recheck of hemoglobin and neutrophil counts is recommended 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens (AI).
- Routine measurement of serum lactate is not recommended. However, measurement can be considered if an infant develops severe clinical symptoms of unknown etiology (particularly neurologic symptoms) (CIII).
- Virologic tests are required to diagnose HIV infection in infants aged <18 months and should be performed within the first 14 to 21 days of life and at age 1 to 2 months and age 4 to 6 months (AII).
- To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to HIV-infected women should begin PCP prophylaxis at ages 4 to 6 weeks, after completing their ARV prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see the Pediatric Opportunistic Infections Guidelines) (AII).
- Health care providers should routinely inquire about premastication, instruct HIV-infected caregivers to avoid this practice, and advise on safer feeding options (AII).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

A complete blood count (CBC) and differential should be performed on HIV-exposed newborns before initiation of infant antiretroviral (ARV) drug prophylaxis. Decisions about the timing of hematologic monitoring of infants after birth depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the infants, which ARV drugs are being administered, receipt of concomitant medications, and maternal antepartum ARV drug regimen. Anemia is the primary complication seen in neonates given the standard 6-week postnatal zidovudine regimen. In PACTG 076, infants in the zidovudine group had lower hemoglobin levels at birth than those in the placebo group, with the maximal difference (1 g/dL) occurring at age 3 weeks. The lowest mean value for hemoglobin levels (10 g/dL) occurred at age 6 weeks in the zidovudine group. By age 12 weeks, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed between groups.

Some experts recheck hematologic values in healthy infants receiving zidovudine prophylaxis only if symptoms are present. Hematologic safety data are limited on administration of 4 mg/kg of zidovudine twice daily in infants. When administering this dosing regimen, some experts recheck hemoglobin and neutrophil counts routinely after 4 weeks of zidovudine prophylaxis and/or when diagnostic HIV polymerase chain reaction (PCR) tests are obtained.

In utero exposure to maternal combination ARV drug regimens may be associated with some increase in anemia and/or neutropenia compared with that seen in infants exposed to zidovudine alone. In PACTG 316, where 77% of mothers received antenatal combination therapy, significant Grade 3 or higher anemia
was noted in 13% and neutropenia in 12% of infants, respectively. Depending on the combination regimen the mother has received, some experts advise more intensive laboratory monitoring, including serum chemistry and transaminases at birth plus a CBC at the time of diagnostic HIV PCR testing; monitoring of bilirubin levels can be considered for infants exposed antenatally to atazanavir.

In addition, data are limited on infants receiving zidovudine in combination with other ARVs for prophylaxis. However, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine combination prophylaxis compared with those receiving zidovudine alone or zidovudine plus nevirapine. A recheck of hemoglobin levels and neutrophil counts, therefore, is recommended for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens 4 weeks after initiation of prophylaxis and/or at the time that diagnostic HIV PCR testing is done.

If hematologic abnormalities are found, decisions on whether to continue infant ARV prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether related symptoms are present, duration of infant prophylaxis, risk of HIV infection (as assessed by the mother’s history of ARV prophylaxis, viral load near delivery, and mode of delivery), and the availability of alternative interventions such as erythropoietin and transfusion. Consideration can be given to reducing the duration of infant prophylaxis from 6 to 4 weeks, as is the case in many European centers. In a recent prospective, observational study, the 4-week regimen was found to allow earlier recovery from anemia in otherwise healthy infants compared with the 6-week regimen. Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.

Hyperlactatemia has been reported in infants with in utero exposure to ARVs, but it appears to be transient and, in most cases, asymptomatic. Routine measurement of serum lactate is not recommended in asymptomatic neonates to assess for potential mitochondrial toxicity because the clinical relevance is unknown and the predictive value for toxicity appears poor. Serum lactate measurement should be considered, however, for infants who develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms. In infants with symptoms, if the levels are significantly abnormal (>5 mmol/L), ARV prophylaxis should be discontinued and an expert in pediatric HIV infection should be consulted regarding potential alternate prophylaxis.

To prevent Pneumocystis jirovecii pneumonia, all infants born to HIV-infected women should begin trimethoprim-sulfamethoxazole prophylaxis at age 6 weeks, after completion of the infant ARV prophylaxis regimen, unless there is adequate virologic test information to presumptively exclude HIV infection (see the Pediatric Opportunistic Infections Guidelines). HIV infection in infants should be diagnosed using HIV nucleic acid amplification virologic assays (NATs), which include DNA and RNA PCR and related assays. Maternal HIV antibody crosses the placenta and will be detectable in all HIV-exposed infants up to age 18 months; therefore, standard antibody tests should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed within the first 14 to 21 days of life and at age 1 to 2 months and age 4 to 6 months. Some experts also perform a virologic test at birth, especially in women who have not had good virologic control during pregnancy or if adequate follow-up of the infant may not be assured. A positive HIV virologic test should be confirmed as soon as possible with a second HIV virologic test on a different specimen. Two positive HIV tests constitute a diagnosis of HIV infection. Data do not indicate any delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the zidovudine regimen. However, the effect of maternal or infant exposure to combination ARV drug regimens on the sensitivity of infant virologic diagnostic testing—particularly using HIV RNA assays—is unknown. Therefore, although HIV RNA assays may be acceptable for diagnosis (particularly in older infants), HIV DNA PCR assays may be optimal for diagnosing infection in the neonatal period. Any newly diagnosed infant should undergo viral resistance testing by genotype and/or phenotype to assess for susceptibility to combination antiretroviral therapy.

HIV can be presumptively excluded with two or more negative tests: one at age 14 days or older and the
other at age 1 month or older. **Definitive** exclusion of HIV in non-breastfed infants can be based on two negative virologic tests, with one test performed at age 1 month or older and the other test at age 4 months or older. Many experts confirm HIV-negative status with an HIV antibody test at age 12 to 18 months. **Persistence of HIV antibodies can occasionally occur at or beyond age 18 months.** Alternative algorithms exist for presumptive and definitive HIV exclusion.12 This testing algorithm applies mainly to exposure to HIV subtype B, which is the predominant viral subtype found in the United States. Non-subtype B viruses predominate in some other parts of the world. Non-subtype B infection may not be detected by many commercially available nucleic acid tests, particularly HIV DNA PCR. Many of the newer HIV RNA assays have improved detection of non-subtype B HIV, but there are still variants that are either poorly detected or undetectable. If non-subtype B HIV infection is suspected based on maternal origins, then newer HIV RNA assays that have improved ability to detect non-subtype B HIV should be used as part of the initial diagnostic algorithm. Exposed infants also should be closely monitored and undergo definitive HIV serologic testing at age 18 months (see the Pediatric Antiretroviral Guidelines).

Following birth, HIV-exposed infants should have a detailed physical examination, and a thorough maternal history should be obtained. HIV-infected mothers may be coinfected with other pathogens that can be transmitted from mother to child, such as cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis. Infants born to mothers with such coinfections should undergo appropriate evaluation, as indicated by maternal CD4 T lymphocyte count and evidence of disease activity, to rule out transmission of additional infectious agents. The routine primary immunization schedule should be followed for HIV-exposed infants born to HIV-infected mothers. Modifications in the schedule for live virus vaccines may be required for infants with known HIV infection (see the Pediatric Opportunistic Infections Guidelines).

No evidence is available to enable the Panel to assess whether any changes in routine bathing practices, or timing of circumcision, are indicated for HIV-exposed newborns.

**Infant Feeding Practices and Risk of HIV Transmission**

In the United States, where safe infant feeding alternatives are available and free for women in need, HIV-infected women should not breastfeed their infants.15 Maternal receipt of combination ARV regimens is likely to reduce free virus in the breast milk, but the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and, therefore, may continue to pose a transmission risk.16 Late HIV transmission events in infancy have been reported in HIV-infected children suspected of acquiring HIV infection as a result of consuming premasticated food given to them by their caregivers. Phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history and investigations identified the practice of feeding premasticated foods to infants as a potential risk factor for HIV transmission. Health care providers should routinely inquire about premastication, instruct HIV-infected caregivers against this feeding practice, and advise on safer feeding options.17,18

**References**

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Data remain insufficient to address the effect that exposure to zidovudine or other antiretroviral (ARV) agents in utero might have on long-term risk of neoplasia or organ system toxicities in children. Data from follow-up of PACTG 076 infants through age 6 years did not indicate any differences in immunologic, neurologic, and growth parameters between infants who were exposed to the zidovudine regimen and those who received placebo, and no malignancies were noted.\(^1\)\(^2\) Data are conflicting regarding whether mitochondrial dysfunction is associated with perinatal exposure to ARV drugs. Children with in utero exposure to ARVs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction.\(^4\)\(^5\) It is also unclear from laboratory-based and long-term clinical studies of infants and preadolescent children with in utero exposure to ARV drugs whether residual effects of these medications result in clinical consequences.\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) Studies should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of the nucleoside analogue ARV drugs. Long-term follow-up should include annual physical examinations of all children exposed to ARV drugs. Innovative methods are needed to provide follow-up of infants, children, and youth with in utero exposure to ARV drugs. Information regarding such exposure should be part of ongoing permanent medical records for children, particularly those who are uninfected.

Evaluation is ongoing of early and late effects of in utero exposure to ARV drugs, including the Pediatric HIV/AIDS Cohort Study, Surveillance Monitoring of Antiretroviral Toxicity Study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and the Centers for Disease Control and Prevention. Because most of the available follow-up data relate to in utero exposure to antenatal zidovudine alone and most HIV-infected pregnant women currently receive combination ARV drug regimens, it is critical that studies to evaluate potential adverse effects of in utero drug exposure continue to be supported. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning in utero exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defect and cancer registries to identify potential adverse outcomes.

References


One of the major achievements in HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group 076 (PACTG 076) clinical trial that administration of zidovudine to pregnant women and their infants could reduce risk of perinatal transmission by nearly 70%. Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. A number of regimens have been identified that are effective in reducing perinatal transmission in resource-limited countries (see Supplemental Table 1). This Appendix provides a table summarizing results of major studies of antiretroviral (ARV) prophylaxis to prevent perinatal transmission and a brief discussion of lessons learned. In many cases, direct comparison of results from trials of these regimens is not possible because the studies involved diverse patient populations residing in different geographic locations, infected with diverse viral subtypes, and with different infant feeding practices. However, some generalizations are relevant to understanding use of ARV drugs for prevention of perinatal transmission in both resource-limited and resource-rich countries.

Combination antenatal prophylaxis taken over a longer duration is more effective than a short-course single-drug regimen in reducing perinatal transmission.

The use of ARV drugs to prevent transmission is highly effective, even in HIV-infected women with advanced disease. Efficacy has been demonstrated for a number of short-course ARV regimens, including those with zidovudine alone; zidovudine plus lamivudine; single-dose nevirapine; and single-dose nevirapine combined with either short-course zidovudine or zidovudine/lamivudine. In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission. In addition, for prevention of perinatal transmission, administration of ARV drugs during the antepartum, intrapartum, and postpartum periods is superior to administration of ARV drugs only during the antepartum and intrapartum periods or intrapartum and postpartum periods.

Almost all trials in resource-limited countries have included oral intrapartum prophylaxis, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. Perinatal transmission is reduced by regimens with antenatal components starting as late as 36 weeks’ gestation and lacking an infant prophylaxis component. However, longer-duration antenatal ARV prophylaxis is more effective than shorter-duration ARV prophylaxis. The European National Study of HIV in Pregnancy and Childhood demonstrated that each additional week of a triple-drug regimen corresponded to a 10% reduction in risk of transmission. More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.

No trials have directly compared the efficacy of zidovudine plus single-dose nevirapine with a triple-drug ARV regimen for prevention of in utero transmission in women with higher CD4 T lymphocyte (CD4) cell counts. In African women with CD4 cell counts ranging from 200 to 500 cells/mm³, the Kesho Bora trial compared a triple-ARV drug prophylaxis regimen with zidovudine plus single-dose nevirapine prophylaxis, both started at 28 weeks’ gestation or later, with women in the triple-drug arm continuing the drugs until breastfeeding ceased; those in the zidovudine/single-dose nevirapine arm did not receive postnatal prophylaxis. Although the rate of postnatal transmission was significantly lower in the triple-drug arm than in the zidovudine/single-dose nevirapine arm without postnatal prophylaxis, the rates of transmission at birth were similar in women randomized to a triple-drug regimen (1.8%) and women randomized to antepartum zidovudine/single-dose nevirapine (2.5%); for women with CD4 cell counts from 350 to 500 cells/mm³, the rate of infection at birth was 1.7% in each arm. However, the study was not powered to address equivalence between regimens in preventing in utero infection in women with higher CD4 cell counts and the drugs in both arms were administered antepartum for only 6 weeks.
Regimens that do not include maternal ARV prophylaxis during pregnancy have been evaluated because some women may lack antenatal care and present for prenatal care for the first time when they go into labor. Regimens that include only intrapartum and postpartum drug administration also have been shown to be effective in reducing perinatal transmission.4-6 However, without continued infant post-exposure prophylaxis, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor drugs (zidovudine/lamivudine) is not effective in reducing transmission.5 The SAINT trial demonstrated that intrapartum/postpartum zidovudine/lamivudine and single-dose intrapartum/newborn nevirapine are similar in efficacy and safety.6

**Combination infant ARV prophylaxis is recommended in the United States for infants whose mothers have not received antenatal ARV drugs.**

In some situations, it may be impossible to administer maternal antepartum and intrapartum therapy and only infant prophylaxis may be an option. In the absence of maternal therapy, the standard infant prophylaxis regimen of 6 weeks of zidovudine was effective in reducing HIV transmission compared with no prophylaxis, based on epidemiologic data in resource-rich countries.18 A trial in Malawi in breastfeeding infants demonstrated that adding 1 week of zidovudine therapy to infant single-dose nevirapine reduced risk of transmission by 36% compared with infant single-dose nevirapine alone.7

To define the optimal infant prophylaxis regimen in the absence of maternal antepartum ARV drug administration in a formula-fed population of infants such as in the United States, the NICHD-HPTN 040/P1043 (NCT00099359) clinical trial compared 3 infant ARV regimens in formula-fed infants born to mothers who did not receive ARV drugs during the current pregnancy: standard 6 weeks of zidovudine alone versus 6 weeks of zidovudine plus 3 doses of nevirapine given in the first week of life (first dose birth to 48 hours; second dose 48 hours after first dose; third dose 96 hours after second dose) versus 6 weeks of zidovudine plus lamivudine and nelfinavir given from birth through age 2 weeks.19 The study demonstrated that both the dual and triple combination regimens reduced risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with zidovudine alone, although there was more hematologic toxicity with the triple regimen (see Supplemental Table 1). Based on these data, combination ARV prophylaxis is now recommended in the United States for infants whose mothers have not received antenatal ARV drugs, with the dual regimen of zidovudine plus 3 doses of nevirapine in the first week of life being preferred due to lower rates of toxicity (see Infant Antiretroviral Prophylaxis).

**Adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis.**

Several studies in formula-fed and breastfed populations in resource-limited countries have found that adding maternal/infant single-dose nevirapine to a maternal short-course zidovudine or zidovudine/lamivudine regimen increased efficacy compared with the short-course regimen alone.15,20,21 However, PACTG 316, a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas, demonstrated that for non-breastfeeding women in resource-rich countries, the addition of single-dose nevirapine did not offer significant benefit in the setting of combination ARV prophylaxis throughout pregnancy and very low viral load at the time of delivery.22 Thus, adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis (see Intrapartum Antiretroviral Therapy/Prophylaxis).

**Breastfeeding by HIV-infected women is not recommended in the United States.**

Breastfeeding by HIV-infected women (including those receiving ARV drugs) is not recommended in the United States where replacement feeding is affordable, feasible, acceptable, sustainable, and safe and the risk of infant mortality due to diarrheal and respiratory infections is low.23 Clinical trials have demonstrated that both infant prophylaxis (primarily using daily infant nevirapine) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease postnatal infection (see Supplemental Table 1).2,17,24-29 However, maternal triple-drug prophylaxis may be less effective than infant prophylaxis if the maternal
regimen is first started postpartum or late in pregnancy because it takes several weeks to months before full viral suppression in breast milk is achieved. Importantly, although significantly lowering the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis completely eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for HIV-infected women in the United States (including those receiving combination ARV drug regimens). Finally, both infant nevirapine prophylaxis and maternal triple-drug prophylaxis during breastfeeding may be associated with development of ARV drug resistance in infants who become infected despite prophylaxis; multi-class drug resistance has been described in breastfeeding infants infected despite maternal triple-drug prophylaxis.

Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 1 of 6)

<table>
<thead>
<tr>
<th>Study; Location(s); Mode of Infant Feeding</th>
<th>Antiretroviral Drugs</th>
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<th>Postpartum</th>
<th>Perinatal Transmission Rate and Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACTG 076; United States, France; Formula feeding</td>
<td>ZDV vs. placebo</td>
<td>Long (from 14 weeks) IV IP</td>
<td>Long (6 weeks); infant only</td>
<td>Perinatal transmission at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).</td>
</tr>
<tr>
<td>CDC short-course ZDV trial; Thailand; Formula feeding</td>
<td>ZDV vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>None</td>
<td>Perinatal transmission at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).</td>
</tr>
<tr>
<td>DITRAME (ANRS 049a) trial; Ivory Coast, Burkina Faso; Breastfeeding</td>
<td>ZDV vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>Short (1 week); mother only</td>
<td>Perinatal transmission was 18.0% in ZDV arm vs. 27.5% in placebo arm at 6 months (38% efficacy) and 21.5% vs. 30.6% at 15 months (30% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).</td>
</tr>
<tr>
<td>CDC short-course ZDV trial; Ivory Coast; Breastfeeding</td>
<td>ZDV vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>None</td>
<td>Perinatal transmission was 16.5% in ZDV arm vs. 26.1% in placebo arm at 3 months (37% efficacy). Perinatal transmission was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).</td>
</tr>
<tr>
<td>PETRA trial; South Africa, Tanzania, and Uganda; Breastfeeding and formula feeding</td>
<td>AP/IP/PP ZDV + 3TC vs. IP/PP ZDV + 3TC vs. IP-only ZDV + 3TC vs. placebo</td>
<td>Short (from 36 weeks) Oral IP</td>
<td>Short (1 week); mother and infant</td>
<td>Perinatal transmission was 5.7% at 6 weeks for AP/IP/PP ZDV + 3TC, 8.9% for IP/PP ZDV + 3TC, 14.2% for IP-only ZDV + 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively). Perinatal transmission was 14.9% at 18 months for AP/IP/PP ZDV + 3TC, 18.1% for IP/PP ZDV + 3TC, 20.0% for IP-only ZDV + 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).</td>
</tr>
<tr>
<td>HIVNET 012 trial; Uganda; Breastfeeding</td>
<td>SD NVP vs. ZDV</td>
<td>No AP ARV Oral IP: SD NVP vs. oral ZDV</td>
<td>SD NVP within 72 hours of birth, infant only vs. ZDV (1 week); infant only</td>
<td>Perinatal transmission was 11.8% in NVP arm vs. 20.0% in ZDV arm at 6–8 weeks (42% efficacy); 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).</td>
</tr>
</tbody>
</table>
### Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 2 of 6)

<table>
<thead>
<tr>
<th>Study; Location(s); Mode of Infant Feeding</th>
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<tbody>
<tr>
<td>SAINT trial; South Africa; Breastfeeding and formula feeding</td>
<td>SD NVP vs. ZDV + 3TC</td>
<td>No AP ARV Oral IP: SD NVP vs. ZDV + 3TC</td>
<td>SD NVP within 48 hours of birth, mother and infant vs. ZDV + 3TC (1 week); mother and infant</td>
<td>Perinatal transmission was 12.3% in SD NVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, ( P = 0.11 )).</td>
</tr>
<tr>
<td>Perinatal HIV Prevention Trial (PHPT-1); Thailand; Formula feeding</td>
<td>Four ZDV regimens with different durations of AP and infant PP administration; no placebo</td>
<td>Long (from 28 weeks), short (from 36 weeks) Oral IP</td>
<td>Long (6 weeks), short (3 days); infant only</td>
<td>Short-short arm stopped at interim analysis (10.5%). Perinatal transmission was 6.5% in long-long arm vs. 6.6% in short-long arm at 6 months (no statistical difference). <em>In utero</em> transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.0%).</td>
</tr>
<tr>
<td>PACTG 316 trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States; Formula feeding</td>
<td>SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)</td>
<td>Non-study ARV regimen Oral IP: placebo vs. SD NVP + IV ZDV</td>
<td>Placebo vs. SD NVP within 72 hours of birth + nonstudy ARV drugs (ZDV); infant only</td>
<td>77% of women received dual- or triple-combination ARV regimens during pregnancy. Trial stopped early because of very low perinatal transmission in both arms: 1.4% in SD NVP arm vs. 1.6% in placebo arm (53% of perinatal transmission was <em>in utero</em>).</td>
</tr>
<tr>
<td>Perinatal HIV Prevention Trial (PHPT-2); Thailand; Formula feeding</td>
<td>ZDV alone vs. ZDV + maternal and infant SD NVP vs. ZDV + maternal SD NVP</td>
<td>ZDV from 28 weeks Oral IP: ZDV alone or ZDV + SD NVP</td>
<td>ZDV for 1 week with or without SD NVP; infant only</td>
<td>ZDV-alone arm was stopped because of higher perinatal transmission than the NVP-NVP arm (6.3% vs. 1.1%). In arms in which the mother received SD NVP, perinatal transmission rate did not differ significantly between the infant receiving or not receiving SD NVP (2.0% vs. 2.8%).</td>
</tr>
<tr>
<td>DITRAME Plus (ANRS 1201.0) trial; Ivory Coast; Breastfeeding and formula feeding</td>
<td>Open label, ZDV + SD NVP</td>
<td>ZDV from 36 weeks Oral IP: ZDV plus SD NVP</td>
<td>SD NVP + ZDV for 1 week; infant only</td>
<td>Perinatal transmission was 6.5% (95% CI, 3.9%–9.1%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.</td>
</tr>
<tr>
<td>DITRAME Plus (ANRS 1201.1) trial; Ivory Coast; Breastfeeding and formula feeding</td>
<td>Open label, ZDV + 3TC + SD NVP</td>
<td>ZDV + 3TC from 32 weeks (stopped at 3 days PP) Oral IP: ZDV + 3TC + SD NVP</td>
<td>SD NVP + ZDV for 1 week; infant only</td>
<td>Perinatal transmission was 4.7% (95% CI, 2.4%–7.0%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.</td>
</tr>
<tr>
<td>NVAZ trial; Malawi; Breastfeeding</td>
<td>Neonatal SD NVP vs. SD NVP + ZDV</td>
<td>No AP or IP ARV (latecomers)</td>
<td>SD NVP with or without ZDV for 1 week; infant only</td>
<td>Perinatal transmission was 15.3% in SD NVP + ZDV arm and 20.9% in SD NVP-only arm at 6–8 weeks. Perinatal transmission rate at 6–8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).</td>
</tr>
</tbody>
</table>
### Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 3 of 6)

<table>
<thead>
<tr>
<th>Study; Location(s); Mode of Infant Feeding</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Postnatal NVP + ZDV trial; Malawi; Breasftfeeding</strong></td>
<td>Neonatal SD NVP vs. SD NVP + ZDV</td>
<td>No AP ARV Oral IP: SD NVP</td>
<td>SD NVP with or without ZDV for 1 week; infant only</td>
<td>Perinatal transmission was 16.3% in NVP + ZDV arm and 14.1% in SD NVP-only arm at 6–8 weeks (difference not statistically significant). Perinatal transmission rate at 6–8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.</td>
</tr>
<tr>
<td><strong>Post-Exposure Infant Prophylaxis; South Africa; Breastfeeding and formula feeding</strong></td>
<td>Neonatal SD NVP vs. ZDV for 6 weeks</td>
<td>No AP or IP ARV</td>
<td>SD NVP vs. ZDV for 6 weeks</td>
<td>For formula-fed infants only, perinatal transmission was 14.3% in SD NVP arm vs. 14.1% in ZDV arm at 6 weeks (not significant, ( P = 0.30 )). For breastfed infants only, perinatal transmission was 12.2% in SD NVP arm and 19.6% in ZDV arm (( P = 0.03 )).</td>
</tr>
<tr>
<td><strong>Mashi; Botswana; Breastfeeding and formula feeding</strong></td>
<td>Initial: short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding Revised: short-course ZDV + infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 cell counts &lt;200 cells/mm³ receive combination therapy</td>
<td>First Randomization: ZDV from 34 weeks Oral IP: ZDV + either SD NVP or placebo Second Randomization: Breastfeeding + ZDV (infant) 6 months + SD NVP; infant only vs. Formula feeding + ZDV (infant) 4 weeks + SD NVP; infant only</td>
<td>Initial Design: In formula-feeding arm, perinatal transmission at 1 month was 2.4% in maternal and infant SD NVP arm and 8.3% in placebo arm (( P = 0.05 )). In breastfeeding + infant ZDV arm, perinatal transmission at 1 month was 8.4% in SD NVP arm and 4.1% in placebo arm (difference not statistically significant). Revised Design: Perinatal transmission at 1 month was 4.3% in maternal + infant SD NVP arm and 3.7% in maternal placebo + infant SD NVP arm (no significant difference; no interaction with mode of infant feeding). Perinatal transmission at 7 months was 9.1% in breastfeeding + ZDV arm and 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding + ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% breastfeeding + ZDV arm versus 14.2% formula-feeding arm.</td>
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</tbody>
</table>
| **SWEN; Uganda, Ethiopia, India; Breastfeeding** | SD NVP vs. NVP for 6 weeks | No AP ARV Oral IP: SD NVP | Infant SD NVP vs. NVP for 6 weeks | Postnatal Infection in Infants Uninfected at Birth:  
• Perinatal transmission at 6 weeks was 5.3% in SD NVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, \( P = 0.009 \)).  
• Perinatal transmission at 6 months was 9.0% in SD NVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, \( P = 0.16 \)). HIV-free survival was significantly lower in extended NVP arm at both 6 weeks and 6 months of age. |
Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 4 of 6)

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<tr>
<th>Study; Location(s); Mode of Infant Feeding</th>
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<th>Perinatal Transmission Rate and Efficacy</th>
</tr>
</thead>
</table>
| PEPI-Malawi Trial; Malawi; Breastfeeding | SD NVP + ZDV for 1 week (control) vs. two extended infant regimens (NVP or NVP/ZDV) for 14 weeks | No AP ARV Oral IP: SD NVP (if mother presents in time) | Infant SD NVP + ZDV for 1 week (control) vs. control + NVP for 14 weeks vs. control + NVP/ZDV for 14 weeks | Postnatal Infection in Infants Uninfected at Birth:  
• Perinatal transmission at age 6 weeks was 5.1% in control vs. 1.7% in extended NVP (67% efficacy) and 1.6% in extended NVP/ZDV arms (69% efficacy).  
• Perinatal transmission at age 9 months was 10.6% in control vs. 5.2% in extended NVP (51% efficacy) and 6.4% in extended NVP/ZDV arms (40% efficacy).  
No significant difference in perinatal transmission between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV. |
| MITRA; Tanzania; Breastfeeding | Infant 3TC for 6 months (observational) | ZDV/3TC from 36 weeks through labor | Maternal ZDV/3TC for 1 week, infant 3TC for 6 months | Perinatal transmission at age 6 months was 4.9% (postnatal perinatal transmission between ages 6 weeks and 6 months was 1.2%). |
| Kisumu Breastfeeding Study (KiBS); Kenya; Breastfeeding | Maternal triple-drug prophylaxis (observational) | ZDV/3TC/NVP (NFV if CD4 cell count >250 cells/mm³) from 34 weeks through labor | Maternal ZDV/3TC/NVP (NFV if CD4-cell count >250 cells/mm³) for 6 months, infant SD NVP | Perinatal transmission at age 6 months was 5.0% (postnatal perinatal transmission between ages 7 days and 6 months was 2.6%). |
| MITRA-PLUS; Tanzania; Breastfeeding | Maternal triple-drug prophylaxis (observational) | ZDV/3TC/NVP (NFV if CD4 cell count >200 cells/mm³) from 34 weeks through labor | Maternal ZDV/3TC/NVP (NFV if CD4-cell count >200 cells/mm³) for 6 months, infant SD NVP | Perinatal transmission at age 6 months was 5.0% (postnatal perinatal transmission between ages 6 weeks and 6 months was 0.9%), not significantly different from 6-month infant prophylaxis in MITRA. |
| Kesho Bora; Multi-African; Breastfeeding primarily | Antepartum ZDV/SD NVP with no postnatal prophylaxis vs. maternal triple-drug prophylaxis in women with CD4 cell counts 200–500 cells/mm³ | Arm 1: ZDV/3TC/LPV/r  
Arm 2: ZDV + SD NVP  
From 28 weeks through labor | Arm 1: Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP + ZDV for 1 week  
Arm 2: Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis), infant SD NVP + ZDV for 1 week (no further postnatal prophylaxis) | Perinatal transmission at birth was 1.8% with maternal triple-drug prophylaxis Arm 1 and 2.5% with ZDV/SD NVP Arm 2, not significantly different. In women with CD4 cell counts 350–500 cells/mm³, perinatal transmission at birth was 1.7% in both arms.  
Perinatal transmission at age 12 months was 5.4% with maternal triple-drug prophylaxis Arm 1 and 9.5% with ZDV/SD NVP (with no further postnatal prophylaxis after 1 week) Arm 2 ($P = 0.029$). |
## Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 5 of 6)

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</thead>
<tbody>
<tr>
<td>Mma Bana; Botswana; Breastfeeding</td>
<td>Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 cell counts &gt;200 cells/mm³</td>
<td>Arm 1: ZDV/3TC/ABC</td>
<td>Arm 1: Maternal ZDV/3TC/ABC for 6 months, infant SD NVP + ZDV for 4 weeks</td>
<td>Perinatal transmission at age 6 months overall was 1.3%; 2.1% in ZDV/3TC/ABC Arm 1 and 0.4% in ZDV/3TC/LPV/r Arm 2 (P = 0.53).</td>
</tr>
<tr>
<td>BAN; Malawi; Breastfeeding</td>
<td>Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 cell counts ≥250 cells/mm³</td>
<td>No AP drugs</td>
<td>Arm 1 (Control): Maternal ZDV/3TC for 1 week, infant SD NVP + ZDV/3TC for 1 week</td>
<td>Postnatal Infection in Infants Uninfected at Age 2 Weeks:</td>
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<td>Arm 2: ZDV/3TC + SD NVP</td>
<td>Arm 2: Control as above, then maternal ZDV/3TC/LPV/r for 6 months</td>
<td>• Perinatal transmission at age 28 weeks was 5.7% in control Arm 1; 2.9% in maternal triple-drug prophylaxis Arm 2 (P = 0.009 vs. control); 1.7% in infant NVP Arm 3 (P &lt;0.001 vs. control).</td>
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<td>Arm 3: ZDV/3TC + SD NVP</td>
<td>Arm 3: Control as above, then infant NVP for 6 months</td>
<td>• Perinatal transmission at age 48 weeks was 7.0% in control Arm 1; 4% in maternal triple-drug prophylaxis Arm 2 (P = 0.0273 vs. control); 4% in infant NVP Arm 3 (P = 0.0027 vs. control).</td>
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<td>No significant difference between maternal triple-drug prophylaxis Arm 2 and infant NVP Arm 3 (P = 0.12 at 28 weeks and P = 0.426 at 48 weeks).</td>
</tr>
<tr>
<td>HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe; Breastfeeding</td>
<td>Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP</td>
<td>AP drugs allowed if required for maternal health</td>
<td>All infants received daily NVP from birth through age 6 weeks.</td>
<td>In infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3%–1.8%) in the extended NVP Arm 1 and 2.4% (1.3%–3.6%) in the placebo Arm 2 (P = 0.048).</td>
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<td>Arm 1: Daily infant NVP from 6 weeks through 6 months of age</td>
<td>Arm 1: Daily infant NVP from 6 weeks through 6 months of age</td>
<td>At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-drug ARV regimen for treatment of HIV.</td>
</tr>
<tr>
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<td>Arm 2: Daily infant placebo from age 6 weeks through age 6 months</td>
<td>Arm 2: Daily infant placebo from age 6 weeks through age 6 months</td>
<td>For mothers receiving triple-drug ARV regimens at the time of randomization, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.2% and not statistically different between extended NVP Arm 1 (0.5%) and placebo Arm 2 (0%).</td>
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<td>For mothers with CD4 cell counts &gt;350 cells/mm³ who were not receiving triple-drug ARV regimens, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.7% (0%–1.5%) in the extended NVP Arm 1 and 2.8% (1.3%–4.4%) in the placebo Arm 2 (P = 0.014).</td>
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</tbody>
</table>
### Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 6 of 6)

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<tr>
<td>NICHD-HPTN 040/PACTG 1043 trial; Argentina, Brazil, South Africa, United States; Formula feeding</td>
<td>Infant prophylaxis with 6 weeks ZDV vs. 6 weeks infant ZDV plus three doses of NVP in first week of life vs. 6 weeks infant ZDV plus 2 weeks of 3TC/NFV</td>
<td>No AP drugs if mother presented early enough, IV ZDV during labor through delivery</td>
<td>Arm 1 (control): Infant ZDV for 6 weeks Arm 2: Control as above plus NVP with first dose within 48 hours of birth, second dose 48 hours later, and third dose 96 hours after the second dose Arm 3: Control as above, plus 3TC and NFV from birth through 2 weeks of age</td>
<td>IP HIV transmission among infants with negative HIV test at birth: 4.8% (3.2%–7.1%) ZDV (Arm 1) vs. 2.2% (1.2%–3.9%) in ZDV plus NVP (Arm 2) (P = 0.046 compared with Arm 1) vs. 2.4% (1.4%–4.3%) in ZDV plus 3TC/NFV (Arm 3) (P = 0.046 compared with Arm 1). Overall HIV transmission rates, including in utero infection: 11.0% (8.7%–14.0%) ZDV (Arm 1) vs. 7.1% (5.2%–9.6%) in ZDV plus NVP (Arm 2) (P = 0.035 compared with Arm 1) vs. 7.4% (5.4%–9.9%) in ZDV plus 3TC/NFV (Arm 3) (P = 0.035 compared with Arm 1). Grade 3 or 4 neutropenia more frequent in ZDV/3TC/NFV Arm 3, 70 infants, compared with ZDV alone Arm 1, 33 infants, or ZDV/NVP Arm 2, 32 infants (P &lt;0.001).</td>
</tr>
</tbody>
</table>

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**Key to Acronyms:**

- 3TC = lamivudine
- ABC = abacavir
- AP = antepartum
- ARV = antiretroviral
- CDC = Centers for Disease Control and Prevention
- CI = confidence interval
- IP = intrapartum
- IV = intravenous
- LPV/r = ritonavir-boosted lopinavir
- NFV = nelfinavir
- NVP = nevirapine
- PP = postpartum
- SD = single-dose
- ZDV = zidovudine

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**References**


Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy  (Last updated March 28, 2014; last reviewed March 28, 2014)

Glossary of Terms for Supplement

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenic</td>
<td>Producing or tending to produce cancer</td>
</tr>
<tr>
<td>Clastogenic</td>
<td>Causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
<td>Genotoxic</td>
<td>Damaging to genetic material such as DNA and chromosomes</td>
</tr>
<tr>
<td>Mutagenic</td>
<td>Inducing or capable of inducing genetic mutation</td>
</tr>
<tr>
<td>Teratogenic</td>
<td>Interfering with fetal development and resulting in birth defects</td>
</tr>
</tbody>
</table>

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Six nucleoside analogue reverse transcriptase inhibitors (nucleoside NRTIs) and one nucleotide reverse transcriptase inhibitor (nucleotide NRTI) are currently approved; zalcitabine is no longer available in the United States. Data are available from clinical trials in human pregnancy for the nucleoside NRTIs zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleotide NRTI tenofovir. The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. Tenofovir, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base and, hence, requires only two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnancy and to the infant, see NRTI Drugs and Mitochondrial Toxicity.

Abacavir (Ziagen, ABC)

(Last updated March 28, 2014; last reviewed March 28, 2014)

Abacavir is classified as Food and Drug Administration (FDA) Pregnancy Category C.

Animal Carcinogenicity Studies

Abacavir is mutagenic and clastogenic in some in vitro and in vivo assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.

Reproduction/Fertility

No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).

Teratogenicity/Developmental Toxicity

Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve [AUC]). Toxicity to the developing embryo and fetus (increased resorptions and

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decreased fetal body weight) occurred with administration of 500 mg/kg/day of abacavir to pregnant rodents. The offspring of female rats were treated with 500 mg/kg of abacavir, beginning at embryo implantation and ending at weaning. In these animals, an increased incidence of stillbirth and lower body weight was seen throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to abacavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with abacavir. Among cases of first-trimester abacavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.1% (26 of 848 births; 95% confidence interval [CI], 2.0%-4.5%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.

**Placental and Breast Milk Passage**

Abacavir crosses the placenta and is excreted into the breast milk of lactating rats. In the Mma Bana study, at 1 month postpartum, the median breast milk-to-plasma ratio for abacavir was 0.85 in the 15 women tested, and the drug was detected in the plasma of 1/9 breastfeeding infants whose mothers were receiving abacavir.

**Human Studies in Pregnancy**

A Phase I study of abacavir in pregnant women indicates that the AUC drug concentration during pregnancy was similar to that at 6 to 12 weeks postpartum and in non-pregnant individuals. Thus, no dose adjustment for abacavir is needed during pregnancy. Serious hypersensitivity reactions have been associated with abacavir therapy in non-pregnant adults, but these reactions have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will occur within hours and may include life-threatening hypotension and death.

**References**


**Didanosine (Videx, ddI)**

*(Last updated March 28, 2014; last reviewed March 28, 2014)*

Didanosine is classified as FDA Pregnancy Category B.

**Animal Carcinogenicity Studies**

Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies at human exposures of 0.7 to 1.7 times in mice and 3 times in rats have been negative.

**Reproduction/Fertility**

At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.

**Teratogenicity/Developmental Toxicity**

No evidence of teratogenicity or toxicity was observed with administration of didanosine at 12 and 14 times human exposure, respectively, in pregnant rats and rabbits. Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.8% (20 of 413 births; 95% CI, 3.0%–7.4%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance. All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be closely monitored.

**Placental and Breast Milk Passage**

Placental transfer of didanosine was *low-moderate* in a Phase I/II safety and pharmacokinetic (PK) study. This was confirmed in a study of 100 HIV-infected pregnant women who were receiving nucleoside reverse transcriptase inhibitors (generally as part of a two- or three-drug combination antiretroviral [ARV] regimen). At the time of delivery, cord-to-maternal blood ratio for didanosine (*n* = 10) was 0.38 (range 0.0–2.0) and in 15 of 24 (62%) samples, cord blood concentrations for didanosine were below the limits of detection. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. It is not known if didanosine is excreted in human breast milk.

**Human Studies in Pregnancy**

A Phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum. The drug was well tolerated during pregnancy by the women and the fetuses. PK parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

Lactic acidosis, fatal in some cases, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents; the Food and Drug Administration and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination. These two drugs should be prescribed together to pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

**References**


Emtricitabine (Emtriva, FTC)
(Last updated March 28, 2014; last reviewed March 28, 2014)
Emtricitabine is classified as Food and Drug Administration (FDA) Pregnancy Category B.

Animal Carcinogenicity Studies
Emtricitabine was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 26 times the human systemic exposure or in rats at doses up to 31 times the human systemic exposure at the therapeutic dose.

Reproduction/Fertility
No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by area under the curve [AUC]) approximately 60-fold higher in female mice and 140-fold higher in male rats than observed with human exposure at the recommended therapeutic dose.

Teratogenicity/Developmental Toxicity
Incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice that resulted in systemic drug exposure 60-fold higher than observed with human exposure at recommended doses or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 2-fold increased risk of overall birth defects. No such increase in birth defects has been observed with emtricitabine. Among cases of first-trimester emtricitabine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (27 of 1,068 births; 95% CI, 1.7%–3.7%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.

Placental and Breast Milk Passage
Emtricitabine has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits. Emtricitabine has been shown to have excellent placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine once daily during pregnancy, mean cord blood concentration was 300 ± 268 ng/mL and the mean ratio of cord blood/maternal emtricitabine concentrations was 1.17 ± 0.6 (n = 9). In a study of 15 women enrolled in IMPAACT P1026s who received emtricitabine during pregnancy, the mean cord to maternal blood ratio was 1.2 (90% CI, 1.0–1.5). In 8 women enrolled in PACTG 394 who were given a single dose of 600 mg emtricitabine with 900 mg of tenofovir, the median cord blood emtricitabine concentration was 717 ng/mL (range 21–1,072), and the median cord blood/maternal ratio was 0.85 (range, 0.46–1.07). Emtricitabine is excreted into human milk. In a study in the Ivory Coast, 5 HIV-infected women who chose to exclusively breastfeed their newborn infants were given 400 mg emtricitabine, 600 mg tenofovir, and 200 mg of nevirapine at onset of labor, followed by 200 mg of emtricitabine and 300 mg of tenofovir once daily for 7 days postpartum. The median minimal and maximal concentrations of emtricitabine in breast milk were 177 and 679 ng/mL, respectively (interquartile ranges 105–254 and 658–743 ng/mL, respectively), well above the estimated emtricitabine IC50 for HIV-1.

Human Studies in Pregnancy
Emtricitabine pharmacokinetic (PK) parameters have been evaluated in 18 HIV-infected pregnant women receiving antiretroviral therapy including emtricitabine (200 mg once daily) at 30 to 36 weeks’ gestation and 6 to 12 weeks postpartum. Emtricitabine exposure was modestly lower during the third trimester (8.6 µg*h/mL [5.2–15.9]) compared with the postpartum period (9.8 µg*h/mL [7.4–30.3]). Two-thirds (12 of 18)
of pregnant women versus 100% (14 of 14) of postpartum women met the AUC target (10th percentile in non-pregnant adults). Trough emtricitabine levels were also lower during pregnancy (minimum plasma concentration [C\text{min}] 52 ng/mL [14–180]) compared with the postpartum period (86 ng/mL [<10 to 306]). In the IMPAACT P1026s study, 26 women had emtricitabine PKs assessed during the third trimester (median 35 weeks) and 22 postpartum (mean 8 weeks postpartum). The PK parameters during pregnancy were slightly altered with respect to the postpartum period, with higher emtricitabine clearance (25.0 vs. 20.6 L/hour during pregnancy vs. postpartum, respectively) and lower 24-hour post-dose levels (0.058 vs. 0.085 mg/L), but the 24-hour, post-dose levels were well above the inhibitory concentration 50% (IC\text{50}) in all patients. Similar differences in PK parameters of emtricitabine among women during pregnancy or after delivery were found in the PACTG 394 study, and in a European study. Thus, these changes are not believed to be large enough to warrant dosage adjustment during pregnancy.

References
**Lamivudine (Epivir, 3TC)**
*(Last updated March 28, 2014; last reviewed March 28, 2014)*

Lamivudine is classified as Food and Drug Administration Pregnancy Category C.

**Animal Carcinogenicity Studies**
Lamivudine has weak mutagenic activity in one *in vitro* assay but no evidence of *in vivo* genotoxicity in rats at 35 to 45 times human exposure. Long-term animal carcinogenicity screening studies at 10 and 58 times human exposure have been negative in mice and rats, respectively.

**Reproduction/Fertility**
Lamivudine administered to rats at doses up to 4000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the offspring’s survival, growth, and development up to the time of weaning.

**Teratogenicity/Developmental Toxicity Studies**
There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits. Early embryolethality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the most commonly occurring birth defects, such as defects of the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with lamivudine. Among cases of first-trimester lamivudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.2% (133 of 4,185 births; 95% CI, 2.7%–3.8%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.

**Placental and Breast Milk Passage**
Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations. In a study of 123 mother/infant pairs, the placental transfer expressed as fetal-to-maternal area under the curve (AUC) ratio was 0.86, and the lamivudine amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9. Other studies have also noted accumulation of lamivudine in amniotic fluid. This is likely secondary to renal excretion of lamivudine by the fetus; lamivudine diffuses from maternal to fetal blood through the placenta and the fetal kidney removes lamivudine from fetal blood and concentrates it in urine, with fetal micturition causing a rise in the concentration of lamivudine in amniotic fluid.

Lamivudine is excreted into human breast milk. In a study in Kenya of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56. In infants who received lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (half-maximal IC₅₀ of wild-type HIV against lamivudine = 0.6–21 ng/mL).

**Human Studies in Pregnancy**
Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in two separate studies. This was confirmed in a larger analysis of 114 pregnant women, 123 women in labor, and 47 non-pregnant women, in which all received standard once- or twice-daily lamivudine doses. Pregnant women had a 22% higher apparent clearance than non-pregnant and postpartum women, but this increase did not lead to sub-therapeutic exposure. The level of lamivudine exposure in pregnant women, although lower than exposure in non-pregnant and parturient women, was relatively close to data reported previously for non-pregnant women.
pregnant adults. Thus, no dose adjustment in pregnancy is necessary.

References


**Stavudine (Zerit, d4T)**

_Last updated March 28, 2014; last reviewed March 28, 2014_

Stavudine is classified as Food and Drug Administration (FDA) Pregnancy Category C.

**Animal Carcinogenicity Studies**

Stavudine is clastogenic in _in vitro_ and _in vivo_ assays but not mutagenic in _in vitro_ assays. In 2-year carcinogenicity studies in mice and rats, stavudine was non-carcinogenic in doses producing exposures 39 (mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.

**Reproduction/Fertility**

Stavudine has not been shown to have an effect on reproduction or fertility in rodents. A dose-related cytotoxic effect has been observed on pre-implantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100 µM and of post-blastocyst development at 10 µM.\(^1\)

**Teratogenicity/Developmental Toxicity Studies**

No evidence of teratogenicity was noted in rats or rabbits with exposures (based on C\(_{\text{max}}\)) up to 399 and 183 times, respectively, that seen at a clinical dosage of 1 mg/kg/day. In rat fetuses, the incidence of a common skeletal variation—unossified or incomplete ossification of sternebra—was increased at 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times human exposure, with no effect noted at approximately 135 times human exposure. An increase in early rat neonatal mortality (birth to Day 4) occurred at 399 times human exposure, although survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to stavudine in humans have been monitored to be able to detect at least a two-fold increased risk of overall birth defects. No such increase in birth defects has been observed with stavudine. Among cases of first-trimester stavudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (20 of 801 births; 95% CI, 1.5% to 3.8%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance.\(^2\)

**Placental and Breast Milk Passage**

Stavudine crosses the rat placenta _in vivo_ and the human placenta _ex vivo_, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pig-tailed macaques), fetal/maternal plasma concentrations were approximately 0.80.\(^3\) Stavudine is excreted into the breast milk of lactating rats. Stavudine also crosses into human breast milk, resulting in breast milk/maternal plasma concentrations of 1.0–1.76. Concentrations in nursing infants were negligible.\(^4,5\)

**Human Studies in Pregnancy**

A Phase I/II safety and pharmacokinetic (PK) study has been conducted of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332). Both drugs were well tolerated, with stavudine PKs similar to those in non-pregnant adults.\(^6\) Data from primate studies also indicated that pregnancy did not affect the PKs of stavudine.\(^7\)

Lactic acidosis, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral (ARV) agents.\(^8,9\) The FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of...
fatal lactic acidosis when prescribed didanosine and stavudine in combination (see NRTI Drugs and Mitochondrial Toxicity). These drugs should be prescribed together for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

Although the standard adult dosing in the U.S. is weight-based, the World Health Organization recommends 30 mg, twice-daily dosing regardless of body weight.\(^1\)

### References


**Tenofovir Disoproxil Fumarate (Viread, TDF)**

*(Last updated March 28, 2014; last reviewed March 28, 2014)*

Tenofovir disoproxil fumarate (hereafter, tenofovir) is classified as Food and Drug Administration Pregnancy Category B.

**Animal Carcinogenicity Studies**

Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at 16 times (mice) and 5 times (rats) human exposure. In female mice, liver adenomas were increased at exposures 16 times that observed in humans at therapeutic doses. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

**Reproduction/Fertility**

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus associated with tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days before mating and to female rats for 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day. A retrospective analysis of 7,275 women (1,199 receiving tenofovir-based combination antiretroviral therapy) demonstrated a slight reduction in pregnancy rates but the findings were limited by the observational nature of the data and additional studies are needed for confirmation.1

**Teratogenicity/Developmental Toxicity**

Chronic exposure of fetal monkeys to tenofovir at high doses (i.e., exposure equivalent to 25 times the area under the curve achieved with therapeutic dosing in humans) resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and were associated with lower overall body weights. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment. Significant changes in maternal monkey bone biomarkers were noted but were primarily limited to the treatment period and were reversible.2 In newborn macaques exposed to tenofovir at high dose over a prolonged period, similar changes have been noted, as well as osteomalacia, bone fracture, hypophosphatemia, and nephrotoxicity. These toxicities appear to be dose- and age-related and are reversible. In contrast, no detectable effects on growth have been seen with administration of tenofovir for shorter durations or at lower doses to newborn or infant macaques.3,4

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to tenofovir in humans have been monitored to be able to detect at least a 2-fold increased risk of overall birth defects. No such increase in birth defects has been observed with tenofovir. Among cases of first-trimester tenofovir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (31 of 1,370 births; 95% CI, 1.5% to 3.2%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.5 In addition, no association was seen between tenofovir administration and birth defects in two large U.S. cohorts, PACT 219/219C (n = 2,202) and P1025 (n = 1,112).6,7

**Placental and Breast Milk Passage**

Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir does cross the placenta.8 In studies of pregnant women on chronic tenofovir dosing, the cord-to-maternal-blood ratio ranged from 0.60 to 1.03, indicating high placental transfer.9,12 In studies of pregnant women receiving single-dose tenofovir (with and without
emtricitabine) in labor, the drugs were well-tolerated and the median tenofovir cord to maternal-blood ratio at delivery ranged from 0.55 to 0.73.\textsuperscript{13,14} In a study evaluating intracellular tenofovir levels in newborns, intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a maternal single dose of 600 mg tenofovir disoproxil fumarate with 400 mg emtricitabine, but intracellular tenofovir diphosphate was detectable in only 2 (5.5\%) of 36.\textsuperscript{15} Two studies of neonatal dosing of tenofovir disoproxil fumarate resulted in tenofovir and tenofovir diphosphate levels similar to those in adults following either a single neonatal dose of 13 mg/kg or a regimen of 6 mg/kg administered daily for 7 days.\textsuperscript{14,15}

Sixteen breast milk samples were obtained from five women who received 600 mg of tenofovir at the start of labor followed by 300 mg daily for 7 days. Tenofovir levels in breast milk ranged from 5.8 to 16.3 ng/mL, and nursing infants received an estimated 0.03\% of the proposed oral dose of tenofovir disoproxil fumarate for neonates.\textsuperscript{16}

Human Studies in Pregnancy

A retrospective population pharmacokinetic (PK) study was performed on samples collected for therapeutic drug monitoring from 46 pregnant women and 156 non-pregnant women receiving combination regimens including tenofovir.\textsuperscript{17} Pregnant women had a 39\% higher apparent clearance compared with non-pregnant women, which decreased slightly but significantly with increasing age. In study P1026s, tenofovir PKs were evaluated in 19 pregnant women receiving tenofovir-based combination therapy at 30 to 36 weeks’ gestation and 6 to 12 weeks postpartum.\textsuperscript{18} The percentage of women with tenofovir area under the curve exceeding the target of 2 μg*hour/mL (the 10th percentile in non-pregnant adults) was lower in the third trimester (74\%, 14 of 19 women) than postpartum (86\%, 12 of 14 women) (\( P = .02 \)); however, trough levels were similar in the two groups. A study of 34 women receiving tenofovir plus emtricitabine in the third trimester and postpartum has recently been reported.\textsuperscript{11} Although similar decreases in PK parameters were observed during pregnancy, they were not associated with virologic failure. At the present time, standard dosing during pregnancy continues to be recommended.

A case series found tenofovir to be well tolerated in 76 pregnant women, with only 2 stopping therapy, 1 for rash and the other for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV uninfected.\textsuperscript{18} A follow-up study of 20 of the tenofovir-exposed infants and 20 controls found no differences between the groups in renal function, including cystatin C levels, through age 2 years.\textsuperscript{19} A retrospective review of 16 pregnancy outcomes in 15 heavily antiretroviral- experienced women demonstrated that tenofovir was well tolerated by the women and associated with normal growth and development in the infants.\textsuperscript{20} In a cross-sectional study of 68 HIV-exposed uninfected infants who had in utero exposure to combination regimens with (\( N = 33 \)) or without (\( N = 35 \)) tenofovir, the incidence of low birth weight and length measurements (<10th percentile) was comparable in the 2 groups and evaluation of quantitative bone ultrasound and parameters of bone metabolism gave similar measures between groups.\textsuperscript{21} Among 382 pregnancies occurring in 302 women in Uganda and Zimbabwe participating in the DART trial—approximately two-thirds of whom received tenofovir through more than 90\% of their pregnancies—there were no differences noted in mortality, birth defects, or growth.\textsuperscript{22} The Pediatric HIV/AIDS Cohort Study from the United States reported on the association of tenofovir use during pregnancy with early growth parameters in 449 HIV-exposed but HIV-uninfected infants.\textsuperscript{23} Of 2,029 infants, 449 (21\%) had in utero exposure to tenofovir. There was no difference at birth between those exposed to combination drug regimens with or without tenofovir in low birth weight, small-for-gestational-age, and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively). At age 1 year, infants exposed to combination regimens with tenofovir had a slight but significantly lower adjusted mean LAZ and HCAZ than those without tenofovir exposure (LAZ: -0.17 vs. -0.03, \( P = .04 \); HCAZ: 0.17 vs. 0.42, \( P = .02 \)), but not lower weight-for-age z-score. However, there were no significant differences between those with and without tenofovir exposure at age 1 year when defining low LAZ or HCAZ as <-1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.

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function in HIV-exposed children. 17th Conference on Retoviruses and Opportunistic Infections; February 27-March 2, 2010; San Francisco, CA.


Zalcitabine (HIVID, ddC)
(Last updated March 28, 2014; last reviewed March 28, 2014)
Zalcitabine is no longer available in the United States.

Zidovudine (Retrovir, AZT, ZDV)
(Last updated March 28, 2014; last reviewed March 28, 2014)
Zidovudine is classified as Food and Drug Administration Pregnancy Category C.

Animal Carcinogenicity Studies
Zidovudine was shown to be mutagenic in two in vitro assays and clastogenic in one in vitro and two in vivo assays, but not cytogenic in a single-dose in vivo rat study. Long-term carcinogenicity studies have been performed with zidovudine in mice and rats. In mice, 7 late-appearing (>19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of an animal given an intermediate dose. No vaginal tumors were found at the lowest dose. In rats, 2 late-appearing (>20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex in either species. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by area under the curve [AUC]) was approximately three times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours. How predictive the results of rodent carcinogenicity studies may be for humans is unknown.

Two transplacental carcinogenicity studies were conducted in mice. In 1 study, zidovudine was administered at doses of 20 mg/kg/day or 40 mg/kg/day from gestation Day 10 through parturition and lactation, with postnatal dosing continuing in offspring for 24 months. The drug doses administered in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. In a second study, zidovudine was administered at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1000 mg/kg non-pregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 to 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose of zidovudine.

Reproduction/Fertility
When administered to male and female rats at doses up to seven times the usual adult dose based on body surface area, zidovudine had no effect on fertility, as judged by rates of conception.

Zidovudine has been shown to have no effect on reproduction or fertility in rodents. A dose-related cytotoxic effect on pre-implantation mouse embryos can occur, with inhibition of blastocyst and post-blastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses.

Teratogenicity/Developmental Toxicity
Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity, as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times and in rabbits 12 to 87 times mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose.
In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations (estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day). No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Increased fetal resorption occurred in pregnant rats and rabbits treated with zidovudine doses that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100 mg dose of zidovudine. No other developmental anomalies were reported. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen.5,6 Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts, PACTG 219/219C and P1025.7,8 A previous report from the Women and Infants Transmission Study described a 10-fold increased risk of hypospadias, but this finding was not confirmed in a more detailed analysis.9,10 In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to zidovudine have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased incidence of defects in the more common classes, including the genitourinary system. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.3% (124 of 3,789 births; 95% CI, 2.7% to 3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance.11

**Placental and Breast Milk Passage**

Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal-blood ratios of about 0.80. The ratio of zidovudine in amniotic fluid to that in maternal plasma is 1.5.12 Zidovudine is excreted into human breast milk with breast milk-to-maternal-plasma zidovudine concentration ranging from 0.44 to 0.77.13,14 No zidovudine was detectable in the plasma of the nursing infants, who received zidovudine only via breast milk.

**Human Studies in Pregnancy**

Zidovudine is well tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg/kg body weight orally every 6 hours.5,15 Long-term data on the safety of *in utero* drug exposure in humans are not available for any antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. In PACTG 076, no difference in disease progression was seen between women who received zidovudine and those who received placebo, based on follow-up through 4 years postpartum.16 Additionally, no differences in immunologic, neurologic, or growth parameters were seen between infants with *in utero* zidovudine exposure and those who received placebo, based on nearly 6 years of follow-up.6,17

**References**


Non-Nucleoside Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Glossary of Terms for Supplement</th>
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</thead>
<tbody>
<tr>
<td><strong>Carcinogenic:</strong> Producing or tending to produce cancer</td>
</tr>
<tr>
<td>• Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.</td>
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<tr>
<td>• Genetic mutations and/or chromosomal damage can contribute to cancer formation.</td>
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<tr>
<td><strong>Clastogenic:</strong> Causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
<td><strong>Genotoxic:</strong> Damaging to genetic material such as DNA and chromosomes</td>
</tr>
<tr>
<td><strong>Mutagenic:</strong> Inducing or capable of inducing genetic mutation</td>
</tr>
<tr>
<td><strong>Teratogenic:</strong> Interfering with fetal development and resulting in birth defects</td>
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Five non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) are currently approved (delavirdine is no longer available in the United States). Nevirapine and efavirenz have been studied in human pregnancy. No adequate and well-controlled studies of etravirine or rilpivirine use in pregnant women have been conducted.

For information about potential interactions between NNRTIs and methergine, see the Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use sections in the perinatal guidelines. For more information regarding nevirapine hepatic/rash toxicity, see the Nevirapine and Hepatic/Rash Toxicity section in the perinatal guidelines.

**Delavirdine (Rescriptor, DLV)**  
(Last updated March 28, 2014; last reviewed March 28, 2014)

Delavirdine is no longer available in the United States.

**Efavirenz (Sustiva, EFV)**  
(Last updated March 28, 2014; last reviewed March 28, 2014)

Efavirenz is classified as Food and Drug Administration (FDA) Pregnancy Category D.

**Animal Carcinogenicity Studies**

Efavirenz was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Long-term animal carcinogenicity studies with efavirenz have been completed in mice and rats. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice, but in female mice, an increase above background was seen in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas. No increase in tumor incidence above background was observed in male and female rats with systemic drug exposures lower than that in humans receiving therapeutic doses.

**Reproduction/Fertility Animal Studies**

No effect of efavirenz on reproduction or fertility in rodents has been seen.

**Teratogenicity/Developmental Toxicity**

An increase in fetal resorption was observed in rats at efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily). Central nervous system (CNS) malformations and cleft palate were observed in 3 of 20 infants born to pregnant cynomolgus...
monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 60 mg/kg/day (resulting in plasma concentrations 1.3 times that of systemic human therapeutic exposure, with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values). The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

**Placental and Breast Milk Passage**

Efavirenz readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations. In a study of 25 mother-infant pairs, median efavirenz cord blood/maternal blood concentration was 0.49 (range 0.37–0.74). In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery. Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz concentration was significantly higher in maternal plasma than skim breast milk (mean breast milk to mean maternal plasma concentration ratio 0.54) and higher in skim breast milk than in infant plasma (mean skim breast milk to mean newborn plasma concentration ratio 4.08). Mean infant plasma efavirenz concentrations were 13.1% of maternal plasma levels. In a study of plasma and hair drug concentration in 56 mother-infant pairs receiving efavirenz-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested moderate *in utero* transfer during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative with 15% during breastfeeding). All mothers and infants had detectable efavirenz plasma levels at 0, 8, and 12 weeks and mean infant to maternal hair concentration at 12 weeks postpartum was 0.40 for efavirenz.

No data currently are available about the safety and pharmacokinetics of efavirenz in neonates.

**Human Studies in Pregnancy**

In a study of 25 pregnant women receiving efavirenz during the third trimester as part of clinical care, efavirenz clearance was slightly increased and trough levels were decreased compared with levels measured postpartum. These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy.

In a pharmacogenomics study, non-pregnant individuals with the CYP2B6 516 TT genotype had more than 3-fold increases in both short-term and long-term efavirenz exposure, as measured by plasma and hair drug levels, suggesting there could be significant variation in drug levels with CYP2B6 polymorphisms. The frequency of this allele varies between different ethnic populations, ranging from 3.4% in white, 6.7% in Hispanic and 20% in African Americans.

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry (APR) through July 2013, birth defects were observed in 18 of 766 live births with first-trimester exposure (2.3%, 95% confidence interval [CI], 1.4%–3.7%). Although these data provide sufficient numbers of first-trimester exposures to rule out a two-fold or greater increase in the risk of overall birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the APR of defects after first-trimester efavirenz exposure have documented one neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and one case of bilateral facial clefts, anophthalmia, and amniotic band. Among retrospective cases, there are six reports of CNS defects, including three cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester. Retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

In an updated meta-analysis of 19 studies (including the Antiretroviral Pregnancy Registry data) reporting on birth outcomes among women exposed to efavirenz during the first trimester, there were 39 infants with birth defects among live births in 1,437 women receiving first-trimester efavirenz (rate of overall birth defects, 2.0%, 95% CI, 0.8–3.2%). The rate of overall birth defects was similar among women exposed to efavirenz-
containing regimens (1,290 live births) and non-efavirenz containing regimens (8,122 births) during the first trimester (pooled relative risk [RR] 0.85, 95% CI, 0.61–1.20). Across all births (1,437 live births with first-trimester efavirenz exposure), 1 neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.07% (95% CI, 0.002–0.39), within the range reported in the general population. However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a significant increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02%–0.2%).

Although two small studies (Pediatric AIDS Clinical Trials Group [PACTG] protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to efavirenz compared with those without exposure, the number of exposures was small (35 exposures in PACTG 219/219C and 42 in P1025) and there is overlap in defect cases between the 2 studies.9-11 Thus, additional data are needed on first-trimester efavirenz exposures to more conclusively determine if risk of neural tube defects is elevated.

Efavirenz is classified as FDA Pregnancy Category D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Although the limited data on first-trimester efavirenz exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from the meta-analysis on >1,400 births suggest that there is not a large increase (such as a 10-fold increase to a rate of 1%) in the risk of neural tube defects with first-trimester exposure. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first 8 weeks of pregnancy (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy. Alternate antiretroviral (ARV) regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman’s health. However, given that the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after last menstrual period), pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and ARV drug changes in pregnancy may be associated with loss of viral control and thus increase risk of transmission to the infant,12 efavirenz can be continued in pregnant women receiving efavirenz-based antiretroviral therapy who present for antenatal care in the first trimester, provided that the regimen produces virologic suppression. In such situations, additional fetal monitoring (e.g., second-trimester ultrasound) should be considered to evaluate fetal anatomy.

Pharmacokinetic (PK) interactions of efavirenz with some hormonal contraceptives have been reported, with the potential for failure of the progesterone component, particularly when used for emergency contraception.13-16 Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman’s health. Barrier contraception should always be used in combination with other methods of contraception such as hormonal contraceptives and intrauterine devices. A study evaluating the interaction between efavirenz and depot medroxyprogesterone acetate (DMPA) in 17 women found no change in the PK profile of either efavirenz or DMPA with concomitant use.17 DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

References


Etravirine (Intelicence, ETV)
(Last updated March 28, 2014; last reviewed March 28, 2014)

Etravirine is classified as Food and Drug Administration Pregnancy Category B.

Animal Carcinogenicity Studies
Etravirine was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200, and 400 mg/kg were administered to mice and doses of 70, 200, and 600 mg/kg were administered to rats in the initial period of approximately 41 to 52 weeks. The high and middle doses were subsequently adjusted because of tolerability and reduced by 50% in mice and by 50% to 66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were observed in either sex. The relevance to humans of these liver tumor findings in mice is unknown. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal versus human area under the curve ratios being 0.6-fold (mice) and 0.2- to 0.7-fold (rats).

Reproduction/Fertility
No effect on fertility and early embryonic development was observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).

Teratogenicity/Developmental Toxicity
Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1000 mg/kg/day). In both species, no treatment-related embryo-fetal effects (including malformations) were observed. In addition, no treatment effects were observed in a separate prenatal and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day). In seven reported cases of etravirine use in pregnancy, no maternal, fetal, or neonatal toxicity was noted. One infant was born with a small accessory auricle on the right ear with no other malformations, but no birth defects were noted in the other children. Fewer than 200 first-trimester pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.

Placental and Breast Milk Passage
Etravirine concentrations in cord blood and maternal plasma at delivery were 112 ng/mL and 339 ng/mL, respectively (cord/maternal ratio of 33%), in one mother-infant pair. Placental passage of etravirine was described in a report of the use of etravirine, ritonavir-boosted darunavir, and enfuvirtide in a pregnant woman who gave birth to twins, with cord blood etravirine levels of 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (no maternal delivery etravirine concentration reported). There are no data describing etravirine excretion in human breast milk.

Human Studies in Pregnancy
No adequate and well-controlled studies of etravirine use in pregnant women have been conducted. Very limited case report data are available describing etravirine use in a total of 7 pregnant women. No adverse effects associated with etravirine use were reported. One report described etravirine pharmacokinetics (PK) in four pregnant women whose etravirine PK parameters were similar to those in non-pregnant adults.
References


Nevirapine (Viramune, NVP)
(Last updated March 28, 2014; last reviewed March 28, 2014)

Nevirapine is classified as Food and Drug Administration Pregnancy Category B.

Animal Carcinogenicity Studies
Nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of in vitro and in vivo studies. Hepatocellular adenomas and carcinomas were increased at all doses in male mice and rats and at higher doses in female mice and rats. Systemic exposure at all doses studied was lower than systemic exposure in humans receiving therapeutic nevirapine doses. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is unknown.

Reproduction/Fertility
Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.

Teratogenicity/Developmental Toxicity
Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits at systemic exposures approximately equivalent to or 50% greater than the recommended human dose (based on area under the curve [AUC]). In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to nevirapine in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in more commonly seen classes of birth defects in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nevirapine. Among cases of first-trimester nevirapine exposure reported to the APR, the prevalence of birth defects was 3.0% (31 of 1,049 births; 95% CI, 2.0% to 4.2%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.

Placental and Breast Milk Passage
Nevirapine demonstrates rapid and effective placental transfer, achieving near equivalent concentrations in maternal and cord blood (cord to maternal blood ratio ranging from 0.60–1.02). Nevirapine has also been shown to be excreted into human breast milk. In a study of 57 Malawian women receiving postpartum nevirapine-based therapy, breast milk to maternal serum concentration ratio was approximately 0.6; detectable nevirapine concentrations were found in the breastfeeding infants (intra-quartile range 0.54–1.06 ug/mL). In data from 15 breastfeeding women receiving nevirapine-based therapy in Botswana, median maternal plasma concentration at 1 month postpartum was 6.71 ug/mL and median maternal breast milk concentration was 1.83 ug/mL, for a median maternal breast milk to plasma ratio of 0.27. Infant exposure was measured at 1 month in nine infants; all infants had biologically significant detectable nevirapine concentrations in their blood, with a median level of 0.37 ug/mL (range, 0.24–1.2 ug/mL), representing approximately 6% of median maternal value. Similar data were reported in a study of 67 mothers receiving nevirapine-based therapy in Kenya; the median concentration of nevirapine in breast milk was 4.55 ug/mL, with median concentrations at 2, 6, and 14 weeks postpartum in breastfeeding infants of 0.99 ug/mL, 1.03 ug/mL and 0.73 ug/mL, respectively.

Human Studies in Pregnancy
The pharmacokinetics (PKs) of nevirapine have been evaluated in pregnant women receiving nevirapine as part of combination antiretroviral therapy (cART) during pregnancy. A study that determined nevirapine PKs in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine PK parameters. In contrast, nevirapine clearance was 20% greater, AUC was 28% lower, and maximum plasma concentration was 30% lower in 16
pregnant women compared with 13 non-pregnant women, based on nevirapine PK data from a therapeutic
drug monitoring program that included 12-hour sampling; they also reported high variability in plasma
nevirapine concentrations. A Dutch study reported a non-significant trend toward lower nevirapine exposure
during pregnancy, with steady-state nevirapine concentrations of 5.2 ug/mL in 45 pregnant women compared
to 5.8 ug/mL in 152 non-pregnant women ($P = 0.08$). No dose adjustment during pregnancy is currently
recommended for nevirapine.

Severe, life-threatening, and (in some cases) fatal hepatotoxicity—including fulminant and cholestatic
hepatitis, hepatic necrosis, and hepatic failure and severe, life-threatening hypersensitivity skin reactions,
including Stevens-Johnson syndrome—has been reported in HIV-infected patients receiving nevirapine in
combination with other drugs for treatment of HIV disease and in a small number of individuals receiving
nevirapine as part of cART for post-exposure prophylaxis of nosocomial or sexual exposure to HIV. In
general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range
2.5% to 11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure
or hepatic mortality has been lower, in the range of 0.04% to 0.40%. Risk of severe or life-threatening
adverse events occurs in approximately 2% of patients receiving nevirapine. The greatest risk of severe rash
or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past
this period and monitoring should continue at frequent intervals.

Incidence of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in
women than men and has been reported in pregnant women. Other studies have found that hepatic
adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men. Several
studies suggest that the degree of risk of hepatic toxicity varies with CD4 T lymphocyte (CD4) cell
count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell
counts $>250$ cells/mm$^3$ were 9.8 times more likely than women with lower CD4 cell counts to experience
symptomatic, often rash-associated, nevirapine-related hepatotoxicity. Higher CD4 cell counts have also
been associated with increased risk of severe nevirapine-associated skin rash. Rates of hepatotoxicity and
rash similar to those in U.S. studies have been seen in international cohorts of non-pregnant women,
although not all have reported an association with CD4 cell counts $>250$ cells/mm$^3$. In a study of 359 non-
pregnant women randomized to nevirapine-based therapy in sub-Saharan Africa, higher nevirapine exposure
was associated with development of severe skin toxicity, and baseline CD4 cell counts $>250$ cells/mm$^3$ was
associated with nevirapine-related liver toxicity and drug discontinuation. Some researchers have suggested
that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants) and immune human
leukocyte antigen loci may be associated with higher risk of nevirapine-associated adverse events and that
the relationship between genetic variants and adverse effects may vary by race.

Although deaths as a result of hepatic failure have been reported in HIV-infected pregnant women receiving
nevirapine as part of a combination ARV regimen, it is uncertain whether pregnancy increases the risk of
hepatotoxicity in women receiving nevirapine or other antiretroviral drugs. In a systematic review of 20
studies including 3,582 pregnant women from 14 countries, the pooled proportion of women experiencing a
severe hepatoxic event was 3.6% (95% CI, 2.4% to 4.8%) and severe rash was 3.3% (95% CI, 2.1% to
4.5%); overall 6.2% of women stopped nevirapine due to an adverse event (95% CI, 4.0% to 8.4%). These
results were comparable to published frequencies in the general adult population and frequencies comparable
to non-pregnant women within the same cohorts. These data suggest that the frequency of adverse events
associated with nevirapine during pregnancy is not higher than reported for nevirapine in the general
population, consistent with data from two multicenter prospective cohorts in which pregnancy was not
associated with an increased risk of nevirapine-associated hepatic toxicity.

In the systematic review, there was a non-significant trend toward an increased likelihood of cutaneous
events (OR 1.1, 95% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 cell
counts $\geq 250$ cell/mm$^3$ (OR 1.4, 95% CI 0.8-2.4). A separate systematic review of 14 studies did report a
significant association of increased toxicity risk with initiation of nevirapine-based therapy during pregnancy.
in women with CD4 cell counts ≥250 cells/mm³. Nevirapine should be used as a component of a combination regimen in pregnant women with CD4 cell counts ≥250 cells/mm³ only if the benefit clearly outweighs the risk. Women with CD4 cell counts <250 cells/mm³ can receive nevirapine-based regimens, and women who become pregnant while taking nevirapine and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication. Frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is necessary, particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, and then monthly for the first 18 weeks (Adult and Adolescent Antiretroviral Guidelines); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter. Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or have asymptomatic but severe transaminase elevations should stop nevirapine and not receive the drug in the future.

References


**Rilpivirine (Edurant, RPV)**

(Last updated March 28, 2014; last reviewed March 28, 2014)

Rilpivirine is classified as Food and Drug Administration Pregnancy Category B.

**Animal Carcinogenicity Studies**

Rilpivirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Rilpivirine was not carcinogenic in rats when administered at doses 3 times higher than exposure in humans at the recommended dose of 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses 21 times that of human therapeutic exposure; the observed hepatocellular findings in mice may be rodent-specific.

**Reproduction/Fertility**

No effect on fertility was observed when rilpivirine was tested in rats at maternal doses up to 400 mg/kg/day, resulting in systemic drug exposure equivalent to 40 times the recommended human dose.

**Teratogenicity/Developmental Toxicity**

No evidence of embryonic or fetal toxicity or an effect on reproductive function was observed in rat and rabbit dams treated with rilpivirine during pregnancy and lactation at doses 15 and 70 times higher, respectively, than exposure in humans at the recommended dose of 25 mg once daily.

**Placental and Breast Milk Passage**

No data exist on whether rilpivirine crosses the placenta or is excreted in breast milk in humans. Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk.

**Human Studies in Pregnancy**

No adequate and well-controlled studies of rilpivirine use in pregnant women have been conducted.

**Reference**

Protease Inhibitors
(Last updated March 28, 2014; last reviewed March 28, 2014)

Ten protease inhibitors (PIs) are currently approved (amprenavir is no longer available in the United States). Data are available from clinical trials in human pregnancy for atazanavir, ritonavir-boosted lopinavir fixed-dose drug formulation, nelfinavir, ritonavir, and saquinavir. Data in pregnancy are limited for darunavir, fosamprenavir, and indinavir. Very limited data in pregnancy are available for tipranavir.

For information regarding the PI class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see Combination Antiretroviral Drug Regimens and Pregnancy Outcome.

Amprenavir (Agenerase, APV)
(Last updated March 28, 2014; last reviewed March 28, 2014)
Amprenavir is no longer available in the United States.

Atazanavir (Reyataz, ATV)
(Last updated March 28, 2014; last reviewed March 28, 2014)
Atazanavir is classified as Food and Drug Administration (FDA) Pregnancy Category B.

Animal Carcinogenicity Studies
In in vitro and in vivo assays, atazanavir shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. In female mice, the incidence of benign hepatocellular adenomas was increased at systemic exposures 2.8- to 2.9-fold higher than those in humans at the recommended therapeutic dose (300 mg atazanavir boosted with 100 mg ritonavir once daily). There were no increases in the incidence of tumors in male mice at any dose. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 1.1-fold (males) or 3.9-fold (females) higher than those in humans at the recommended therapeutic dose.¹

Reproduction/Fertility
No effect of atazanavir on reproduction or fertility in male and female rodents was seen at systemic drug exposures. The area under the curve (AUC) at this exposure level in rats was 0.9-fold in males and 2.3-fold in females compared with the exposures achieved in humans at the recommended therapeutic dose.¹

Teratogenicity/Developmental Toxicity
In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg atazanavir boosted with 100 mg ritonavir once daily). In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure 1.3

Glossary of Terms for Supplement

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenic</td>
<td>Producing or tending to produce cancer</td>
</tr>
<tr>
<td>Mutagenic</td>
<td>Inducing or capable of inducing genetic mutation</td>
</tr>
<tr>
<td>Genotoxic</td>
<td>Damaging to genetic material such as DNA and chromosomes</td>
</tr>
<tr>
<td>Clastogenic</td>
<td>Causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
<td>Teratogenic</td>
<td>Interfering with fetal development and resulting in birth defects</td>
</tr>
<tr>
<td>Mutagenic</td>
<td>Inducing or capable of inducing genetic mutation</td>
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</table>

¹ For information regarding the PI class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see Combination Antiretroviral Drug Regimens and Pregnancy Outcome.
times the human exposure also resulted in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposure equivalent to that observed in humans at the recommended therapeutic dose.¹

In a retrospective analysis from London of atazanavir used in 31 women during 33 pregnancies (20 of whom were receiving atazanavir at conception), there were two miscarriages at 12 and 16 weeks, 26 infants born, and five women still pregnant.² No infant required phototherapy and no birth defects were seen; none of the infants were HIV-infected. In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to atazanavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.1% (16 of 746 births; 95% confidence interval [CI], 1.2%–3.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.³

Placental and Breast Milk Passage

In studies of women receiving ritonavir-boosted atazanavir-based combination therapy during pregnancy, cord blood atazanavir concentration averaged 13% to 21% of maternal serum levels at delivery.¹,⁴,⁵ Atazanavir is excreted in the milk of lactating rats. In a study of three women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.⁶

Human Studies in Pregnancy

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of ritonavir-boosted atazanavir in pregnancy.⁷ Overall, most pregnant patients achieved undetectable HIV RNA at the time of delivery.¹,⁴,⁵,⁸,⁹ In a retrospective study reporting trough atazanavir concentrations in 19 pregnant women receiving atazanavir 300 mg and ritonavir 100 mg once daily at a median of 30 weeks’ gestation (14 in the third trimester), all but 2 women had a trough atazanavir concentration >100 ng/mL.² In studies that have evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy, atazanavir AUC was lower during pregnancy than in historic data from HIV-infected non-pregnant patients.⁴,⁵,⁸,¹⁰,¹¹ In one of the studies there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than in non-pregnant HIV-infected historic controls.¹ In the other studies, atazanavir AUC was lower during pregnancy than in the same patients postpartum and in non-pregnant control populations.⁵,⁸-¹¹

Although use of ritonavir-based atazanavir combined with tenofovir and emtricitabine as a complete once-a-day dosing combination antiretroviral (ARV) regimen is becoming increasingly common in pregnancy, tenofovir reduces atazanavir exposure by 25% in non-pregnant adults.¹⁰ This drug-drug interaction also is present during pregnancy, with a 25% reduction in atazanavir AUC in pregnant women also receiving tenofovir compared with the same women postpartum and a 50% reduction compared with postpartum levels in women who did not receive tenofovir.⁵

Use of an increased dose of atazanavir of 400 mg with 100 mg ritonavir once daily during pregnancy has been investigated in two studies.¹² In both studies pregnant women receiving the increased dose without tenofovir had an atazanavir AUC equivalent to that seen in historic non-pregnant HIV-infected controls receiving standard-dose atazanavir without tenofovir. Pregnant women receiving the increased atazanavir dose with tenofovir had an AUC equivalent to that seen in non-pregnant HIV-infected patients receiving standard-dose atazanavir and tenofovir.¹² Although some experts recommend increased atazanavir dosing in all women during the second and third trimesters, the package insert recommends increased atazanavir dosing only for ARV-experienced pregnant women in the second and third trimesters also receiving either tenofovir or an H₂-receptor antagonist. For additional details about dosing with interacting concomitant medications, please see Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.
Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir. The effects of elevated maternal indirect bilirubin throughout pregnancy on the fetus are unknown. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received atazanavir during pregnancy.\textsuperscript{1,2,4,5,8,12-14} Although some studies have suggested that neonatal bilirubin elevations requiring phototherapy occur more frequently after prenatal atazanavir exposure, decisions to use phototherapy to treat infants with hyperbilirubinemia frequently are subjective and guidelines for phototherapy of infants vary between countries, making it difficult to compare the severity of hyperbilirubinemia between patients within a study and in different studies.\textsuperscript{12,13} Elevated neonatal bilirubin in atazanavir-exposed neonates is not associated with UGT-1 genotypes associated with decreased UGT function.\textsuperscript{14}

In an evaluation of neurodevelopment in 374 HIV-exposed uninfected infants aged 9 to 15 months, the adjusted mean on the Language domain of the Bayley-III test was significantly lower for infants with perinatal exposure to atazanavir compared to other drugs.\textsuperscript{15} In a study of language assessments among 792 1- and 2-year-old HIV-exposed uninfected children, atazanavir was also associated with increased risk of late language emergence at age 12 months (adjusted odds ratio 1.83, 95% CI, 1.10–3.04) compared with atazanavir-unexposed infants but the association was not significant at 24 months.\textsuperscript{16}

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis has been reported in three of 38 atazanavir-exposed infants with glucose samples collected in the first day of life. All three hypoglycemic infants’ glucose samples were adequately collected and processed in a timely fashion.\textsuperscript{1} This finding of infant hypoglycemia is similar to a prior report in which two (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life.\textsuperscript{17}

References


Darunavir (Prezista, DRV)
(Last reviewed March 28, 2014; last updated March 28, 2014)
Darunavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Carcinogenicity Studies
Darunavir was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in both male and female mice and rats as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on area under the curve) were between 0.4- and 0.7-fold (mice) and 0.7-and 1-fold (rats) those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg/day).

Reproduction/Fertility
No effects on fertility and early embryonic development were seen with darunavir in rats.

Teratogenicity/Developmental Toxicity
No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits. Because of limited bioavailability of darunavir in animals and dosing limitation, the plasma exposures were approximately 50% (mice and rats) and 5% (rabbits) of those obtained in humans. In the rat prenatal and postnatal development study, a reduction in pup weight gain was observed with darunavir alone or with ritonavir exposure via breast milk during lactation. In juvenile rats, single doses of darunavir (20 mg/kg–160 mg/kg at ages 5–11 days) or multiple doses of darunavir (40 mg/kg–1000 mg/kg at age 12 days) caused mortality. The deaths were associated with convulsions in some of the animals. Within this age range, exposures in plasma, liver, and brain were dose- and age-dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the cytochrome P450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or mating performance of offspring was not affected by maternal treatment. Fewer than 200 first-trimester pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.

Placental and Breast Milk Passage
No animal studies of placental passage of darunavir have been reported. Although variable transplacental transfer of darunavir has been observed in some case reports, in a study of 14 mother/infant pairs, the median (range) ratio of darunavir concentration in cord blood to that in maternal delivery plasma was 24% (6%–58%). Passage of darunavir into breast milk has been noted in rats; whether breast milk passage of darunavir occurs in humans is unknown.

Human Studies in Pregnancy
Currently, limited data exist about darunavir in pregnancy. Three intensive pharmacokinetic studies of darunavir/ritonavir administered as 600 mg/100 mg twice a day or 800 mg/100 mg once a day during pregnancy demonstrate 17% to 35% reductions in darunavir plasma concentration during the third trimester compared with postpartum. Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy. A study of use of an increased twice-daily darunavir dose during pregnancy is under way. Darunavir plasma protein binding decreases during pregnancy, which increases the unbound plasma darunavir fraction and may partially mitigate the decrease in total darunavir concentration.
References


**Fosamprenavir (Lexiva, FPV)**

(Last updated March 28, 2014; last reviewed March 28, 2014)

Fosamprenavir is classified as Food and Drug Administration Pregnancy Category C.

**Animal Carcinogenicity Studies**

Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only, there was an increase in interstitial cell hyperplasia at higher doses and an increase in uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus the relevance of the uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 1400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily.

**Reproduction/Fertility**

No impairment of fertility or mating was seen in rats at doses providing 3 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No effect was seen on the development or maturation of sperm in rats at these doses.

**Teratogenicity/Developmental Toxicity**

Fosamprenavir was studied in rabbits at 0.8 and in rats at 2 times the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination) the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at 2 times human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls. The number of first-trimester exposures to fosamprenavir that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.\[1\]

**Placental and Breast Milk Passage**

In a small study of women receiving fosamprenavir during pregnancy, the median (range) amprenavir concentration in cord blood was 0.27 (0.09–0.60) ug/mL and the median (range) ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery was 0.24 (0.06–0.93).\[2\] A second small study in pregnancy yielded a similar mean ratio (95% CI) of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (0.24, 0.30).\[3\] Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

**Human Studies in Pregnancy**

Data on fosamprenavir in pregnant women are very limited. Fosamprenavir pharmacokinetic data have been reported in 26 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700
mg and ritonavir 100 mg, fosamprenavir area under the curve and 12-hour trough concentration were somewhat lower during pregnancy and higher postpartum compared to historical data. Fosamprenavir exposure during pregnancy appeared to be adequate for patients without protease inhibitor resistance mutations. A pediatric liquid formulation is approved for children older than age 2 years, but no dosing information is available for neonates.

References


**Indinavir (Crixivan, IDV)**
(Last updated March 28, 2014; last reviewed March 28, 2014)

Indinavir is classified as Food and Drug Administration Pregnancy Category C.

**Animal Carcinogenicity Studies**
Indinavir is neither mutagenic nor clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.

**Reproduction/Fertility**
No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.

**Teratogenicity/Developmental Toxicity**
There has been no evidence of teratogenicity or treatment-related effects on embryonic/fetal survival or fetal weights of indinavir in rats, rabbits, or dogs at exposures comparable to, or slightly greater than, therapeutic human exposure. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related, external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold greater than controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester. In Rhesus monkeys, fetal plasma drug levels were approximately 1% to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to indinavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with indinavir. Among cases of first-trimester indinavir exposure reported to the APR, defects have been seen in 2.4% (7/287, 95% CI: 1.0%–5.0%) compared to total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention surveillance of 2.7%.

**Placental and Breast Milk Passage**
Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In studies of pregnant women receiving unboosted indinavir and their infants, transplacental passage of indinavir was minimal. In a study of Thai pregnant women receiving ritonavir-boosted indinavir, median cord blood indinavir concentration was 0.12 μg/mL, median maternal plasma delivery concentration was 0.96 μg/mL, and the median ratio between indinavir concentrations in cord blood and maternal plasma at delivery was 12%. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels (milk-to-plasma ratio 1.26 to 1.45); whether indinavir is excreted in human milk is unknown.

**Human Studies in Pregnancy**
The optimal dosing regimen for use of indinavir in pregnant patients has not been established. Two studies of the pharmacokinetics (PKs) of unboosted indinavir (800 mg 3 times/day) during pregnancy demonstrated significantly lower indinavir plasma concentrations during pregnancy than postpartum. Use of unboosted indinavir is not recommended in HIV-infected pregnant patients because of the substantially lower...
Several reports have investigated use of ritonavir-boosted indinavir during pregnancy. In an intensive PK study of 26 Thai pregnant women receiving 400 mg indinavir/100 mg ritonavir twice a day, indinavir plasma concentrations were significantly lower during pregnancy than postpartum. The median trough indinavir concentration was 0.13 ug/mL; 24% of subjects had trough concentrations below 0.10 ug/mL, the target trough concentration used in therapeutic drug monitoring (TDM) programs; and 81% had RNA viral loads <50 copies/mL at delivery. In a study of pregnant French women receiving 400 mg indinavir/100 mg ritonavir twice a day, the median indinavir trough concentration was 0.16 ug/mL, 18% of subjects had trough concentrations below 0.12 ug/mL, and 93% had HIV RNA level <200 copies/mL at delivery. In a small study of two who received indinavir 800 mg and ritonavir 200 mg twice daily, third-trimester indinavir area under the curve exceeded that for historical non-pregnant control. The available data are insufficient to allow for definitive dosing recommendations for use of ritonavir-boosted indinavir during pregnancy.

References


**Ritonavir-Boosted Lopinavir (Kaletra, LPV/r)**

*(Last updated March 28, 2014; last reviewed March 28, 2014)*

LPV/r is classified as FDA Pregnancy Category C.

**Animal Carcinogenicity Studies**

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The ritonavir-boosted lopinavir (LPV/r) combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increased incidence of benign hepatocellular adenomas and increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on AUC$_{0-24hr}$ measurement). Administration of LPV/r did not cause a statistically significant increase in incidence of any other benign or malignant neoplasm in mice or rats.

**Reproduction/Fertility**

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

**Teratogenicity/Developmental Toxicity**

No evidence exists of teratogenicity with administration of LPV/r to pregnant rats or rabbits. In rats treated with a maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (e.g., early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations, and skeletal ossification delays) were observed. Drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose. In a perinatal and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred with exposure to 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to LPV/r have been monitored for detection of at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with LPV/r. Among cases of first-trimester exposure to LPV/r reported to the APR, the prevalence of birth defects was 2.4% (23 of 969; 95% CI, 1.5% to 3.5%) compared with a total prevalence of 2.7% in the U.S. population, based on CDC surveillance.

**Placental and Breast Milk Passage**

Lopinavir crosses the human placenta; in the P1026s PK study, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20 ± 0.13. In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving LPV/r during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested significant *in utero* transfer: 41% of infants had detectable plasma lopinavir concentrations at birth and mean infant to maternal hair concentrations at 12 weeks postpartum were 0.87 for lopinavir. However, transfer during breastfeeding was not observed, and no infant had detectable plasma lopinavir levels at 12 weeks. Lopinavir concentrations in human breast milk are very low to undetectable and lopinavir concentrations in breastfeeding infants whose mothers received lopinavir are not clinically significant.
Human Studies in Pregnancy

The original capsule formulation of LPV/r has been replaced by a new tablet formulation that is heat-stable, has improved bioavailability characteristics, and does not have to be administered with food.\(^7,8\)

Pharmacokinetic studies of standard adult LPV/r doses (400 mg/100 mg twice a day) using either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with that in non-pregnant adults.\(^9-11\) Increasing dose of LPV/r during pregnancy to 600 mg/150 mg (tablets) results in lopinavir plasma concentrations equivalent to those seen in non-pregnant adults receiving standard doses.\(^12,13\) Reports of clinical experience suggest that most, but not all, pregnant women receiving standard LPV/r tablet dosing during pregnancy will have trough lopinavir concentrations that exceed 1.0 mcg/mL, the usual trough concentration target used in therapeutic drug monitoring programs for antiretroviral-naïve subjects, but not the higher trough concentrations recommended for protease inhibitor-experienced subjects.\(^7,10\) Lopinavir plasma protein binding is reduced during pregnancy, but the resulting increase in free (unbound) drug is insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.\(^14,15\)

These PK studies suggest that LPV/r doses should be increased to 600 mg/150 mg twice a day in all HIV-infected pregnant women during the second and third trimesters. If standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations, if available, should be monitored. An alternative strategy for increasing exposure to LPV/r during pregnancy is to add a pediatric LPV/r tablet (100/25 mg) to the standard dose of two adult 200/50 mg tablets.\(^15\) Once-daily dosing of LPV/r is not recommended in pregnancy because no data exist to address whether drug levels are adequate with such administration.

LPV/r oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Reduced hepatic metabolic and kidney excretory function in newborns can lead to accumulation of lopinavir as well as alcohol and propylene glycol, resulting in adverse events such as serious cardiac, renal, metabolic, or respiratory problems. Preterm babies may be at increased risk because their metabolism and elimination of lopinavir, propylene glycol, and alcohol are further reduced. Post-marketing surveillance has identified 10 neonates (i.e., babies aged <4 weeks), nine of whom were born prematurely, who received LPV/r and experienced life-threatening events.\(^16\) In a separate report comparing 50 HIV-exposed newborns treated with LPV/r after birth to 108 HIV-exposed neonates treated with zidovudine alone, elevated concentrations of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21α-hydroxylase activity, were seen only in the lopinavir-exposed infants. All term infants were asymptomatic but three of eight preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.\(^17\) LPV/r oral solution should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth, plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

References


Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

G-40

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Nelfinavir (Viracept, NFV)
(Last updated March 28, 2014; last reviewed March 28, 2014)

Nelfinavir is classified as Food and Drug Administration (FDA) Pregnancy Category B.

Animal Carcinogenicity Studies
Nelfinavir was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. However, incidence of thyroid follicular cell adenomas and carcinomas was increased over baseline in male rats receiving nelfinavir dosages of 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses).

Reproduction/Fertility
No effect of nelfinavir has been seen on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Maternal exposure to nelfinavir also did not affect subsequent reproductive performance of the offspring.

Teratogenicity/Developmental Toxicity
No evidence of teratogenicity has been observed in pregnant rats at exposures comparable to human exposure and in rabbits with exposures significantly less than human exposure.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased risk of birth defects in the more common classes of birth defects—the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nelfinavir. Among cases of first-trimester nelfinavir exposure reported to the APR, prevalence of birth defects was 3.9% (47 of 1,207 births; 95% CI, 2.9% to 5.2%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.¹

Placental and Breast Milk Transfer
Transplacental passage of nelfinavir has been minimal to low in humans. In a Phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal.² In addition, in a study of cord blood samples from 38 women treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 µg/mL) in the remaining 14 women.³ Among 20 mother-infant pairs in the Netherlands, the cord to maternal plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.⁴

Nelfinavir also has low breast milk passage. In a pharmacokinetic (PK) study conducted in Kisumu, Kenya, nelfinavir and its active metabolite M8 concentrations were measured in maternal plasma and breast milk from 26 mothers and from their 27 infants at birth, 2, 6, 14, and 24 weeks among women receiving nelfinavir as part of combination antiretroviral therapy.⁵ Peak nelfinavir concentrations in maternal plasma and breast milk were at Week 2. Median breast milk to plasma ratio was 0.12 for nelfinavir and 0.03 for its active metabolite (i.e., M8). Nelfinavir and M8 concentrations were below the limit of detection in 20/28 (71%) infant plasma dried blood spots tested from nine infants over time points from delivery though Week 24. Overall transfer to breast milk was low and resulted in non-significant exposure to nelfinavir among breastfed infants through age 24 weeks.
Human Studies in Pregnancy

A Phase I/II safety and PK study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants. In the first 9 pregnant HIV-infected women enrolled in the study, nelfinavir administered at a dose of 750 mg three times daily produced drug exposures that were variable and generally lower than those reported in non-pregnant adults with both twice- and three-times-daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1250 mg twice daily), which resulted in adequate levels of the drug in pregnancy. However, in two other small studies of women given 1250 mg nelfinavir twice daily in the second and third trimesters, drug concentrations in the second and third trimesters were somewhat lower than in non-pregnant women.

In a PK study of combination therapy including the new nelfinavir 625 mg tablet formulation (given as 1250 mg twice daily) in 25 women at 30 to 36 weeks' gestation (and 12 at 6–12 weeks postpartum), peak levels and area under the curve were lower in the third trimester than postpartum. Only 16% (4 of 25) of women during the third trimester and 8% (1/12) women postpartum had trough values greater than the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

Some nelfinavir manufactured before 2008 may have contained low levels of ethyl methane sulfonate (EMS), a process-related impurity. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data exist in humans and no increase in birth defects has been observed in the APR. All nelfinavir manufactured and released since March 31, 2008, meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients.

References

Ritonavir (Norvir, RTV)
Ritonavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Carcinogenicity Studies
Ritonavir was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of 50, 100, or 200 mg/kg/day; based on area under the curve, exposure in male mice at the highest dose was approximately 0.3-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.

Reproduction/Fertility
No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.

Teratogenicity/Developmental Toxicity
No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the APR, the prevalence of birth defects was 2.3% (45 of 1,923 births; 95% CI, 1.7%–3.1%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.¹

Placental and Breast Milk Transfer
Transplacental passage of ritonavir has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses. In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.² In a Phase I study of pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal.³ In addition, in a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 83% and was only 0.38 µg/mL in the remaining woman.⁴ In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving ritonavir-boosted-lopinavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested in utero transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth and mean infant-to-maternal-hair concentrations at 12 weeks postpartum was 0.47 for ritonavir.⁵ However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

Human Studies in Pregnancy
A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States
G-44
Downloaded from http://aidsinfo.nih.gov/guidelines on 4/8/2014
combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants showed lower levels of ritonavir during pregnancy than postpartum. Ritonavir concentrations are also reduced during pregnancy versus postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors.

References


3. Scott GB, Rodman JH, Scott WA, al e. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-10-infected pregnant women and their infants. 9th Conference on Retroviruses and Opportunistic Infections; 2002; Seattle.


Saquinavir (Invirase, SQV)
(Last updated March 28, 2014; last reviewed March 28, 2014)

Saquinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Carcinogenicity Studies
Saquinavir was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years at plasma exposures approximately 60% of those obtained in humans at the recommended therapeutic dose (rats) and at exposures equivalent to those in humans at the recommended therapeutic dose (mice).

Reproduction/Fertility
No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Teratogenicity/Developmental Toxicity
No evidence of embryotoxicity or teratogenicity of saquinavir has been found in rabbits or rats. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (area under the curve [AUC] values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Too few first-trimester saquinavir exposures have been monitored by the Antiretroviral Pregnancy Registry to be able to accurately calculate the prevalence of birth defects in exposed cases.1

Placental and Breast Milk Transfer
Placental transfer of saquinavir in the rat and rabbit was minimal. In a Phase I study in pregnant women and their infants (PACTG 386, see below), transplacental passage of saquinavir was minimal.2 In addition, in a study of cord blood samples from eight women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was less than the assay limit of detection in samples from all women.3 Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

Human Studies in Pregnancy

Studies of saquinavir pharmacokinetics (PK) in pregnancy with the original hard-gel capsule formulation demonstrated reduced saquinavir exposures compared to postpartum and dosing recommendations for 800 to 1200 mg saquinavir with 100 mg ritonavir.4-8 The PK of saquinavir with the current 500 mg tablets boosted with ritonavir at a dose of 1000 mg saquinavir /100 mg ritonavir given twice daily has been studied in pregnant women in two studies.9,10 One study performed intensive sampling on HIV-infected pregnant women at 20 weeks’ gestation (n = 16), 33 weeks’ gestation (n = 31), and 6 weeks postpartum (n = 9). PK parameters were comparable during pregnancy and postpartum.9 The second study performed intensive sampling in 14 pregnant women at 24 and 34 weeks’ gestation and 6 weeks postpartum. Saquinavir AUC was similar during the second trimester and postpartum. Although there was a 50% reduction in saquinavir AUC in the third trimester compared to postpartum, no subject experienced loss of virologic control and all but one maintained adequate third-trimester trough levels of saquinavir.11 In an observational study of saquinavir concentrations collected as part of clinical care between 11 and 13 hours after dosing with the tablet formulation (1000 mg saquinavir/100 mg ritonavir) in HIV-infected pregnant women during the third trimester (n = 20) and at delivery (n = 5), saquinavir plasma concentrations averaged around 1.15 mg/L and exceeded the usual trough drug concentration target for saquinavir of 0.1 mg/L in all but one subject.10

One study of a ritonavir-boosted-saquinavir-based combination antiretroviral drug regimen in 42 pregnant
women reported abnormal transaminase levels in 13 women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity Grade 1–2 in most, Grade 3 in 1 woman).12 In a study of 62 pregnant women on a saquinavir-ritonavir-based regimen, one severe adverse event occurred (maternal grade 3 hepatotoxicity).10

References


*Tipranavir (Aptivus, TPV)*

**(Last reviewed March 28, 2014; last updated March 28, 2014)**

Tipranavir is classified as Food and Drug Administration Pregnancy Category C.

**Animal Carcinogenicity Studies**

Tipranavir was neither mutagenic nor clastogenic in a battery of five *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150, or 300 mg/kg/day tipranavir, 150/40 mg/kg/day ritonavir-boosted tipranavir (TPV/r) in combination, or 40 mg/kg/day ritonavir. Incidence of benign hepatocellular adenomas and combined adenomas/carcinomas was increased in females of all groups except females given the low dose of tipranavir. Such tumors also were increased in male mice at the high dose of tipranavir and in the TPV/r combination group. Incidence of hepatocellular carcinoma was increased in female mice given the high dose of tipranavir and in both sexes receiving TPV/r. The combination of tipranavir and ritonavir caused an exposure-related increase in this same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on area under the curve [AUC] or maximum plasma concentration) at all dose levels tested were below those in humans receiving the recommended dose level. Rats were administered 30, 100, or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day TPV/r in combination, or 10 mg/kg/day ritonavir. No drug-related findings were observed in male rats. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the recommended therapeutic dose. This finding is probably not relevant to humans because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.

**Reproduction/Fertility**

Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels similar to human exposures at the recommended clinical dose (500/200 mg/day of TPV/r).

**Teratogenicity/Developmental Toxicity**

No teratogenicity was detected in studies of pregnant rats and rabbits at exposure levels approximately 1.1-fold and 0.1-fold human exposure. Fetal toxicity (decreased ossification and body weights) was observed in rats exposed to 400 mg/kg/day or more of tipranavir (~0.8-fold human exposure). Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold human exposures. In rats, no adverse effects on development were seen at levels of 40 mg/kg/day (~0.2-fold human exposure), but at 400 mg/kg/day (~0.8-fold human exposure), growth inhibition in pups and maternal toxicity were seen.

The number of first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.¹

**Placental and Breast Milk Passage**

No animal studies of placental or breast milk passage of tipranavir have been reported. It is unknown if placental or breast milk passage of tipranavir occurs in humans.

**Human Studies in Pregnancy**

No studies of tipranavir have been completed in pregnant women or neonates. A case report with pharmacokinetic measurements of tipranavir used in a single pregnancy showed relatively high levels of tipranavir in the third trimester and relatively high placental transfer (0.41), as measured by cord blood.² Whether this finding will be applicable to other pregnancies is unclear.
References


Entry Inhibitors
(Last updated March 28, 2014; last reviewed March 28, 2014)

Glossary of Terms for Supplement

<table>
<thead>
<tr>
<th>Term</th>
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<tr>
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<td>Causing disruption of or breakages in chromosomes</td>
</tr>
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<td>Damaging to genetic material such as DNA and chromosomes</td>
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<tr>
<td>Teratogenic</td>
<td>Interfering with fetal development and resulting in birth defects</td>
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Two drugs have been approved in this class of antiretroviral (ARV) drugs aimed at inhibiting viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein (gp)120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor such as CCR5 or CXCR4 on the host cell; binding of gp120 to the co-receptor causes subsequent conformational changes in the viral transmembrane gp41, exposing the fusion peptide of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a zipping together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous (SQ) administration, is a synthetic 36-amino-acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41, and the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other ARV drugs to treat advanced HIV infection in adults and children aged 6 years or older. Maraviroc interferes with viral entry at the chemokine co-receptor level; it is a CCR5 co-receptor antagonist approved for combination therapy for HIV infection in adults infected with CCR5-tropic virus.

**Enfuvirtide (Fuzeon, T-20)**
(Last updated March 28, 2014; last reviewed March 28, 2014)

Enfuvirtide is classified as Food and Drug Administration (FDA) Pregnancy Category B.

Animal Carcinogenicity Studies
Enfuvirtide was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Reproduction/Fertility Animal Studies
Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up to 30 mg/kg/day administered SQ (1.6 times the maximum recommended adult human daily dose on an m² body surface area basis).

Teratogenicity/Developmental Toxicity Animal Studies
Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.2 times, respectively, the adult human daily dose on an m² basis.

Placental and Breast Milk Passage

In vitro and in vivo studies suggest that enfuvirtide does not readily cross the human placenta. Published reports of a total of 8 peripartum patients and their neonates and data from an ex vivo human placental

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

cotyledon perfusion model demonstrated minimal placental passage of enfuvirtide.1-5 Studies of radiolabeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not known if this reflected radiolabeled enfuvirtide or metabolites (e.g., amino acid and peptide fragments) of enfuvirtide.

**Human Studies in Pregnancy**

Data on the use of enfuvirtide in human pregnancy are limited to case reports of a small number of women treated with the drug.1,5-10

**References**


Maraviroc (Selzentry, MVC)

(Last updated March 28, 2014; last reviewed March 28, 2014)

Maraviroc is classified as Food and Drug Administration (FDA) Pregnancy Category B.

Animal Carcinogenicity Studies

Maraviroc was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Long-term animal carcinogenicity studies of maraviroc showed no drug-related increases in tumor incidence.

Reproduction/Fertility Animal Studies

Reproductive toxicity has been evaluated in rats and rabbits. Maraviroc produced no adverse effects on fertility of male or female rats at doses with exposures (area under the curve [AUC]) up to 20-fold higher than in humans given the recommended 300 mg twice-daily dose.

Teratogenicity/Developmental Toxicity Animal Studies

The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies in rats at AUC approximately 20-fold higher (and in rabbits at approximately 5-fold higher) than human exposures at the recommended 300 mg, twice-daily dose (up to 1000 mg/kg/day in rats and 75 mg/kg/day in rabbits).

Placental and Breast Milk Passage

An ex vivo human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.1 This was also demonstrated in a study of single-dose maraviroc in rhesus macaques that showed poor placental transfer and rapid clearance from infant monkeys’ blood.2 In a study in humans of six mother/infant pairs, the median ratio of cord blood to maternal plasma drug concentrations was 0.33 (0.03–0.56).3 Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. Whether maraviroc is secreted into human milk is unknown.

Human Studies in Pregnancy

Safety and efficacy of maraviroc have not been established in pregnancy. Data on the use of maraviroc in human pregnancy are limited to a small pharmacokinetic study that found exposure to maraviroc was 21% lower during the third trimester than postpartum.3 The Antiretroviral Pregnancy Registry lists only 13 pregnancies with first-trimester exposure to entry inhibitors, with no malformations noted.4

References


Integrase Inhibitors

Three drugs have been approved in this new class of antiretroviral (ARV) drugs aimed at inhibiting integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA and a final “strand transfer” step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step in the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects retrotranscription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

**Dolutegravir (Tivicay, DTG)**

*(Last updated March 28, 2014; last reviewed March 28, 2014)*

Dolutegravir is classified as Food and Drug Administration Pregnancy Category B.

**Animal Carcinogenicity Studies**

Dolutegravir was not genotoxic or mutagenic in vitro. No carcinogenicity was detected in 2-year long-term studies in mice at exposures up to 14-fold higher than that achieved with human systemic exposure at the recommended dose, or in rats at exposures up to 10-fold higher in males and 15-fold higher in females than human exposure at the recommended dose.

**Reproduction/Fertility Animal Studies**

Dolutegravir did not affect fertility in male and female rats and rabbits at exposures approximately 27-fold higher than human clinical exposure, based on area under the curve, at the recommended dose.

**Teratogenicity/Developmental Toxicity Animal Studies**

Studies in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity or effect on reproductive function with dolutegravir.

**Placental and Breast Milk Passage**

Studies in rats have demonstrated that dolutegravir crosses the placenta in animal studies and is excreted into breast milk in rats. No human data on placental passage or breast milk excretion are available.

**Human Studies in Pregnancy**

No studies of dolutegravir use in human pregnancy have been reported.

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**Glossary of Terms for Supplement**

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*Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
Genetic mutations and/or chromosomal damage can contribute to cancer formation.*
Elvitegravir (Only Available as Stribild [Co-Formulated with Cobicistat/Tenofovir/Emtricitabine], EVG/COBI/TDF/FTC) is classified as Food and Drug Administration Pregnancy Category B.

(Last updated March 28, 2014; last reviewed March 28, 2014)

Animal Carcinogenicity Studies
Elvitegravir was not genotoxic or mutagenic in vitro. No carcinogenicity was detected in long-term studies in mice at exposures up to 14-fold and rats at exposures up to 27-fold that achieved human systemic exposure at the recommended dose. Cobicistat was not genotoxic or mutagenic in vitro. Long-term carcinogenicity testing is ongoing for cobicistat.

Reproduction/Fertility Animal Studies
Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures than in humans at standard dosing. Fertility was normal in offspring. Cobicistat did not affect fertility in male and female rats at exposures approximately 4-fold higher than in humans. Fertility was normal in exposed offspring.

Teratogenicity/Developmental Toxicity Animal Studies
Studies in rats and rabbits have shown no evidence of teratogenicity or effect on reproductive function with elvitegravir or cobicistat.

Placental and Breast Milk Passage
Studies in rats have demonstrated that elvitegravir and cobicistat are secreted in milk. No human data are available for either drug. No data on placental passage are available for elvitegravir or cobicistat.

Human Studies in Pregnancy
No studies of elvitegravir/cobicistat use in human pregnancy have been reported.
**Raltegravir (Isentress, RAL)**

(Last updated March 28, 2014; last reviewed March 28, 2014)

Raltegravir is classified as Food and Drug Administration Pregnancy Category C.

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**Animal Carcinogenicity Studies**

Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential at systemic exposures 1.8-fold (females) or 1.2-fold (males) greater than human exposure at the recommended dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir (exposure 3-fold higher than in humans at the recommended adult dose) for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats receiving doses resulting in systemic exposures that were 1.7-fold (males) to 1.4-fold (females) greater than the human exposure at the recommended dose.

**Reproduction/Fertility Animal Studies**

Raltegravir produced no adverse effects on fertility of male or female rats at doses up to 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended adult human dose).

**Teratogenicity/Developmental Toxicity Animal Studies**

Studies in rats and rabbits revealed no evidence of treatment-related effects on embryonic/fetal survival or fetal weights from raltegravir administered in doses producing systemic exposures approximately 3- to 4-fold higher than the exposure at the recommended adult human daily dose. In rabbits, no treatment-related external, visceral, or skeletal changes were observed. However, treatment-related increases in the incidence of supernumerary ribs were seen in rats given raltegravir at 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended human daily dose).

**Placental and Breast Milk Passage**

Placental transfer of raltegravir was demonstrated in both rats and rabbits. In rats given a maternal dose of 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5- to 2.5-fold higher than in maternal plasma at 1 and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentrations in fetal plasma were approximately 2% of the mean maternal plasma concentration at both 1 and 24 hours following a maternal dose of 1000 mg/kg/day.

In humans, raltegravir appears to readily cross the placenta. In P1026s, maternal and cord blood from six deliveries of mothers receiving raltegravir-based therapy during pregnancy were evaluated; the ratio of cord blood to maternal plasma was 0.98 (95% confidence interval, 0.09–2.26).\(^1\) Other case reports have shown similarly high cord blood/maternal blood drug level ratios of 1.00 to 1.06.\(^2,3\) In a report of three pregnant women with multiresistant HIV-1 who were given raltegravir in late pregnancy to rapidly reduce maternal viral load, raltegravir concentrations within 3 hours of delivery in the neonates of two patients were approximately 7 and 9.5 times higher than in the mother’s paired sample; in the third infant, maternal plasma was not available but neonatal concentration was still high 2.5 hours after delivery.\(^4\) However, no adverse reactions were observed in mothers or infants. In a series of three cases with preterm deliveries at 29 to 33 weeks’ gestation (in 2 cases raltegravir was added to the maternal antiretroviral regimen shortly before anticipated preterm delivery), cord blood-to-maternal-plasma ratios ranged from 0.44 to 1.88.\(^5\)

Raltegravir is secreted in the milk of lactating rats, with mean drug concentrations in milk about 3-fold higher than in maternal plasma at a maternal dose of 600 mg/kg/day. No effects in rat offspring were attributable to raltegravir exposure through breast milk. Whether raltegravir is secreted in human breast milk is unknown.
Human Studies in Pregnancy

Only limited data exist on the use of raltegravir in pregnancy. Raltegravir pharmacokinetics (PK) were evaluated in 10 women in the IMPAACT P1026s study. Raltegravir PKs showed extensive variability but did not appear to be consistently altered during the third trimester compared with postpartum and historical data in non-pregnant individuals; thus the standard dose appears appropriate in pregnancy.\(^1\) In multiple case reports and case series of 4, 5, and 14 pregnant women treated with raltegravir in combination with 2 or 3 other antiretroviral drugs because of persistent viremia or late presentation, the drug was well tolerated and led to rapid reduction in HIV RNA levels.\(^6\)\(^-\)\(^10\) However, in one case of similar use, 10- to 23-fold increases in liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.\(^11\) Drug levels were not measured in any of those studies.

Because raltegravir is highly protein bound to albumin, there is concern about displacement of bilirubin from albumin in the neonate potentially increasing the risk of neonatal hyperbilirubinemia. In an in vitro study of the effect of raltegravir on bilirubin-albumin binding, raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5 µM and 10 µM, caused a small but statistically significant increase in unbound bilirubin at 100 µM, and caused potentially harmful increases at 500 and 1000 µM.\(^12\) These data suggest that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant at typical peak concentrations reached in adults with usual dosing (adult concentrations with standard raltegravir doses were geometric mean C\(_{\text{max}}\) of 4.5 µM, median C\(_{\text{max}}\) of 6.5 µM and maximum observed C\(_{\text{max}}\) of 10.2 µM).\(^12\) Raltegravir should not be used in neonates until PK and toxicity studies have been completed.

Chewable tablets contain phenylalanine.

References


Antiretroviral Pregnancy Registry  (Last updated March 28, 2014; last reviewed March 28, 2014)

The Antiretroviral Pregnancy Registry (APR) is an epidemiologic project to collect observational, non-experimental data on antiretroviral (ARV) drug exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners.

It is strongly recommended that health care providers who are treating HIV-infected pregnant women and their newborns report cases of prenatal exposure to ARV drugs (either alone or in combination) to the APR. The registry does not use patient names and birth outcome follow-up is obtained from the reporting physician by registry staff.

Referrals should be directed to:

Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405
Telephone: 1–800–258–4263
Fax: 1–800–800–1052
http://www.APRegistry.com
### Appendix C: Acronyms  
(Last updated March 28, 2014; last reviewed March 28, 2014)

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<tr>
<th>Acronym/Abbreviation</th>
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<tr>
<td>3TC</td>
<td>lamivudine</td>
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<tr>
<td>ABC</td>
<td>abacavir</td>
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<tr>
<td>ACOG</td>
<td>American College of Obstetricians and Gynecologists</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>DRV/r</td>
<td>ritonavir-boosted darunavir</td>
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DTG  dolutegravir
DSMB  Data and Safety Monitoring Board
EC  enteric coated
ECG  electrocardiogram
EFV  efavirenz
EMS  ethyl methane sulfonate
EPPICCC  The European Pregnancy and Paediatric HIV Cohort Collaboration
ETR  etravirine
EVG  elvitegravir
FDA  Food and Drug Administration
FDC  fixed drug combination
FPV  fosamprenavir
FPV/r  ritonavir-boosted fosamprenavir
FTC  emtricitabine
gp  glycoprotein
HAV  hepatitis A virus
HBIG  hepatitis B immune globulin
HBsAg  hepatitis B surface antigen
HBV  hepatitis B virus
HCV  hepatitis C virus
HELLP  hemolysis, elevated liver enzymes, and low platelets
HGC  hard gel capsule
HR  hazard ratio
HRSA  Health Resources and Services Administration
HSR  hypersensitivity reaction
IC50  inhibitory concentration 50%
IDV  indinavir
IDV/r  ritonavir-boosted indinavir
IGF  insulin-like growth factor
IP  intrapartum
IQR  interquartile range
IRIS  immune reconstitution inflammatory syndrome
IUD  intrauterine device
IV  intravenous/intravenously
LPV  lopinavir
LPV/r  ritonavir-boosted lopinavir
MAC  *Mycobacterium avium* complex
MACDP  Metropolitan Atlanta Congenital Defects Program
MIRIAD  Mother-Infant Rapid Intervention at Delivery (study)
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<td>uridine diphosphate glucuronosyltransferase</td>
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<td>WITS</td>
<td>Women and Infants Transmission Study</td>
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<td>ZDV</td>
<td>zidovudine</td>
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Revised Surveillance Case Definition for HIV Infection — United States, 2014
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Revised Surveillance Case Definition for HIV Infection — United States, 2014

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Summary
Following extensive consultation and peer review, CDC and the Council of State and Territorial Epidemiologists have revised and combined the surveillance case definitions for human immunodeficiency virus (HIV) infection into a single case definition for persons of all ages (i.e., adults and adolescents aged ≥13 years and children aged <13 years). The revisions were made to address multiple issues, the most important of which was the need to adapt to recent changes in diagnostic criteria. Laboratory criteria for defining a confirmed case now accommodate new multitest algorithms, including criteria for differentiating between HIV-1 and HIV-2 infection and for recognizing early HIV infection. A confirmed case can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown); early infection, recognized by a negative HIV test within 6 months of HIV diagnosis, is classified as stage 0, and acquired immunodeficiency syndrome (AIDS) is classified as stage 3. Criteria for stage 3 have been simplified by eliminating the need to differentiate between definitive and presumptive diagnoses of opportunistic illnesses. Clinical (nonlaboratory) criteria for defining a case for surveillance purposes have been made more practical by eliminating the requirement for information about laboratory tests. The surveillance case definition is intended primarily for monitoring the HIV infection burden and planning for prevention and care on a population level, not as a basis for clinical decisions for individual patients. CDC and the Council of State and Territorial Epidemiologists recommend that all states and territories conduct case surveillance of HIV infection using this revised surveillance case definition.

Introduction
Since the first cases of acquired immunodeficiency syndrome (AIDS) were reported in the United States in 1981, surveillance case definitions for human immunodeficiency virus (HIV) infection (the cause of AIDS) and AIDS have undergone several revisions to respond to diagnostic advances (1–5). This document updates the surveillance case definitions published in 2008 (5). It addresses multiple issues, the most important of which was the need to adapt to recent changes in diagnostic criteria. Other needs that prompted the revision included 1) recognition of early HIV infection, 2) differentiation between HIV-1 and HIV-2 infections, 3) consolidation of staging systems for adults/adolescents and children, 4) simplification of criteria for opportunistic illnesses indicative of AIDS, and 5) revision of criteria for reporting diagnoses without laboratory evidence.

Summary of Revisions to Surveillance Case Definition
The most important update is revision of the laboratory criteria for a confirmed case, which addresses the development of new diagnostic testing algorithms that do not use the Western blot or immunofluorescence HIV antibody assays. During 2009–2011, CDC and the Association of Public Health Laboratories proposed new diagnostic algorithms (6,7), and in June 2011 the Clinical and Laboratory Standards Institute (CLSI) published updated laboratory testing procedures for diagnosis of HIV infection (8). In these multitest algorithms, “supplemental” HIV tests (for confirming or verifying the presence of HIV infection after a positive [or “reactive”] result from an initial HIV test) can now include antibody immunoassays formerly used only as initial tests (e.g., conventional immunoassays or rapid tests) or can include nucleic acid tests (NAT). The 2008 surveillance case definition was not clearly consistent with the new algorithms because it specified that a test used for confirmation must be a “supplemental HIV antibody test (e.g., Western blot or indirect...
immonofluorescence assay test)” (5). This revised surveillance case definition explicitly allows these new testing algorithms.

Some new multitest algorithms lead to a conclusion that laboratories might classify as a “presumptive positive” result. Persons with a presumptive positive test result are expected to receive subsequent tests, such as a quantitative viral load, to confirm their HIV diagnosis, but results of those tests might not be immediately available to surveillance programs. To avoid unnecessary complexity for surveillance, the revised surveillance case definition, like the earlier definition, does not make a distinction between presumptive and definitive diagnoses. If subsequent test results reveal that the person is not infected, the case and previous test results should be deleted from the surveillance database.

Another important change is the addition of “stage 0” based on a sequence of negative and positive test results indicative of early HIV infection. This addition takes advantage of tests incorporated in the new algorithms that are more sensitive during early infection than previously used tests, and that together with a less sensitive antibody test, yield a combination of positive and negative results enabling diagnosis of acute (primary) HIV infection, which occurs before the antibody response has fully developed. The addition of stage 0 allows for routine monitoring of the number of cases diagnosed within several months after infection, which includes the most highly infectious period when viral loads are extremely high and intervention might be most effective in preventing further transmission. The definition of stage 0 also will reduce confusion between acute HIV infection (part of stage 0), when CD4+ T-lymphocyte counts can be transiently depressed, and stage 3 (AIDS), an advanced stage of HIV infection when CD4+ T-lymphocyte values are usually persistently depressed (9).

The revised case definition adds other criteria and eliminates several criteria that were impractical or difficult to implement uniformly across all states and territories. Specifically, the revised case definition:

- Adds specific criteria for defining a case of HIV-2, which were not included in the 2008 case definition. The new definition incorporates criteria for HIV-2 infection used in a report of surveillance for HIV-2 infection (10) and included in one of the new CLSI testing algorithms (8).
- Eliminates the requirement to indicate if opportunistic illnesses (AIDS-defining conditions) indicative of stage 3 (AIDS) were diagnosed by “definitive” or “presumptive” methods. This requirement has been impractical to implement because the criteria to distinguish between “definitive” and “presumptive” methods were not interpreted in a standard, uniform way by state and local surveillance programs.
- Classifies stages 1–3 of HIV infection on the basis of the CD4+ T-lymphocyte count unless persons have had a stage-3–defining opportunistic illness. The CD4+ T-lymphocyte percentage is used only when the corresponding CD4+ T-lymphocyte count is unknown. This avoids overestimating the proportion of cases in stage 3, which occurred when the stage was based on whichever CD4+ T-lymphocyte test result (count or percentage) indicated the more advanced stage. Clinical evidence suggests the percentage has little effect on prognosis after adjusting for the count (11,12).
- Removes the requirement that a “physician-documented” diagnosis must be based on laboratory evidence. This revision allows clinical evidence to be sufficient to define a case when it is impractical to retrieve laboratory test information regarding the initial diagnosis. The new definition also clarifies that the date of a physician-documented diagnosis is the diagnosis date recorded in a medical record note, rather than the date that the physician wrote the note.
- Combines the adult and pediatric criteria for a confirmed case of HIV infection and specifies different criteria for staging HIV infection among three age groups (<1 year, 1–5 years, and ≥6 years).
- Eliminates the distinction between definitive and presumptive diagnoses of HIV infection in children aged <18 months.
- Removes lymphoid interstitial pneumonia (pulmonary lymphoid hyperplasia) from the list of opportunistic illnesses indicative of stage 3 in children because this illness is associated with moderate rather than severe immunodeficiency (4).
- Eliminates the requirement that evidence of HIV infection in a child’s biologic mother is needed to define a case of HIV infection in a child aged ≤18 months when laboratory testing of the infant independently confirms HIV infection. This change was recommended in a position statement approved at the June 2009 annual meeting of the Council of State and Territorial Epidemiologists (CSTE) (13).
- Extends the use of CD4+ T-lymphocyte counts and percentages for determining the stage of HIV infection to children as well as adults and adolescents, and now determines the stage in children aged 6–12 years the same way as in adults and adolescents. In the 2008 case definition, only the presence or absence of opportunistic illnesses was used as criteria for staging cases among children aged <13 years.
Scope and Applicability of the Surveillance Case Definition

This revised case definition, like the earlier one, is intended primarily for public health surveillance of HIV infection on a population level. Early diagnosis and viral suppression facilitate prevention of HIV transmission, morbidity, and mortality. This case definition’s staging system allows for health departments to evaluate prevention and care, which can be measured by analyzing cases by their stage at diagnosis and how rapidly they progress to more advanced stages. For various reasons, it would be inappropriate for clinicians to use the surveillance staging system as a guide to manage patients. United States national panels on antiretroviral guidelines recommend antiretroviral therapy for all HIV-infected adults, adolescents, and infants, and the staging system does not include criteria strongly recommended as indicators for more rapid initiation of therapy (e.g., HIV nephropathy, hepatitis B coinfection, viral load >100,000 copies/mL, and a decline in CD4+ T-lymphocyte count by >100 cells/µL per year) (14–16). Treatment guidelines for children aged >1 year also recommend starting therapy on the basis of criteria other than stage, such as a viral load >100,000 copies/mL or conditions that are important (e.g., clinical category B [13]) but do not indicate stage 3, if treatment had been deferred after diagnosis (16, 17).

Methods

The revised case definition was developed in several stages. First, in 2010, HIV surveillance experts at CDC convened six work groups that included both CDC and external subject matter experts, including health-care providers, surveillance health department staff, and representatives from academic institutions and public health and commercial laboratories. The names of work group members are listed at the end of this report. The six topic areas were new HIV testing algorithms, acute HIV infection, HIV-2 infection, opportunistic illnesses, pediatric HIV infection, and physician-documented diagnosis. Each work group examined research and program information about the topic areas and elicited experience and expert opinion from federal, state, and local HIV surveillance programs; clinicians who diagnose HIV infection; and laboratories that report HIV test results.

Second, all work groups presented a summary of their reports at a consultation convened by CDC in February 2012. The consultation included additional experts in HIV surveillance, laboratory testing, and clinical care, including members of CSTE.

Third, most of the recommendations from the consultation were incorporated in a position statement developed in collaboration with CDC that was approved at the June 2012 annual meeting of CSTE (18). The revisions of the surveillance case definition in this document are based largely on that position statement. Finally, this document underwent peer review (described at http://www.cdc.gov/hiv/pdf/policies_PRP_Revised_HIV_Case_Def.pdf) by health-care professionals in compliance with the Office of Management and Budget requirements for the dissemination of influential scientific information.

Revised Surveillance Case Definition

Section 1: Criteria for a Confirmed Case

Criteria for a confirmed case can be met by either laboratory evidence or clinical evidence, as described below. Laboratory evidence is preferred over clinical evidence.

1.1: Persons Aged ≥18 Months and Children Aged <18 Months whose Mothers were Not Infected

1.1.1: Laboratory Evidence

Laboratory criteria require reporting of the date of the specimen collection for positive test results in multitest algorithms or stand-alone virologic tests and enough information about the tests to determine that they meet any of the following criteria:

- A multitest algorithm consisting of
  - A positive (reactive) result from an initial HIV antibody or combination antigen/antibody test, and
  - An accompanying or subsequent positive result from a supplemental HIV test different from the initial test (8).

The initial HIV antibody or antigen/antibody test and the supplemental HIV test that is used to verify the result from the initial test can be of any type used as an aid to diagnose HIV infection. For surveillance purposes, supplemental tests can include some not approved by the Food and Drug Administration (FDA) for diagnosis (e.g., HIV-1 viral load test, HIV-2 Western blot/immunoblot antibody test, and HIV-2 NAT). However, the initial and supplemental tests must be “orthogonal” (i.e., have different antigenic constituents or use different principles) to minimize the possibility of concurrent nonspecific reactivity. Because the antigenic constituents and test principles are proprietary information that might not be publicly available for some tests, tests will be assumed to be orthogonal if they are of different types. For example:
  - One test is a combination antigen/antibody test and the other an antibody-only test.
  - One test is an antibody test and the other a NAT.
– One test is a rapid immunoassay (a single-use analytical device that produces results in <30 minutes) and the other a conventional immunoassay.
– One test is able to differentiate between HIV-1 and HIV-2 antibodies and the other is not.

Tests also will be assumed to be orthogonal if they are of the same type (e.g., two conventional immunoassays) but made by different manufacturers. The type of HIV antibody test that verifies the initial test might be one formerly used only as an initial test (e.g., conventional or rapid immunoassay, HIV-1/2 type-differentiating immunoassay), or it might be one traditionally used as a supplemental test for confirmation (e.g., Western blot, immunofluorescence assay).

• A positive result of a multitest HIV antibody algorithm from which only the final result was reported, including a single positive result on a test used only as a supplemental test (e.g., HIV Western blot, immunofluorescence assay) or on a test that might be used as either an initial test or a supplemental test (e.g., HIV-1/2 type-differentiating rapid antibody immunoassay) when it might reasonably be assumed to have been used as a supplemental test (e.g., because the algorithm customarily used by the reporting laboratory is known).
• A positive result or report of a detectable quantity (i.e., within the established limits of the laboratory test) from any of the following HIV virologic (i.e., nonantibody) tests:
  – Qualitative HIV NAT (DNA or RNA)
  – Quantitative HIV NAT (viral load assay)
  – HIV-1 p24 antigen test
  – HIV isolation (viral culture) or
  – HIV nucleotide sequence (genotype).

1.1.2: Clinical (Nonlaboratory) Evidence

Clinical criteria for a confirmed case (i.e., a “physician-documented” diagnosis for which the surveillance staff have not found sufficient laboratory evidence described above) are met by the combination of:
• A note in a medical record by a physician or other qualified medical-care provider that states that the patient has HIV infection, and
• One or both of the following:
  – The laboratory criteria for a case were met based on tests done after the physician’s note was written (validating the note retrospectively).
  – Presumptive evidence of HIV infection (e.g., receipt of HIV antiretroviral therapy or prophylaxis for an opportunistic infection), an otherwise unexplained low CD4+ T-lymphocyte count, or an otherwise unexplained diagnosis of an opportunistic illness (Appendix).

1.2: Children Aged <18 Months Born to Mothers Who Have an Unknown Infection Status or Were Known to be Infected

1.2.1: Laboratory Evidence

A child aged <18 months is categorized for surveillance purposes as HIV infected if all of the following criteria are met:
• Positive results on at least one specimen (not including cord blood) from any of following HIV virologic tests:
  – HIV-1 NAT (DNA or RNA)
  – HIV-1 p24 antigen test, including neutralization assay for a child aged >1 month
  – HIV isolation (viral culture) or
  – HIV nucleotide sequence (genotype).
• The test date (at least the month and year) is known.
• One or both of the following:
  – Confirmation of the first positive result by another positive result on one of the above virologic tests from a specimen obtained on a different date or
  – No subsequent negative result on an HIV antibody test, and no subsequent negative result on an HIV NAT before age 18 months.

1.2.2: Clinical Evidence

• The same criteria as in section 1.1.2 or
• All three of the following alternative criteria:
  – Evidence of perinatal exposure to HIV infection before age 18 months
    ○ A mother with documented HIV infection or
    ○ A confirmed positive test for HIV antibody (e.g., a positive initial antibody test or antigen/antibody test, confirmed by a supplemental antibody test) and a mother whose infection status is unknown or undocumented.
  – Diagnosis of an opportunistic illness indicative of stage 3 (Appendix).
  – No subsequent negative result on an HIV antibody test.

1.3: Definition for Date of Diagnosis of a Confirmed Case for all Ages

1.3.1: Laboratory Criteria

If the diagnosis is based on laboratory evidence, the diagnosis date is defined as the earliest date on which the specimen was obtained for a positive HIV test result.

1.3.2: Clinical Criteria

If the diagnosis was based on clinical evidence (“physician-documented”) rather than laboratory evidence, the diagnosis
date is defined as the date (at least the year) of diagnosis reported in the content of the medical record. If the diagnosis date was not reported in the note, the date when the note was written can be used as a proxy.

Section 2: Criteria for Classifying the HIV Type as HIV-2

All HIV infections in the United States should be assumed to be type 1 (HIV-1) unless laboratory test results are sufficient to classify the infection as type 2 (HIV-2), dual HIV-1 and HIV-2 infections, or undifferentiated HIV infection, as described below. Clinical or epidemiologic evidence might lead to laboratory testing for HIV-2 but is insufficient for classifying the HIV type as HIV-2.

2.1: Persons Aged ≥18 Months and Children Aged <18 Months Not Perinatally Exposed

HIV-2 infection

For HIV-2 infection, one or more of the following laboratory criteria are necessary and sufficient:

- FDA-approved HIV1/2 type-differentiating antibody test result positive for HIV-2 and negative for HIV-1.
- Positive HIV-2 Western blot (WB) (or immunoblot or line assay) result and negative or indeterminate HIV-1 WB result.
- Positive qualitative HIV-2 NAT result.
- Detectable quantitative HIV-2 NAT (viral load).
- Laboratory results interpreted as consistent with HIV-2 infection by a laboratory expert experienced in differentiating HIV-2 from HIV-1 if laboratory evidence for HIV-2 is ambiguous.

Dual infection with HIV-1 and HIV-2

The HIV type is classified as “dual” infection (both HIV-1 and HIV-2) if both an HIV-1 NAT and an HIV-2 NAT are positive.

Undifferentiated HIV type

The HIV type is classified as “undifferentiated” if there is no positive or detectable result from an HIV-1 NAT and a laboratory expert cannot resolve ambiguous evidence for HIV-2, such as:

- HIV-2 WB is positive and HIV-1 WB is HIV positive or
- HIV-1/HIV-2 type-differentiating antibody test result interpretation is “undifferentiated” (positive for both HIV-1 and HIV-2).

2.2: Difficulty of Diagnosing HIV-2 Infection in Children Aged <18 Months Born to Mothers Known to be HIV-infected or whose HIV Infection Status is Unknown

In perinatally exposed children aged <18 months, antibody tests are not used to diagnose HIV infection because of the expectation that they might be false indicators of infection in the child due to passive transfer of maternal antibody. The HIV-1 NAT routinely used to diagnose HIV-1 infection in children of this age is likely to be negative in an HIV-2-infected child because it is insensitive to HIV-2. A positive HIV-2 NAT result would satisfy the criteria for a case. Otherwise, the diagnosis of HIV-2 infection in a child will need to wait until the child is aged 18 months, when it can be based on antibody test results.

Section 3: Criteria for Uninfected and Indeterminate HIV Infection Status of Perinatally Exposed Children Aged <18 Months

3.1: Uninfected

A child aged <18 months who was born to an HIV-infected mother or had a positive HIV antibody test result is classified for surveillance purposes as not infected with HIV if all three of the following criteria are met:

- Laboratory criteria for HIV infection are not met (see section 1.2.1)
- No diagnosis of a stage-3-defining opportunistic illness (Appendix) attributed to HIV infection and
- Either laboratory or clinical evidence of absence of HIV infection as described below.

3.1.1: Laboratory Evidence

Definitively Uninfected

- No positive HIV NAT (RNA or DNA) and
- At least one of the following criteria:
  - At least two negative HIV NATs from specimens obtained on different dates, both of which were at age ≥1 month and one of which was at age ≥4 months.
  - At least two negative HIV antibody tests from specimens obtained on different ages at age ≥6 months.

Presumptively Uninfected

- Criteria for definitively uninfected with HIV are not met
- At least one of the following four laboratory criteria are met:
  - At least two negative NATs from specimens obtained on different dates, both of which were at age ≥2 weeks and one of which was at age ≥4 weeks.
– One negative NAT (RNA or DNA) from a specimen obtained at age ≥8 weeks.
– One negative HIV antibody test from a specimen obtained at age ≥6 months.
– If criteria for HIV infection had initially been met by one positive HIV NAT test then it must have been followed by at least two negative test results from specimens obtained on different dates, one of which is:
  ◦ A NAT test from a specimen obtained at age ≥8 weeks, or
  ◦ An HIV antibody test from a specimen obtained at age ≥6 months.

• No subsequent positive NAT.

3.1.2: Clinical Evidence
A note in a medical record by a physician or other qualified medical-care provider states that the patient is not infected with HIV.

3.2: Indeterminate HIV infection status
A child aged <18 months born to an HIV-infected mother is categorized as having perinatal exposure with an indeterminate HIV infection status if neither the criteria for being HIV-infected nor the criteria for being uninfected are met.

Section 4: Criteria for Classifying the Stage of HIV Infection
The stages of HIV infection defined in this document are for surveillance staging of disease and might not be appropriate for patient care, clinical research, or other purposes. A confirmed case that meets the criteria for diagnosis of HIV infection can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown). Stage 0 indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 6 months of a confirmed positive result, and these criteria supersede and are independent of the criteria used for later stages. Stages 1, 2, and 3 are based on the CD4+ T-lymphocyte count. If the CD4+ count is missing or unknown, the CD4+ T-lymphocyte percentage of total lymphocytes can be used to assign the stage.

Cases with no information on CD4+ T-lymphocyte count or percentage are classified as stage unknown. If a stage-3–defining opportunistic illness has been diagnosed, then the stage is 3 regardless of CD4 T-lymphocyte test results, unless the criteria described below for stage 0 are met. CD4+ T-lymphocyte counts or percentages at the time of diagnosis allow classification of cases by stage at diagnosis. Subsequent CD4+ T-lymphocyte counts or percentages help monitor disease progression and whether the person is receiving on-going care.

The stage characterizes the status of HIV disease at a particular point in time. Of primary interest to surveillance is the stage at initial diagnosis, but the stage can change in either direction after diagnosis and might be defined with reference to dates of interest such as the most advanced stage recorded through a particular date. The stages are defined as follows:

Stage 0
The criteria for stage 0 consist of a sequence of discordant test results indicative of early HIV infection in which a negative or indeterminate result was within 180 days of a positive result. The criteria for stage 0 supersede and are independent of the criteria used for other stages.

Stage 0 can be established either:
• Based on testing history (previous negative/indeterminate test results): a negative or indeterminate HIV test (antibody, combination antigen/antibody, or nucleic acid test) result within 180 days before the first confirmed positive HIV test result of any type. The first positive test result could be any time before the positive supplemental test result that confirms it or
• Based on a testing algorithm: a sequence of tests performed as part of a laboratory testing algorithm that demonstrate the presence of HIV-specific viral markers such as p24 antigen or nucleic acid (RNA or DNA) 0–180 days before or after an antibody test that had a negative or indeterminate result. Examples of algorithms that would fulfill this requirement include:
  – A positive initial HIV immunoassay result (e.g., antigen/antibody or antibody only) followed by a negative or indeterminate supplemental antibody test result (e.g., HIV-1/HIV-2 antibody differentiation assay or Western blot) and a positive NAT result. All three tests are usually performed as part of the same testing algorithm but time might elapse between tests if additional specimens must be obtained for definitive supplemental testing.
  – A negative initial HIV immunoassay result followed by a positive NAT result that might have been done to evaluate the presence of acute HIV infection (19,20).

Exception
A confirmed case of HIV infection is not in stage 0 if the negative or indeterminate HIV test used as the criterion for it being a recent infection was preceded >60 days by evidence of HIV infection, such as a confirmed positive HIV test result, a clinical (physician-documented) diagnosis of HIV infection for which the surveillance staff have not found sufficient laboratory evidence, a CD4+ T-lymphocyte test result indicative of stage 3 (Table), or an opportunistic illness indicative of stage 3 (Appendix).
CLASSIFYING A CASE AS STAGE 0 DEPENDS ON DOCUMENTING NEGATIVE HIV ANTIBODY TEST RESULTS IN THE SPECIFIC SITUATIONS DESCRIBED ABOVE. NEGATIVE TEST RESULTS FROM TESTING ALGORITHMS THAT HAVE CONCLUDED THAT THE PERSON IS NOT INFECTED NEED NOT BE REPORTED TO HIV SURVEILLANCE PROGRAMS.

CLASSIFICATION OF HIV INFECTION STAGE

Classifying a case as stage 0 depends on documenting negative HIV antibody test results in the specific situations described above. Negative test results from testing algorithms that have concluded that the person is not infected need not be reported to HIV surveillance programs.

PROGRESSION OF STAGE AFTER INITIAL DIAGNOSIS IN STAGE 0

Although the stage at diagnosis does not change, if >180 days have elapsed after the stage was 0 at diagnosis, the stage at the later date is classified as 1, 2, 3, or unknown, depending on CD4+ T-lymphocyte test results (Table) or whether an opportunistic illness had been diagnosed >180 days after HIV infection diagnosis.

STAGES 1, 2, 3, AND UNKNOWN

If the criteria for stage 0 are not met, the stage is classified as 1, 2, 3, or unknown, depending on CD4+ T-lymphocyte test results or whether an opportunistic illness was diagnosed (Table). Infection among children aged 6–12 years is staged with the same criteria as infection among adults and adolescents, including opportunistic illnesses indicative of stage 3 (Appendix) that formerly applied only to adults and adolescents (i.e., pulmonary tuberculosis, recurrent pneumonia, and cervical cancer). Multiple or recurrent bacterial infections (other than recurrent salmonella septicemia), which formerly applied only to children aged <13 years, now apply only to children aged <6 years. Lymphoid interstitial pneumonia is no longer classified as indicative of stage 3 in children because it is associated with moderate rather than severe immunodeficiency (4). The diagnosis of any of the opportunistic illnesses, irrespective of diagnostic method used, will meet the criteria for staging, thereby eliminating the requirement in the 2008 case definition for some of them to be “definitively” diagnosed.

**TABLE. HIV infection stage* based on age-specific CD4+ T-lymphocyte count or CD4+ T-lymphocyte percentage of total lymphocytes**

<table>
<thead>
<tr>
<th>Age on date of CD4+ T-lymphocyte test</th>
<th>&gt;1 yr</th>
<th>1–5 yrs</th>
<th>≥6 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>≥1,500</td>
<td>≥1,000</td>
<td>≥500</td>
</tr>
<tr>
<td>Stage 1</td>
<td>&lt;1,500</td>
<td>≥1,000</td>
<td>≥500</td>
</tr>
<tr>
<td>Stage 2</td>
<td>&lt;750</td>
<td>≥750</td>
<td>≥200</td>
</tr>
<tr>
<td>Stage 3</td>
<td>&lt;750</td>
<td>&lt;750</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&lt;750</td>
<td>&lt;750</td>
<td>&lt;200</td>
</tr>
</tbody>
</table>

*The stage is based primarily on the CD4+ T-lymphocyte count; the CD4+ T-lymphocyte count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing. There are three situations in which the stage is not based on this table: 1) if the criteria for stage 0 are met, the stage is 0 regardless of criteria for other stages (CD4 T-lymphocyte test results and opportunistic illness diagnoses); 2) if the criteria for stage 0 are not met and a stage-3 defining opportunistic illness has been diagnosed (Appendix), then the stage is 3 regardless of CD4 T-lymphocyte test results; or 3) if the criteria for stage 0 are not met and information on the above criteria for other stages is missing, then the stage is classified as unknown.

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Disclosure of Competing Interests

The federal government employees who prepared this report have no conflict of interest with the manufacturers of the products discussed herein. Competing interests for non-CDC contributors were not assessed except for the five experts who reviewed a draft of this manuscript (external peer review described at http://www.cdc.gov/hiv/pdf/policies_PRP_Revised_HIV_Case_Def.pdf); they had no competing interests.
Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive§
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month’s duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV§
Herpes simplex: chronic ulcers (>1 month’s duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month’s duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
*Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
*Mycobacterium tuberculosis of any site, pulmonary†, disseminated, or extrapulmonary
*Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as “Pneumocystis carinii”) pneumonia
Pneumonia, recurrent‡
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV§

* Only among children aged <6 years.
† Only among adults, adolescents, and children aged ≥6 years.
§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:
CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(No. RR-12).
CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(No. RR-17).
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

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Summary

These recommendations for human immunodeficiency virus (HIV) testing are intended for all health-care providers in the public and private sectors, including those working in hospital emergency departments, urgent care clinics, inpatient services, substance abuse treatment clinics, public health clinics, community clinics, correctional health-care facilities, and primary care settings. The recommendations address HIV testing in health-care settings only. They do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans). The objectives of these recommendations are to increase HIV screening of patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States. These revised recommendations update previous recommendations for HIV testing in health-care settings.
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

settings and for screening of pregnant women (CDC. Recommendations for HIV testing services for inpatients and outpatients in acute-care hospital settings. MMWR 1993;42[No. RR-2]:1--10; CDC. Revised guidelines for HIV counseling, testing, and referral. MMWR 2001;50[No. RR-19]:1--62; and CDC. Revised recommendations for HIV screening of pregnant women. MMWR 2001;50[No. RR-19]:63--85).

Major revisions from previously published guidelines are as follows:

For patients in all health-care settings

- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.

For pregnant women

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.
- HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Repeat screening in the third trimester is recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.

Introduction

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) remain leading causes of illness and death in the United States. As of December 2004, an estimated 944,306 persons had received a diagnosis of AIDS, and of these, 529,113 (56%) had died (1). The annual number of AIDS cases and deaths declined substantially after 1994 but stabilized during 1999--2004 (1). However, since 1994, the annual number of cases among blacks, members of other racial/ethnic minority populations, and persons exposed through heterosexual contact has increased. The number of children reported with AIDS attributed to perinatal HIV transmission peaked at 945 in 1992 and declined 95% to 48 in 2004 (1), primarily because of the identification of HIV-infected pregnant women and the effectiveness of antiretroviral prophylaxis in reducing mother-to-child transmission of HIV (2).

By 2002, an estimated 38%--44% of all adults in the United States had been tested for HIV; 16--22 million persons aged 18--64 years are tested annually for HIV (3). However, at the end of 2003, of the approximately 1.0--1.2 million persons estimated to be living with HIV in the United States, an estimated one quarter (252,000--312,000 persons) were unaware of their infection and therefore unable to benefit from clinical care to reduce morbidity and mortality (4). A number of these persons are likely to have transmitted HIV unknowingly (5).

Treatment has improved survival rates dramatically, especially since the introduction of highly active antiretroviral therapy (HAART) in 1995 (6). However, progress in effecting earlier diagnosis has been insufficient. During 1990--1992, the proportion of persons who first tested positive for HIV <1 year before receiving a diagnosis of AIDS was 51% (7); during 1993--2004, this proportion declined only modestly, to 39% in 2004 (1). Persons tested late in the course of their infection were more likely to be black or Hispanic and to have been exposed through heterosexual contact; 87% received their first positive HIV test result at an acute or referral medical care setting, and 65% were tested for HIV antibody because of illness (8).

These recommendations update previous recommendations for HIV testing in health-care settings (9,10) and for screening of pregnant women (11). The objectives of these recommendations are to increase HIV screening of
patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States.

Single copies of this report are available free of charge from CDC's National Prevention Information Network, telephone 800-458-5231 (Mondays--Fridays, 9:00 a.m.--8:00 p.m. ET).

Background

Definitions

Diagnostic testing. Performing an HIV test for persons with clinical signs or symptoms consistent with HIV infection.

Screening. Performing an HIV test for all persons in a defined population (12).

Targeted testing. Performing an HIV test for subpopulations of persons at higher risk, typically defined on the basis of behavior, clinical, or demographic characteristics (9).

Informed consent. A process of communication between patient and provider through which an informed patient can choose whether to undergo HIV testing or decline to do so. Elements of informed consent typically include providing oral or written information regarding HIV, the risks and benefits of testing, the implications of HIV test results, how test results will be communicated, and the opportunity to ask questions.

Opt-out screening. Performing HIV screening after notifying the patient that 1) the test will be performed and 2) the patient may elect to decline or defer testing. Assent is inferred unless the patient declines testing.

HIV-prevention counseling. An interactive process of assessing risk, recognizing specific behaviors that increase the risk for acquiring or transmitting HIV, and developing a plan to take specific steps to reduce risks (13).

Evolution of HIV Testing Recommendations in Health-Care Settings and for Pregnant Women

In 1985, when HIV testing first became available, the main goal of such testing was to protect the blood supply. Alternative test sites were established to deter persons from using blood bank testing to learn their HIV status. At that time, professional opinion was divided regarding the value of HIV testing and whether HIV testing should be encouraged because no consensus existed regarding whether a positive test predicted transmission to sex partners or from mother to infant (14). No effective treatment existed, and counseling was designed in part to ensure that persons tested were aware that the meaning of positive test results was uncertain.

During the next 2 years, the implications of positive HIV serology became evident, and in 1987, the United States Public Health Service (USPHS) issued guidelines making HIV counseling and testing a priority as a prevention strategy for persons most likely to be infected or who practiced high-risk behaviors and recommended routine testing of all persons seeking treatment for STDs, regardless of health-care setting (15). "Routine" was defined as a policy to provide these services to all clients after informing them that testing would be conducted (15).

In 1993, CDC recommendations for voluntary HIV counseling and testing were extended to include hospitalized patients and persons obtaining health care as outpatients in acute-care hospital settings, including emergency departments (EDs) (10). Hospitals with HIV seroprevalence rates of >1% or AIDS diagnosis rates of >1 per 1,000 discharges were encouraged to adopt a policy of offering voluntary HIV counseling and testing routinely to all patients aged 15--54 years. Health-care providers in acute-care settings were encouraged to structure counseling and testing procedures to facilitate confidential, voluntary participation and to include basic information regarding the medical implications of the test, the option to receive more information, and documentation of informed consent (10).

In 1994, guidelines for counseling and testing persons with high-risk behaviors specified prevention counseling to develop specific prevention goals and strategies for each person (client-centered counseling) (16). In 1995, after perinatal transmission of HIV was demonstrated to be substantially reduced by administration of zidovudine to HIV-
infected pregnant women and their newborns, USPHS recommended that all pregnant women be counseled and encouraged to undergo voluntary testing for HIV (17,18).

In 2001, CDC modified the recommendations for pregnant women to emphasize HIV screening as a routine part of prenatal care, simplification of the testing process so pretest counseling would not pose a barrier, and flexibility of the consent process to allow multiple types of informed consent (11). In addition, the 2001 recommendations for HIV testing in health-care settings were extended to include multiple additional clinical venues in both private and public health-care sectors, encouraging providers to make HIV counseling and testing more accessible and acknowledging their need for flexibility (9). CDC recommended that HIV testing be offered routinely to all patients in high HIV-prevalence health-care settings. In low prevalence settings, in which the majority of clients are at minimal risk, targeted HIV testing on the basis of risk screening was considered more feasible for identifying limited numbers of HIV-infected persons (9).

In 2003, CDC introduced the initiative Advancing HIV Prevention: New Strategies for a Changing Epidemic (19). Two key strategies of this initiative are 1) to make HIV testing a routine part of medical care on the same voluntary basis as other diagnostic and screening tests and 2) to reduce perinatal transmission of HIV further by universal testing of all pregnant women and by using rapid tests during labor and delivery or postpartum if the mother was not screened prenatally (19). In its technical guidance, CDC acknowledged that prevention counseling is desirable for all persons at risk for HIV but recognized that such counseling might not be appropriate or feasible in all settings (20). Because time constraints or discomfort with discussing their patients' risk behaviors caused some providers to perceive requirements for prevention counseling and written informed consent as a barrier (12,21--23), the initiative advocated streamlined approaches.

In March 2004, CDC convened a meeting of health-care providers, representatives from professional associations, and local health officials to obtain advice concerning how best to expand HIV testing, especially in high-volume, high-prevalence acute-care settings. Consultants recommended simplifying the HIV screening process to make it more feasible and less costly and advocated more frequent diagnostic testing of patients with symptoms. In April 2005, CDC initiated a comprehensive review of the literature regarding HIV testing in health-care settings and, on the basis of published evidence and lessons learned from CDC-sponsored demonstration projects of HIV screening in health-care facilities, began to prepare recommendations to implement these strategies. In August 2005, CDC invited health-care providers, representatives from public health agencies and community organizations, and persons living with HIV to review an outline of proposed recommendations. In November 2005, CDC convened a meeting of researchers, representatives of professional health-care provider organizations, clinicians, persons living with HIV, and representatives from community organizations and agencies overseeing care of HIV-infected persons to review CDC's proposed recommendations. Before final revision of these recommendations, CDC described the proposals at national meetings of researchers and health-care providers and, in March 2006, solicited peer review by health-care professionals, in compliance with requirements of the Office of Management and Budget for influential scientific assessments, and invited comment from multiple professional and community organizations. The final recommendations were further refined on the basis of comments from these constituents.

**Rationale for Routine Screening for HIV Infection**

Previous CDC and U.S. Preventive Services Task Force guidelines for HIV testing recommended routine counseling and testing for persons at high risk for HIV and for those in acute-care settings in which HIV prevalence was >1% (9,10,24). These guidelines proved difficult to implement because 1) the cost of HIV screening often is not reimbursed, 2) providers in busy health-care settings often lack the time necessary to conduct risk assessments and might perceive counseling requirements as a barrier to testing, and 3) explicit information regarding HIV prevalence typically is not available to guide selection of specific settings for screening (25--29).

These revised CDC recommendations advocate routine voluntary HIV screening as a normal part of medical practice, similar to screening for other treatable conditions. Screening is a basic public health tool used to identify unrecognized health conditions so treatment can be offered before symptoms develop and, for communicable diseases, so interventions can be implemented to reduce the likelihood of continued transmission (30).
HIV infection is consistent with all generally accepted criteria that justify screening: 1) HIV infection is a serious health disorder that can be diagnosed before symptoms develop; 2) HIV can be detected by reliable, inexpensive, and noninvasive screening tests; 3) infected patients have years of life to gain if treatment is initiated early, before symptoms develop; and 4) the costs of screening are reasonable in relation to the anticipated benefits (30). Among pregnant women, screening has proven substantially more effective than risk-based testing for detecting unsuspected maternal HIV infection and preventing perinatal transmission (31--33).

**Rationale for New Recommendations**

Often, persons with HIV infection visit health-care settings (e.g., hospitals, acute-care clinics, and sexually transmitted disease [STD] clinics) years before receiving a diagnosis but are not tested for HIV (34--36). Since the 1980s, the demographics of the HIV/AIDS epidemic in the United States have changed; increasing proportions of infected persons are aged <20 years, women, members of racial or ethnic minority populations, persons who reside outside metropolitan areas, and heterosexual men and women who frequently are unaware that they are at risk for HIV (37). As a result, the effectiveness of using risk-based testing to identify HIV-infected persons has diminished (34,35,38,39).

Prevention strategies that incorporate universal HIV screening have been highly effective. For example, screening blood donors for HIV has nearly eliminated transfusion-associated HIV infection in the United States (40). In addition, incidence of pediatric HIV/AIDS in the United States has declined substantially since the 1990s, when prevention strategies began to include specific recommendations for routine HIV testing of pregnant women (18,41). Perinatal transmission rates can be reduced to <2% with universal screening of pregnant women in combination with prophylactic administration of antiretroviral drugs (42,43), scheduled cesarean delivery when indicated (44,45), and avoidance of breast feeding (46).

These successes contrast with a relative lack of progress in preventing sexual transmission of HIV, for which screening rarely is performed. Declines in HIV incidence observed in the early 1990s have leveled and might even have reversed in certain populations in recent years (47,48). Since 1998, the estimated number of new infections has remained stable at approximately 40,000 annually (49). In 2001, the Institute of Medicine (IOM) emphasized prevention services for HIV-infected persons and recommended policies for diagnosing HIV infections earlier to increase the number of HIV-infected persons who were aware of their infections and who were offered clinical and prevention services (37). The majority of persons who are aware of their HIV infections substantially reduce sexual behaviors that might transmit HIV after they become aware they are infected (5). In a meta-analysis of findings from eight studies, the prevalence of unprotected anal or vaginal intercourse with uninfected partners was on average 68% lower for HIV-infected persons who were aware of their status than it was for HIV-infected persons who were unaware of their status (5). To increase diagnosis of HIV infection, destigmatize the testing process, link clinical care with prevention, and ensure immediate access to clinical care for persons with newly identified HIV infection, IOM and other health-care professionals with expertise (25,37,50,51) have encouraged adoption of routine HIV testing in all health-care settings.

Routine prenatal HIV testing with streamlined counseling and consent procedures has increased the number of pregnant women tested substantially (52). By contrast, the number of persons at risk for HIV infection who are screened in acute-care settings remains low, despite repeated recommendations in support of routine risk-based testing in health-care settings (9,10,15,34,53,54). In a survey of 154 health-care providers in 10 hospital EDs, providers reported caring for an average of 13 patients per week suspected to have STDs, but only 10% of these providers encouraged such patients to be tested for HIV while they were in the ED (54). Another 35% referred patients to confidential HIV testing sites in the community; however, such referrals have proven ineffective because of poor compliance by patients (55). Reasons cited for not offering HIV testing in the ED included lack of established mechanisms to ensure follow-up (51%), lack of the certification perceived as necessary to provide counseling (45%), and belief that the testing process was too time-consuming (19%) (54).

With the institution of HIV screening in certain hospitals and EDs, the percentage of patients who test positive (2%--7%) often has exceeded that observed nationally at publicly funded HIV counseling and testing sites (1.5%) and STD clinics (2%) serving persons at high risk for HIV (53,56--59). Because patients rarely were seeking testing when
screening was offered at these hospitals, HIV infections often were identified earlier than they might otherwise have been (29). Targeted testing programs also have been implemented in acute-care settings; nearly two thirds of patients in these settings accept testing, but because risk assessment and prevention counseling are time-consuming, only a limited proportion of eligible patients can be tested (29). Targeted testing on the basis of risk behaviors fails to identify a substantial number of persons who are HIV infected (34,35,39). A substantial number of persons, including persons with HIV infection, do not perceive themselves to be at risk for HIV or do not disclose their risks (53,56,59). Routine HIV testing reduces the stigma associated with testing that requires assessment of risk behaviors (60--63). More patients accept recommended HIV testing when it is offered routinely to everyone, without a risk assessment (54,56).

In 1999, to increase the proportion of women tested for HIV, IOM recommended 1) adopting a national policy of universal HIV testing of pregnant women with patient notification (opt-out screening) as a routine component of prenatal care, 2) eliminating requirements for extensive pretest counseling while requiring provision of basic information regarding HIV, and 3) not requiring explicit written consent to be tested for HIV (12). Subsequent studies have indicated that these policies, as proposed by IOM and other professional organizations (12,64,65), reflect an ethical balance among public health goals, justice, and individual rights (66,67). Rates of HIV screening are consistently higher at settings that provide prenatal and STD services using opt-out screening than at opt-in programs, which require pre-test counseling and explicit written consent (52,68--74). Pregnant women express less anxiety with opt-out HIV screening and do not find it difficult to decline a test (68,74). In 2006, approximately 65% of U.S. adults surveyed concurred that HIV testing should be treated the same as screening for any other disease, without special procedures such as written permission from the patient (75).

Adolescents aged 13--19 years represent new cohorts of persons at risk, and prevention efforts need to be repeated for each succeeding generation of young persons (63). The 2005 Youth Risk Behavior Survey indicated that 47% of high school students reported that they had had sexual intercourse at least once, and 37% of sexually active students had not used a condom during their most recent act of sexual intercourse (76). More than half of all HIV-infected adolescents are estimated not to have been tested and are unaware of their infection (77,78). Among young (aged 18--24 years) men who have sex with men (MSM) surveyed during 2004--2005 in five U.S. cities, 14% were infected with HIV; 79% of these HIV-infected MSM were unaware of their infection (56). The American Academy of Pediatrics recommends that clinicians obtain information from adolescent patients regarding their sexual activity and inform them how to prevent HIV infection (79). Evidence indicates that adolescents prefer to receive this information from their health-care providers rather than from their parents, teachers, or friends (80). However, fewer than half of clinicians provide such guidance (81). Health-care providers' recommendations also influence adolescents' decision to be tested. Among reasons for HIV testing provided by 528 adolescents who had primary care providers, 58% cited their provider's recommendation as their reason for testing (82).

The U.S. Preventive Services Task Force recently recommended that clinicians screen for HIV all adults and adolescents at increased risk for HIV, on the basis that when HIV is diagnosed early, appropriately timed interventions, particularly HAART, can lead to improved health outcomes, including slower clinical progression and reduced mortality (24). The Task Force also recommended screening all pregnant women, regardless of risk, but made no recommendation for or against routinely screening asymptomatic adults and adolescents with no identifiable risk factors for HIV. The Task Force concluded that such screening would detect additional patients with HIV, but the overall number would be limited, and the potential benefits did not clearly outweigh the burden on primary care practices or the potential harms of a general HIV screening program (24,83). In making these recommendations, the Task Force considered how many patients would need to be screened to prevent one clinical progression or death during the 3-year period after screening. On the basis of evidence available for its review, the Task Force was unable to calculate benefits attributable to the prevention of secondary HIV transmission to partners (84). However, a recent meta-analysis indicated that HIV-infected persons reduced high-risk behavior substantially when they became aware of their infection (5). Because viral load is the chief biologic predictor of HIV transmission (85), reduction in viral load through timely initiation of HAART might reduce transmission, even for HIV-infected patients who do not change their risk behavior (86). Estimated transmission is 3.5 times higher among persons who are unaware of their infection than among persons who are aware of their infection and contributes disproportionately to the number of new HIV infections each year in the United States (87). In theory, new sexual HIV infections could be reduced >30% per year if all infected persons could learn their HIV status and adopt changes in behavior similar to those adopted by...
Recent studies demonstrate that voluntary HIV screening is cost-effective even in health-care settings in which HIV prevalence is low (26,27,86). In populations for which prevalence of undiagnosed HIV infection is ≥0.1%, HIV screening is as cost-effective as other established screening programs for chronic diseases (e.g., hypertension, colon cancer, and breast cancer) (27,86). Because of the substantial survival advantage resulting from earlier diagnosis of HIV infection when therapy can be initiated before severe immunologic compromise occurs, screening reaches conventional benchmarks for cost-effectiveness even before including the important public health benefit from reduced transmission to sex partners (86).

Linking patients who have received a diagnosis of HIV infection to prevention and care is essential. HIV screening without such linkage confers little or no benefit to the patient. Although moving patients into care incurs substantial costs, it also triggers sufficient survival benefits that justify the additional costs. Even if only a limited fraction of patients who receive HIV-positive results are linked to care, the survival benefits per dollar spent on screening represent good comparative value (26,27,88).

The benefit of providing prevention counseling in conjunction with HIV testing is less clear. HIV counseling with testing has been demonstrated to be an effective intervention for HIV-infected participants, who increased their safer behaviors and decreased their risk behaviors; HIV counseling and testing as implemented in the studies had little effect on HIV-negative participants (89). However, randomized controlled trials have demonstrated that the nature and duration of prevention counseling might influence its effectiveness (90,91). Carefully controlled, theory-based prevention counseling in STD clinics has helped HIV-negative participants reduce their risk behaviors compared with participants who received only a didactic prevention message from health-care providers (90). A more intensive intervention among HIV-negative MSM at high risk, consisting of 10 theory-based individual counseling sessions followed by maintenance sessions every 3 months, resulted in reductions in unprotected sex with partners who were HIV infected or of unknown status, compared with MSM who received structured prevention counseling only twice yearly (91).

Timely access to diagnostic HIV test results also improves health outcomes. Diagnostic testing in health-care settings continues to be the mechanism by which nearly half of new HIV infections are identified. During 2000--2003, of persons reported with HIV/AIDS who were interviewed in 16 states, 44% were tested for HIV because of illness (8). Compared with HIV testing after patients were admitted to the hospital, expedited diagnosis by rapid HIV testing in the ED before admission led to shorter hospital stays, increased the number of patients aware of their HIV status before discharge, and improved entry into outpatient care (92). However, at least 28 states have laws or regulations that limit health-care providers' ability to order diagnostic testing for HIV infection if the patient is unable to give consent for HIV testing, even when the test results are likely to alter the patient's diagnostic or therapeutic management (93).

Of the 40,000 persons who acquire HIV infection each year, an estimated 40%--90% will experience symptoms of acute HIV infection (94--96), and a substantial number will seek medical care. However, acute HIV infection often is not recognized by primary care clinicians because the symptoms resemble those of influenza, infectious mononucleosis, and other viral illnesses (97). Acute HIV infection can be diagnosed by detecting HIV RNA in plasma from persons with a negative or indeterminate HIV antibody test. One study based on national ambulatory medical care surveys estimated that the prevalence of acute HIV infection was 0.5%--0.7% among ambulatory patients who sought care for fever or rash (98). Although the long-term benefit of HAART during acute HIV infection has not been established conclusively (99), identifying primary HIV infection can reduce the spread of HIV that might otherwise occur during the acute phase of HIV disease (100,101).

Perinatal HIV transmission continues to occur, primarily among women who lack prenatal care or who were not offered voluntary HIV counseling and testing during pregnancy. A substantial proportion of the estimated 144--236 perinatal HIV infections in the United States each year can be attributed to the lack of timely HIV testing and treatment of pregnant women (102). Multiple barriers to HIV testing have been identified, including language barriers; late entry into prenatal care; health-care providers' perceptions that their patients are at low risk for HIV; lack of time for counseling and testing, particularly for rapid testing during labor and delivery; and state regulations...
requiring counseling and separate informed consent (103). A survey of 653 obstetrical providers in North Carolina suggested that not all health-care providers embrace universal testing of pregnant women; the strength with which providers recommended prenatal testing to their patients and the numbers of women tested depended largely on the providers' perception of the patients' risk behaviors (21). Data confirm that testing rates are higher when HIV tests are included in the standard panel of screening tests for all pregnant women (52, 69, 104). Women also are much more likely to be tested if they perceive that their health-care provider strongly recommends HIV testing (105). As universal prenatal screening has become more widespread, an increasing proportion of pregnant women who had undiagnosed HIV infection at the time of delivery were found to have seroconverted during pregnancy (106). A second HIV test during the third trimester for women in settings with elevated HIV incidence (≥17 cases per 100,000 person-years) is cost-effective and might result in substantial reductions in mother-to-child HIV transmission (107).

Every perinatal HIV transmission is a sentinel health event, signaling either a missed opportunity for prevention or, more rarely, a failure of interventions to prevent perinatal transmission. When these infections occur, they underscore the need for improved strategies to ensure that all pregnant women undergo HIV testing and, if found to be HIV positive, receive proper interventions to reduce their transmission risk and safeguard their health and the health of their infants.

**Recommendations for Adults and Adolescents**

CDC recommends that diagnostic HIV testing and opt-out HIV screening be a part of routine clinical care in all health-care settings while also preserving the patient's option to decline HIV testing and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. The recommendations are intended for providers in all health-care settings, including hospital EDs, urgent-care clinics, inpatient services, STD clinics or other venues offering clinical STD services, tuberculosis (TB) clinics, substance abuse treatment clinics, other public health clinics, community clinics, correctional health-care facilities, and primary care settings. The guidelines address HIV testing in health-care settings only; they do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans) (9).

**Screening for HIV Infection**

- In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13-64 years. Health-care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be <0.1%. In the absence of existing data for HIV prevalence, health-care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is <1 per 1,000 patients screened, at which point such screening is no longer warranted.
- All patients initiating treatment for TB should be screened routinely for HIV infection (108).
- All patients seeking treatment for STDs, including all patients attending STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavior risks for HIV infection.

**Repeat Screening**

- Health-care providers should subsequently test all persons likely to be at high risk for HIV at least annually. Persons likely to be at high risk include injection-drug users and their sex partners, persons who exchange sex for money or drugs, sex partners of HIV-infected persons, and MSM or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.
- Health-care providers should encourage patients and their prospective sex partners to be tested before initiating a new sexual relationship.
- Repeat screening of persons not likely to be at high risk for HIV should be performed on the basis of clinical judgment.
- Unless recent HIV test results are immediately available, any person whose blood or body fluid is the source of an occupational exposure for a health-care provider should be informed of the incident and tested for HIV.
infection at the time the exposure occurs.

Consent and Pretest Information

- Screening should be voluntary and undertaken only with the patient's knowledge and understanding that HIV testing is planned.
- Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and to decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended.
- Easily understood informational materials should be made available in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.
- If a patient declines an HIV test, this decision should be documented in the medical record.

Diagnostic Testing for HIV Infection

- All patients with signs or symptoms consistent with HIV infection or an opportunistic illness characteristic of AIDS should be tested for HIV.
- Clinicians should maintain a high level of suspicion for acute HIV infection in all patients who have a compatible clinical syndrome and who report recent high-risk behavior. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection (96).
- Patients or persons responsible for the patient's care should be notified orally that testing is planned, advised of the indication for testing and the implications of positive and negative test results, and offered an opportunity to ask questions and to decline testing. With such notification, the patient's general consent for medical care is considered sufficient for diagnostic HIV testing.

Similarities and Differences Between Current and Previous Recommendations for Adults and Adolescents

Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

- HIV testing must be voluntary and free from coercion. Patients must not be tested without their knowledge.
- HIV testing is recommended and should be routine for persons attending STD clinics and those seeking treatment for STDs in other clinical settings.
- Access to clinical care, prevention counseling, and support services is essential for persons with positive HIV test results.

Aspects of these recommendations that differ from previous recommendations are as follows:

- Screening after notifying the patient that an HIV test will be performed unless the patient declines (opt-out screening) is recommended in all health-care settings. Specific signed consent for HIV testing should not be required. General informed consent for medical care should be considered sufficient to encompass informed consent for HIV testing.
- Persons at high risk for HIV should be screened for HIV at least annually.
- HIV test results should be provided in the same manner as results of other diagnostic or screening tests.
- Prevention counseling should not be required as a part of HIV screening programs in health-care settings. Prevention counseling is strongly encouraged for persons at high risk for HIV in settings in which risk behaviors are assessed routinely (e.g., STD clinics) but should not have to be linked to HIV testing.
- HIV diagnostic testing or screening to detect HIV infection earlier should be considered distinct from HIV
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

Recommendations for Pregnant Women

These guidelines reiterate the recommendation for universal HIV screening early in pregnancy but advise simplifying the screening process to maximize opportunities for women to learn their HIV status during pregnancy, preserving the woman's option to decline HIV testing, and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. All women should receive HIV screening consistent with the recommendations for adults and adolescents. HIV screening should be a routine component of preconception care, maximizing opportunities for all women to know their HIV status before conception (109). In addition, screening early in pregnancy enables HIV-infected women and their infants to benefit from appropriate and timely interventions (e.g., antiretroviral medications [43], scheduled cesarean delivery [44], and avoidance of breastfeeding* [46]). These recommendations are intended for clinicians who provide care to pregnant women and newborns and for health policy makers who have responsibility for these populations.

HIV Screening for Pregnant Women and Their Infants

Universal Opt-Out Screening

- All pregnant women in the United States should be screened for HIV infection.
- Screening should occur after a woman is notified that HIV screening is recommended for all pregnant patients and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines (opt-out screening).
- HIV testing must be voluntary and free from coercion. No woman should be tested without her knowledge.
- Pregnant women should receive oral or written information that includes an explanation of HIV infection, a description of interventions that can reduce HIV transmission from mother to infant, and the meanings of positive and negative test results and should be offered an opportunity to ask questions and to decline testing.
- No additional process or written documentation of informed consent beyond what is required for other routine prenatal tests should be required for HIV testing.
- If a patient declines an HIV test, this decision should be documented in the medical record.

Addressing Reasons for Declining Testing

- Providers should discuss and address reasons for declining an HIV test (e.g., lack of perceived risk; fear of the disease; and concerns regarding partner violence or potential stigma or discrimination).
- Women who decline an HIV test because they have had a previous negative test result should be informed of the importance of retesting during each pregnancy.
- Logistical reasons for not testing (e.g., scheduling) should be resolved.
- Certain women who initially decline an HIV test might accept at a later date, especially if their concerns are discussed. Certain women will continue to decline testing, and their decisions should be respected and documented in the medical record.

Timing of HIV Testing

- To promote informed and timely therapeutic decisions, health-care providers should test women for HIV as
early as possible during each pregnancy. Women who decline the test early in prenatal care should be encouraged to be tested at a subsequent visit.

- A second HIV test during the third trimester, preferably <36 weeks of gestation, is cost-effective even in areas of low HIV prevalence and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria:
  --- Women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women aged 15--45 years. In 2004, these jurisdictions included Alabama, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, New York, North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, and Virginia.†
  --- Women who receive health care in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened.
  --- Women who are known to be at high risk for acquiring HIV (e.g., injection-drug users and their sex partners, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than one sex partner during this pregnancy).
  --- Women who have signs or symptoms consistent with acute HIV infection. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection (96).

Rapid Testing During Labor

- Any woman with undocumented HIV status at the time of labor should be screened with a rapid HIV test unless she declines (opt-out screening).
- Reasons for declining a rapid test should be explored (see Addressing Reasons for Declining Testing).
- Immediate initiation of appropriate antiretroviral prophylaxis (42) should be recommended to women on the basis of a reactive rapid test result without waiting for the result of a confirmatory test.

Postpartum/Newborn Testing

- When a woman's HIV status is still unknown at the time of delivery, she should be screened immediately postpartum with a rapid HIV test unless she declines (opt-out screening).
- When the mother's HIV status is unknown postpartum, rapid testing of the newborn as soon as possible after birth is recommended so antiretroviral prophylaxis can be offered to HIV-exposed infants. Women should be informed that identifying HIV antibodies in the newborn indicates that the mother is infected.
- For infants whose HIV exposure status is unknown and who are in foster care, the person legally authorized to provide consent should be informed that rapid HIV testing is recommended for infants whose biologic mothers have not been tested.
- The benefits of neonatal antiretroviral prophylaxis are best realized when it is initiated <12 hours after birth (110).

Confirmatory Testing

- Whenever possible, uncertainties regarding laboratory test results indicating HIV infection status should be resolved before final decisions are made regarding reproductive options, antiretroviral therapy, cesarean delivery, or other interventions.
- If the confirmatory test result is not available before delivery, immediate initiation of appropriate antiretroviral prophylaxis (42) should be recommended to any pregnant patient whose HIV screening test result is reactive to reduce the risk for perinatal transmission.

Similarities and Differences Between Current and Previous Recommendations for Pregnant Women and Their
Infants

Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

- Universal HIV testing with notification should be performed for all pregnant women as early as possible during pregnancy.
- HIV screening should be repeated in the third trimester of pregnancy for women known to be at high risk for HIV.
- Providers should explore and address reasons for declining HIV testing.
- Pregnant women should receive appropriate health education, including information regarding HIV and its transmission, as a routine part of prenatal care.
- Access to clinical care, prevention counseling, and support services is essential for women with positive HIV test results.

Aspects of these recommendations that differ from previous recommendations are as follows:

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women. Patients should be informed that HIV screening is recommended for all pregnant women and that it will be performed unless they decline (opt-out screening).
- Repeat HIV testing in the third trimester is recommended for all women in jurisdictions with elevated HIV or AIDS incidence and for women receiving health care in facilities with at least one diagnosed HIV case per 1,000 pregnant women per year.
- Rapid HIV testing should be performed for all women in labor who do not have documentation of results from an HIV test during pregnancy. Patients should be informed that HIV testing is recommended for all pregnant women and will be performed unless they decline (opt-out screening). Immediate initiation of appropriate antiretroviral prophylaxis should be recommended on the basis of a reactive rapid HIV test result, without awaiting the result of confirmatory testing.

Additional Considerations for HIV Screening

Test Results

- Communicating test results. The central goal of HIV screening in health-care settings is to maximize the number of persons who are aware of their HIV infection and receive care and prevention services. Definitive mechanisms should be established to inform patients of their test results. HIV-negative test results may be conveyed without direct personal contact between the patient and the health-care provider. Persons known to be at high risk for HIV infection also should be advised of the need for periodic retesting and should be offered prevention counseling or referred for prevention counseling. HIV-positive test results should be communicated confidentially through personal contact by a clinician, nurse, mid-level practitioner, counselor, or other skilled staff. Because of the risk of stigma and discrimination, family or friends should not be used as interpreters to disclose HIV-positive test results to patients with limited English proficiency. Active efforts are essential to ensure that HIV-infected patients receive their positive test results and linkage to clinical care, counseling, support, and prevention services. If the necessary expertise is not available in the health-care venue in which screening is performed, arrangements should be made to obtain necessary services from another clinical provider, local health department, or community-based organization. Health-care providers should be aware that the Privacy Rule under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) prohibits use or disclosure of a patient's health information, including HIV status, without the patient's permission.
- Rapid HIV tests. Because of the time that elapses before results of conventional HIV tests are available, providing patients with their test results can be resource intensive and challenging for screening programs, especially in episodic care settings (e.g., EDs, urgent-care clinics, and STD clinics) in which continuing relationships with patients typically do not exist. The use of rapid HIV tests can substantially
decrease the number of persons who fail to learn their test results and reduce the resources expended to locate persons identified as HIV infected. Positive rapid HIV test results are preliminary and must be confirmed before the diagnosis of HIV infection is established (111).

- Participants in HIV vaccine trials. Recipients of preventive HIV vaccines might have vaccine-induced antibodies that are detectable by HIV antibody tests. Persons whose test results are HIV positive and who are identified as vaccine trial participants might not be infected with HIV and should be encouraged to contact or return to their trial site or an associated trial site for the confirmatory testing necessary to determine their HIV status.

- Documenting HIV test results. Positive or negative HIV test results should be documented in the patient's confidential medical record and should be readily available to all health-care providers involved in the patient's clinical management. The HIV test result of a pregnant woman also should be documented in the medical record of her infant. If the mother's HIV test result is positive, maternal health-care providers should, after obtaining consent from the mother, notify pediatric care providers of the impending birth of an HIV-exposed infant and of any anticipated complications. If HIV is diagnosed in the infant first, health-care providers should discuss the implications for the mother's health and help her to obtain care.

Clinical Care for HIV-Infected Persons

Persons with a diagnosis of HIV infection need a thorough evaluation of their clinical status and immune function to determine their need for antiretroviral treatment or other therapy. HIV-infected persons should receive or be referred for clinical care promptly, consistent with USPHS guidelines for management of HIV-infected persons (96). HIV-exposed infants should receive appropriate antiretroviral prophylaxis to prevent perinatal HIV transmission as soon as possible after birth (42) and begin trimethoprim-sulfamethoxazole prophylaxis at age 4--6 weeks to prevent Pneumocystis pneumonia (112). They should receive subsequent clinical monitoring and diagnostic testing to determine their HIV infection status (113).

Partner Counseling and Referral

When HIV infection is diagnosed, health-care providers should strongly encourage patients to disclose their HIV status to their spouses, current sex partners, and previous sex partners and recommend that these partners be tested for HIV infection. Health departments can assist patients by notifying, counseling, and providing HIV testing for partners without disclosing the patient's identity (114). Providers should inform patients who receive a new diagnosis of HIV infection that they might be contacted by health department staff for a voluntary interview to discuss notification of their partners.

Special Considerations for Screening Adolescents

Although parental involvement in an adolescent's health care is usually desirable, it typically is not required when the adolescent consents to HIV testing. However, laws concerning consent and confidentiality for HIV care differ among states (79). Public health statutes and legal precedents allow for evaluation and treatment of minors for STDs without parental knowledge or consent, but not every state has defined HIV infection explicitly as a condition for which testing or treatment may proceed without parental consent. Health-care providers should endeavor to respect an adolescent's request for privacy (79). HIV screening should be discussed with all adolescents and encouraged for those who are sexually active. Providing information regarding HIV infection, HIV testing, HIV transmission, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents as part of primary care (79).

Prevention Services for HIV-Negative Persons

- Risk screening. HIV screening should not be contingent on an assessment of patients' behavioral risks. However, assessment of risk for infection with HIV and other STDs and provision of prevention information should be incorporated into routine primary care of all sexually active persons when doing so
does not pose a barrier to HIV testing. Even when risk information is not sought, notifying a patient that
routine HIV testing will be performed might result in acknowledgement of risk behaviors and offers an
opportunity to discuss HIV infection and how it can be prevented. Patients found to have risk behaviors
(e.g., MSM or heterosexuals who have multiple sex partners, persons who have received a recent
diagnosis of an STD, persons who exchange sex for money or drugs, or persons who engage in substance
abuse) and those who want assistance with changing behaviors should be provided with or referred to
HIV risk-reduction services (e.g., drug treatment, STD treatment, and prevention counseling).

- Prevention counseling. In health-care settings, prevention counseling need not be linked explicitly to HIV
testing. However, because certain patients might be more likely to think about HIV and consider their
risks at the time of HIV testing, testing might present an ideal opportunity to provide or arrange for
prevention counseling to assist with behavior changes that can reduce risks for acquiring HIV infection.
Prevention counseling should be offered or made available through referral in all health-care facilities
serving patients at high risk for HIV and at facilities (e.g., STD clinics) in which information on HIV risk
behaviors is elicited routinely.

HIV/AIDS Surveillance

- Risk-factor ascertainment for HIV-infected persons. CDC recommends that providers ascertain and
document all known HIV risk factors (115). Health-care providers can obtain tools and materials to assist
with ascertainment and receive guidance on risk factors as defined for surveillance purposes from
HIV/AIDS surveillance professionals in their state or local health jurisdiction. This risk-factor
information is important for guiding public health decisions, especially for prevention and care, at
clinical, local, state, and national levels.
- HIV/AIDS case reporting. All states require that health-care providers report AIDS cases and persons
with a diagnosis of HIV infection to the state or local health department. Case report forms are available
from the state or local health jurisdiction.
- Pediatric exposure reporting. CDC and the Council for State and Territorial Epidemiologists recommend
that all states and territories conduct surveillance for perinatal HIV exposure and contact providers after
receiving reports of exposed infants to determine the infant's HIV-infection status. Information
concerning dates of maternal HIV tests, receipt of prenatal care, maternal and neonatal receipt of
antiretroviral drugs, mode of delivery, and breastfeeding is collected on the pediatric HIV/AIDS case
report form (115).

Monitoring and Evaluation

Recommended thresholds for screening are based on estimates of the prevalence of undiagnosed HIV infection
in U.S. health-care settings, for which no accurate recent data exist. The optimal frequency for retesting is not
yet known. Cost-effectiveness parameters for HIV screening were based on existing program models, all of
which include a substantial counseling component, and did not consistently consider secondary infections
averted as a benefit of screening. To assess the need for revised thresholds for screening adults and adolescents
or repeat screening of pregnant women and to confirm their continued effectiveness, screening programs
should monitor the yield of new diagnoses of HIV infection, monitor costs, and evaluate whether patients with a
diagnosis of HIV infection are linked to and remain engaged in care. With minor modifications, laboratory
information systems might provide a practical alternative for clinicians to use in determining HIV prevalence
among their patients who are screened for HIV.

Primary Prevention and HIV Testing in Nonclinical Settings

These revised recommendations are designed to increase HIV screening in health-care settings. Often, however,
the population most at risk for HIV includes persons who are least likely to interact with the conventional
health-care system (47,116). The need to maintain primary prevention activities, identify persons at high risk
for HIV who could benefit from prevention services, and provide HIV testing for persons who are at high risk
for HIV in nonclinical venues remains undiminished. New approaches (e.g., enlisting HIV-infected persons and
HIV-negative persons at high risk for HIV to recruit persons from their social, sexual, and drug-use networks for counseling, testing, and referral) have demonstrated considerable efficacy for identifying persons who were previously unaware of their HIV infection (117).

Regulatory and Legal Considerations

These public health recommendations are based on best practices and are intended to comply fully with the ethical principles of informed consent (67). Legislation related to HIV and AIDS has been enacted in every state and the District of Columbia (118), and specific requirements related to informed consent and pretest counseling differ among states (119). Certain states, local jurisdictions, or agencies might have statutory or other regulatory impediments to opt-out screening, or they might impose other specific requirements for counseling, written consent, confirmatory testing, or communicating HIV test results that conflict with these recommendations. Where such policies exist, jurisdictions should consider strategies to best implement these recommendations within current parameters and consider steps to resolve conflicts with these recommendations.

Other Guidelines

Issues that fall outside the scope of these recommendations are addressed by other USPHS guidelines (Box 1). Because concepts relevant to HIV management evolve rapidly, USPHS updates recommendations periodically. Current updates are available from the National Institutes of Health at http://aidsinfo.nih.gov/. Additional guidelines have been published by CDC and the U.S. Department of Health and Human Services, Office for Civil Rights (Box 2).

Acknowledgment

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* To eliminate the risk for postnatal transmission, HIV-infected women in the United States should not breastfeed. Support services for use of appropriate breast milk substitutes should be provided when necessary. In international settings, UNAIDS and World Health Organization recommendations for HIV and breastfeeding should be followed (46).

† A second HIV test in the third trimester is as cost-effective as other common health interventions when HIV incidence among women of childbearing age is ≥17 HIV cases per 100,000 person-years (107). In 2004, in jurisdictions with available data on HIV case rates, a rate of 17 new HIV diagnoses per year per 100,000 women aged 15--45 years was associated with an AIDS case rate of at least nine AIDS diagnoses per year per 100,000 women aged 15--45 years (CDC, unpublished data, 2005). As of 2004, the jurisdictions listed above exceeded these thresholds. The list of specific jurisdictions where a second test in the third trimester is recommended will be updated periodically based on surveillance data.

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Box 1
The Changing Landscape of State Legislation and Expanded HIV Testing

Jeremy Brown, MD

The Centers for Disease Control and Prevention (CDC) recommendations for routine human immunodeficiency virus (HIV) screening in clinical settings were released in September 2006.1 Although they were the end of one lengthy process of review and development for physicians in practice, they represented the beginning of another, perhaps even more challenging process: implementation. It was clear to me that our emergency department (ED) needed to build an HIV screening program, for we serve Washington, D.C., which has the highest rate of HIV in the nation. As we prepared to implement our program consistent with the new CDC recommendations, I searched for any legislation that could affect the program. I came up empty-handed. There seemed to be no statutes in the District of Columbia (DC) that would affect the way that routine opt-out HIV screening could be conducted. I remained troubled that there were indeed legal requirements, but that I was simply unable to find them.

I need not have been concerned, however, for it turned out that apart from some old legislation affecting those getting an HIV test for insurance purposes, DC had nothing in its statutes that addressed informed consent, counseling, notification, or any of the other issues that can impact HIV screening. In DC, you just needed to ask a patient if he or she wanted an HIV test, and if they agreed, the test could be done. It was that simple.

Two years later, I met with some colleagues from Maryland who were keen to start their own ED testing program based on the successful program we had been running. The first issue we needed to address was the legislation in our neighboring state that might affect the way the program could be structured, and things could not have been more different from DC. Maryland state law at that time required the health-care provider to discuss no fewer than 35 separate issues.2 This contrast between the historical legislation in two neighboring areas—both with frighteningly high rates of HIV—exemplifies the very disparate ways in which states have addressed HIV testing. For many years, these differences could be viewed as reflecting local concerns and biases, but this way of looking at laws that affect HIV screening has changed since CDC published...
its revised recommendations for HIV testing in healthcare settings, including EDs, in 2006.\(^1\)

CDC addressed standards that should be followed in obtaining consent, and recommended that consent for HIV screening should be incorporated into the patient’s general informed consent for medical care on the same basis as other screening or diagnostic tests. A separate consent form for HIV testing was not recommended. With this small step, CDC had encountered the difficult and contentious issue of how jurisdictions should legislate around HIV testing.

In January 2007, the National Alliance of State and Territorial AIDS Directors (NASTAD) held a meeting in Miami where representatives of local and state health departments, EDs, CDC, and experts in infectious diseases met to discuss the implications of CDC’s recommendations. It became apparent that the matter of how states should legislate around routine opt-out HIV screening is one of the most contentious issues facing those involved in the interface of HIV screening and public health. Some argued for detailed legislation regulating precisely how an HIV test can be administered, and what a patient must learn about and sign before such a test is administered. They claimed that despite great strides forward in the medical treatment of HIV infection, prejudice and discrimination still abound, and patients should not have an HIV test unless these issues are discussed fully. Others in the field argued—based on the same data—that the age of exceptionalism in HIV testing was over, and that HIV infection can and should be treated as just another infectious disease. Indeed, they argued that less legislation is the way forward and would result in more patients being aware of their HIV status. Both camps have the patients’ best interests in mind, and yet have conclusions that may be diametrically opposed. In all of this, what is the emergency physician to do when considering undertaking any aspect of ED HIV screening?

There is a great deal of interest in, and increasing federal support of, the implementation of CDC’s recommendations. For example, CDC is sponsoring a number of workshops across the U.S. that bring together those with expertise in ED HIV screening with those who wish to implement the process in their own ED.\(^3\) Federal money is also being targeted to support expanded ED HIV testing. In September 2007, CDC awarded $35 million to support increased HIV testing, and much of this money will be used to finance EDs that offer testing to high-risk populations.\(^4\) To implement these recommendations, a large number of logistical and financial barriers need to be addressed and overcome.\(^5\) Among the most important steps to consider are the specific state laws that impact the feasibility of any ED HIV screening program. Following is a look at these areas of legislation, as well as important recent changes made in several states.

**IMPACT OF STATE LAWS ON CDC’S EXPANDED, INTEGRATED HIV TESTING PROGRAM**

There exists a wide variation in state laws that pertain to HIV testing, including consent, confidentiality, and notification decisions. For those who wish to review specific state laws, the most useful tool is a compendium on state HIV testing laws from the National HIV/AIDS Clinicians’ Consultation Center.\(^6\) In 2003, CDC commissioned the National Conference on State Legislatures (NCSL) to compile a statute database of laws that may have affected CDC’s Advancing HIV Prevention Initiative launched in 2003. The database was reviewed and updated by the National HIV/AIDS Clinicians’ Consultation Center at the University of California San Francisco/San Francisco General Hospital. This database was updated using the Lexis-Nexis database of statutes to ensure that any statutes passed after 2003 were included, and the most recent update to the database was in February 2008.

In some states, the new CDC guidelines cannot be fully implemented without significant changes to the states’ current legislation. It is of course still possible for states to provide opt-out screening under their existing legislation, but such a program would be far from meeting CDC’s full recommendations. Because CDC’s HIV screening guidelines represent a federal recommendation, they can be interpreted as a standard of care, and many states will not be in compliance with these federal recommendations. Three aspects of legal requirements around HIV screening are particularly important considerations for EDs: counseling, informed consent, and disclosure.

**Counseling requirements**

Many states required pretest counseling, which made sense for patients who have approached a health-care worker requesting an HIV test. Precisely how that counseling was conducted and the nature of the information it contained was in some areas laid out in legal detail and in others left to the provider’s discretion. Within the realities of an urban ED, any requirement to provide counseling before being allowed to offer an HIV test would make the test—however technically easy to perform—practically useless, for there simply is not the time available to add this step to an already lengthy ED stay. Moreover, because the vast majority of patients will have a negative HIV screening test,
any requirement to prepare all patients for the possibility of a positive screening test would be a misuse of available resources. Counseling may provide some benefits to those who receive it in terms of the messages of prevention that are taught, but this somewhat intangible benefit comes at an enormous price. Many states now realize that the historic requirements for counseling need to be revisited if widespread ED HIV testing is to become a reality. For example, California has simplified its pretest counseling requirement, and Maine removed its requirement for pretest counseling, now only requiring the counseling of patients who test positive.

**Informed consent**

In some states there is a requirement to obtain written consent before performing an HIV screening test. Other states require written or verbal consent, and still others have a consent requirement but do not specify if it needs to be written or verbal. In Texas, general consent is considered sufficient to perform an HIV screening test.

Although CDC regulations call for consent to HIV screening to be rolled into the patient’s general consent to medical treatment, there are important legal distinctions between the two types of consent. General consent covers procedures whose risks and benefits are generally well-known, whereas informed consent is “…a process of communication between a patient and physician that results in the patient’s authorization or agreement to undergo a specific medical intervention.” The issue of the necessary content of a consent that is to be considered informed has been addressed by the courts. Based on a 1972 federal appeals court decision, the reasonable person standard emerged as a standard that has been adopted by about half of U.S. states. This standard requires that information about risks be determined by what a reasonable person in that patient’s position would want to know. Furthermore, the information that is required to ensure that consent is informed is contextual, and requires that the health-care provider convey any information that a layperson might not otherwise be expected to know. Meeting this requirement regarding an HIV screening test is challenging if the information about this test is bundled into a general consent process.

The CDC recommendations have encouraged several states to reconsider their requirements for written consent. For example, since publication of the recommendations, Maine and Maryland have changed their requirements from written to verbal informed consent. The legislation in Maryland represents an example of how counseling techniques have been updated to thoughtfully address new methods of providing patient education. Maryland now specifies that counseling may be provided “…in writing, verbally or by video, or a combination of these strategies…” allowing the ED to play an information video on a loop and invite those who wish to be tested to watch the contents. This would enable expensive personnel to be redirected from providing counseling to performing testing.

**Disclosure**

Disclosure is another area that affects the way ED HIV screening is performed. Because a positive screening test requires a confirmatory test, it seems reasonable that any disclosure of the test results to the sexual contacts of a patient should only be done once the results have been confirmed. EDs are not set up to provide for any longitudinal patient contact, and to require partner notification would make an ED HIV screening program unworkable. However, in some states, contact tracing or partner notification are performed only by officials with the health department. For example, in New York, the tracing and informing of contacts is not initiated by the physician but rather by the district health officer. In Texas, the law requires the health department to set up a partner notification and referral service. Under this program, a person with HIV may voluntarily disclose the name or names of sexual partners, who are then contacted by a state employee. In general, it seems reasonable to continue to place the requirements of partner notification on state public health officials who are usually contacted directly by the laboratory once a positive test has been confirmed.

**RECENT CHANGES TO STATE LAWS AFFECTING ED HIV TESTING**

Among the CDC recommendations was the realization that states will have differing statutory regulations that may affect—or impede—the ability to perform effective opt-out tests. CDC recommended that, “Where such policies exist, jurisdictions should consider strategies to best implement these recommendations within current parameters and consider steps to resolve conflicts with these recommendations.” It is important to note that in the two years since the recommendations were made public, several states have revisited the language of their legislation affecting HIV testing and have legislated changes making routine opt-out HIV testing more practicable. Some of these changes have been noted previously, and other examples follow:
Effective June 2008, Illinois instituted a change in its requirements counseling, and specified that pretest information must be made available to the person tested. Illinois also changed its requirement of prior “written informed consent” to “documented informed consent.”  

Maryland passed a law (House Bill 991) removing a requirement for specific written consent and reducing the legal requirements governing the content of the pretest counseling offered.

California added language that enables opt-out testing to be performed in a manner consistent with the CDC recommendations. “Prior to ordering a test that identifies infection with HIV, a medical care provider shall inform the patient that the test is planned, provide information about the test, inform the patient that there are numerous treatment options available for a patient who tests positive for HIV and that a person who tests negative for HIV should continue to be routinely tested, and advise the patient that he or she has the right to decline the test. If a patient declines the test, the medical care provider shall note that fact in the patient’s medical file.”

New Hampshire has enacted legislation that consent for an HIV test should be “in accordance with the most current testing and consent recommendations of the Centers for Disease Control and Prevention.”

Rhode Island also references the CDC recommendations specifically as the standard to follow, although it requires written consent.

New Mexico does not require full pretest counseling when the HIV test is “part of routine medical care.”

A bill before the DC Council would require that health insurers provide health insurance benefits to cover the cost of a voluntary HIV test, performed during an insured patient’s visit to a hospital ED, irrespective of the reason for the hospital ED visit.

However, requirements for consent or counseling in some states continue to make routine ED HIV testing difficult to implement. Some creative strategies to comply with the legal requirements while still operating an efficient program have been suggested. For example, in states in which there is a requirement for pretest counseling, it may be possible to play a video loop that contains all the required information.

CONCLUSIONS

Although routine ED HIV testing is in its infancy, complex state laws regulating almost every aspect of HIV testing have existed for many years. Historically, these laws have made implementation of the CDC recommendations very challenging. EDs that are considering following these recommendations should carefully review current laws to ensure that any HIV screening program is compliant with them.

However, there is evidence of a growing trend to streamline these legal requirements. Several states have recently made changes to some of their legislation, allowing for a routine opt-out test to be offered without contravening the letter or spirit of the law. Further efforts will be needed to encourage states to readdress their existing statutes so that new strategies in the delivery of HIV testing services—such as routine ED HIV testing—may be more easily implemented. Early data suggest that patients are in favor of some kind of ED HIV screening program. Bearing this in mind, as the base of scientific literature and public health practice literature grows, and given emerging scientific evidence supporting increased testing as a cost-effective public health measure, legislators and medical communities must work together to ensure that legislation in all states supports the ability to offer large-scale ED HIV testing.

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2. Code of Maryland Regulations (COMAR) 10.18.08.06. Requirements for pretest counseling. B(3)(a)-(q).
8. Maine Revised Statutes (MRS) §19203-A 2.
12. Maine Title 5 §19203-A.
18. Rhode Island General Laws §23-6-12.

**Objectives:** To describe adults/adolescents (age 13 years and older) living with undiagnosed HIV infection in the United States at the end of 2006.

**Methods:** HIV prevalence and percentage undiagnosed were estimated from cumulative HIV incidence using an extended back-calculation model (using both HIV and AIDS data, the time of first diagnosis with HIV, and disease severity at diagnosis) and estimated cumulative deaths.

**Results:** An estimated 1,106,400 adults/adolescents (95% confidence interval = 1,056,400–1,156,400) were living with HIV in the United States at the end of 2006; overall, 21.0% (232,700; 95% confidence interval = 221,200–244,200) were undiagnosed. Whites had the lowest percentage undiagnosed (18.8%) compared with Hispanics/Latinos (21.6%), blacks/African Americans (22.2%), American Indians/Alaska Natives (25.8%), and Asians/Pacific Islanders (29.5%; all P < 0.001). Persons with a behavioral risk of injection drug use (IDU) had the lowest percentage undiagnosed (female IDU: 13.7% and male IDU: 14.5%); men exposed through heterosexual contact had the highest (26.7%) followed by men who have sex with men (23.5%).

**Conclusions:** Differences in undiagnosed HIV were evident across demographic and behavior groups. Effective testing programs and early access to treatment and prevention services are necessary to reduce undiagnosed HIV infections and HIV prevalence.

**Key Words:** undiagnosed HIV prevalence, risk behaviors, disease disparities

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diagnosed and undiagnosed prevalent cases of HIV infection among adults and adolescents (age 13 years and older) in the United States at the end of 2006.

METHODS

Since 1982, all 50 states and the District of Columbia have reported AIDS cases to the Centers for Disease Control and Prevention (CDC) using a standardized case report form. In 1994, CDC implemented data management for national reporting of HIV integrated with AIDS case reporting, and over time, areas have adopted name-based HIV reporting and submitted these data for inclusion in the national surveillance database. We estimated HIV prevalence in the United States at the end of 2006 using information from the national HIV/AIDS reporting system on persons ≥13 years of age diagnosed with HIV before the end of 2006 and reported to CDC by the end of June 2007. AIDS data were reported by all states and the District of Columbia for the entire reporting period. Forty states provided data on both HIV and AIDS diagnoses, whereas 10 states (California, Delaware, Hawaii, Illinois, Maryland, Massachusetts, Montana, Oregon, Rhode Island, and Vermont) and the District of Columbia provided only AIDS data. Model parameters included year of HIV diagnosis, year of AIDS diagnosis, state of residence at diagnosis, sex, race/ethnicity, HIV transmission category, and age at first diagnosis. The data were adjusted for reporting delay, detection and elimination of duplicate reports, and misclassification of the first diagnosis date. Cases reported without HIV risk factor information were redistributed among transmission categories based on the transmission category of cases diagnosed 3–10 years earlier and initially reported without risk factor information but later reclassified based on information obtained through follow-up investigations.

We used an extended back-calculation approach based on the number of HIV diagnoses by calendar year and disease severity (ie, whether the individual received an AIDS diagnosis in the same calendar year as the HIV diagnosis) to estimate the total number of infections (known diagnosed cases plus estimated undiagnosed cases) and then subtracted the estimated number of deaths (obtained from national HIV/AIDS surveillance data) to arrive at estimated prevalence. The expected distribution of the observed HIV diagnoses was specified using basic variables of interest: (1) AIDS hazard (the AIDS hazard in a designated year is the probability that an individual is diagnosed with AIDS in that year given that he/she was AIDS free at the beginning of the year) by time since infection in untreated HIV-infected individuals, (2) HIV testing hazard by year in HIV-infected individuals before AIDS diagnosis, and (3) number of HIV infections by year. The model estimates HIV infections by estimating the expected distribution of the time of infection for the observed HIV diagnoses in combination with estimating the probabilities that infections occurring in each of these prior years would remain undiagnosed at the present time. The model is not dependent on effects of treatment in delaying time from HIV diagnoses to AIDS, as we are interested in disease history only up to the point of initial HIV diagnosis.

To obtain reasonable and stable estimates, assumptions were made about the actual values or structure of the variables described above. The AIDS diagnosis hazards were specified, not estimated, using information from prior studies. The model specified time periods within which, respectively, HIV testing hazards (probability that an HIV-infected person was tested in a designated year given that he/she had not tested positive in a previous year) and the number of HIV infections were assumed to be approximately constant. The HIV testing hazard was restricted to be dependent on calendar time, not time since infection. Also, the HIV testing parameters in the extended back-calculation model do not refer to the overall rate of HIV testing in the general population (most of whom are HIV negative) but to the rate of HIV testing among persons who are HIV positive.

We assumed that the diagnosis counts have a Poisson distribution with expectations equal to a linear function of the 3 sets of model parameters. We used an expectation-maximization algorithm to estimate the unknown parameters in the extended back-calculation model. After specifying some initial starting values for the unknown parameters, the algorithm alternates between an expectation step (which calculates an “expanded” version of the observed dataset that is consistent with both the specified model structures and current “working” parameter values) and a maximization step (which reestimates the parameter values using the observed and the expanded data). In this case, the expanded dataset consists of the number of diagnoses by time of infection, severity of diagnosis, and time of diagnosis. Each case has 3 possible outcomes for each time interval: (1) HIV and AIDS diagnosis within the same year, (2) HIV diagnosis without an AIDS diagnosis in the same year, and (3) no diagnosis (ie, the case remains undetected). Model fit was measured by comparing the observed and expected diagnoses by time period and severity, using a log-likelihood ratio comparison suitable for Poisson random variables.

The population denominators used for rate calculations were based on official postcensus estimates for 2006 from the US Census Bureau and bridged-race estimates for 2006 obtained from the National Center for Health Statistics. The data analyses were generated using SAS software, Version 9.1 of the SAS System for Windows, SAS Institute, Inc and APL*PLUS III, Manugistics, Inc.

RESULTS

Figure 1 displays the changes in estimated HIV prevalence among adults and adolescents (age 13 years and older) living with HIV infection in the United States. At the end of 2006, there were an estimated 1,106,400 [95% confidence interval (CI) = 1,056,400–1,156,400] persons living with HIV infection in the United States (Table 1). Males made up three-quarters (74.8%) of the estimated persons living with HIV (prevalent cases). By race/ethnicity, blacks/African Americans made up 46.1% of estimated prevalent cases, whites 34.6%, Hispanics/Latinos 17.5%, Asians/Pacific Islanders 1.4%, and American Indians/Alaska Natives 0.4%. By HIV transmission category, men who have sex with men
(MSM) made up the largest percentage of persons estimated to be living with HIV (48.1%).

Overall, 21.0% (232,700; 95% CI = 221,200–244,200) of estimated prevalent HIV cases were undiagnosed. The percentage of estimated cases of HIV infection that was undiagnosed varied by demographic and risk factors (Table 1). The difference in the percentage of undiagnosed HIV by sex was small (21.7% for males vs. 19.1% for females). Greater differences were observed by race/ethnicity, age, and transmission category. Whites had a significantly lower percentage of undiagnosed HIV (18.8%) compared with Hispanics/Latinos (21.6%), blacks/African Americans (22.2%), American Indians/Alaska Natives (25.8%), and Asians/Pacific Islanders (29.5%). The youngest age group (13–24 years) had the greatest estimated percentage of undiagnosed HIV (47.8%), and the percentage undiagnosed significantly decreased with age up to age 55 years (Table 1).

By HIV transmission category, cases associated with injection drug use (IDU) had the lowest percentage of undiagnosed HIV, male IDU: 14.5%; female IDU: 13.7%; and male-to-male sexual contact and IDU: 12.1% (Table 1). The highest percentage of undiagnosed HIV (26.7%) was among men with a transmission category of high-risk heterosexual contact (HRHC), defined as reporting heterosexual contact specifically with a person known to have, or to be at high risk for, HIV infection (eg, an injection drug user). The second highest percentage of undiagnosed HIV was among MSM (23.5%). We observed differences in the percent of undiagnosed HIV when risk was stratified by sex and race. In ascending order, the percentage of undiagnosed HIV among male HRHC by race was black/African American male HRHC (25.7%), Hispanic/Latino male HRHC (27.9%), white male HRHC (28.5%), Asian/Pacific Islander male HRHC (33.3%), and American Indian/Alaska Native male HRHC (38.8%; all

![Figure 1. Estimated HIV prevalence among adults and adolescents, United States—1977 to 2006.](https://example.com/figure1.jpg)

**TABLE 1.** Estimated Prevalence of Persons Age ≥13 Years Living With HIV, and Number and Percent Undiagnosed, by Select Characteristics, 2006—United States

<table>
<thead>
<tr>
<th>Persons Living With HIV</th>
<th>Number 95% CI</th>
<th>Persons Undiagnosed</th>
<th>Number 95% CI</th>
<th>%</th>
<th>Odds ratio 95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,106,400 1,056,400–1,156,600</td>
<td>232,700 221,200–244,200</td>
<td>21.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>828,000 786,000–870,000</td>
<td>179,400 169,400–189,400</td>
<td>21.7</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>278,400 253,400–303,400</td>
<td>53,200 47,200–59,200</td>
<td>19.1</td>
<td>0.85</td>
<td>0.84–0.86</td>
<td>—</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–24</td>
<td>48,300 37,300–59,300</td>
<td>23,100 19,200–27,000</td>
<td>47.8</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>25–34</td>
<td>174,900 153,900–195,900</td>
<td>49,700 44,200–55,200</td>
<td>28.4</td>
<td>0.43</td>
<td>0.42–0.44</td>
<td>—</td>
</tr>
<tr>
<td>35–44</td>
<td>391,500 360,500–422,500</td>
<td>76,100 69,300–82,900</td>
<td>19.4</td>
<td>0.26</td>
<td>0.25–0.27</td>
<td>—</td>
</tr>
<tr>
<td>45–54</td>
<td>338,000 308,000–368,000</td>
<td>54,300 48,500–60,100</td>
<td>16.1</td>
<td>0.21</td>
<td>0.20–0.22</td>
<td>—</td>
</tr>
<tr>
<td>≥55</td>
<td>153,600 133,600–173,600</td>
<td>29,300 24,900–33,700</td>
<td>19.1</td>
<td>0.26</td>
<td>0.25–0.27</td>
<td>—</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>382,600 354,600–410,600</td>
<td>72,000 67,500–78,500</td>
<td>18.8</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Black/African American</td>
<td>510,100 478,100–542,100</td>
<td>113,100 105,000–121,200</td>
<td>22.2</td>
<td>1.23</td>
<td>1.22–1.24</td>
<td>—</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>194,000 175,000–213,000</td>
<td>41,900 36,900–46,900</td>
<td>21.6</td>
<td>1.19</td>
<td>1.18–1.20</td>
<td>—</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>15,100 12,600–17,600</td>
<td>4500 3,000–5,000</td>
<td>29.5</td>
<td>1.82</td>
<td>1.75–1.89</td>
<td>—</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>4600 3100–6100</td>
<td>1200 600–1800</td>
<td>25.8</td>
<td>1.52</td>
<td>1.43–1.64</td>
<td>—</td>
</tr>
<tr>
<td>Transmission category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>532,000 492,000–572,000</td>
<td>124,900 116,400–133,400</td>
<td>23.5</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IDU—male</td>
<td>131,500 114,500–148,500</td>
<td>19,000 15,700–22,300</td>
<td>14.5</td>
<td>0.55</td>
<td>0.54–0.56</td>
<td>—</td>
</tr>
<tr>
<td>IDU—female</td>
<td>73,100 62,100–84,100</td>
<td>10,000 7600–12,400</td>
<td>13.7</td>
<td>0.52</td>
<td>0.51–0.53</td>
<td>—</td>
</tr>
<tr>
<td>MSM/IDU</td>
<td>54,900 44,900–64,900</td>
<td>6700 4700–8700</td>
<td>12.1</td>
<td>0.45</td>
<td>0.44–0.46</td>
<td>—</td>
</tr>
<tr>
<td>HRHC—male</td>
<td>104,000 89,000–119,000</td>
<td>27,900 23,900–31,900</td>
<td>26.7</td>
<td>1.19</td>
<td>1.17–1.21</td>
<td>—</td>
</tr>
<tr>
<td>HRHC—female</td>
<td>201,700 179,700–223,700</td>
<td>42,700 37,700–47,700</td>
<td>21.1</td>
<td>0.87</td>
<td>0.86–0.88</td>
<td>—</td>
</tr>
<tr>
<td>Other*</td>
<td>9100 7600–10,600</td>
<td>1600 800–2400</td>
<td>17.6</td>
<td>0.69</td>
<td>0.66–0.73</td>
<td>—</td>
</tr>
</tbody>
</table>

*Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
CI, confidence interval; MSM, men who have sex with men; IDU, injection drug use; HRHC, high-risk heterosexual contact.

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comparisons to black/African American male HRHC, \( P < 0.003 \). In ascending order, the percentage of undiagnosed HIV among race by sex was white MSM (19.8%), American Indian/Alaska Native MSM (25.0%), Hispanic/Latino MSM (26.3%), black/African American MSM (27.2%), and Asian/Pacific Islander MSM (28.6%; all comparisons to white MSM, \( P < 0.001 \)). A similar pattern was seen for female HRHC, with white female HRHC having a lower percentage of undiagnosed HIV (18.0%) than Hispanic/Latino female HRHC (20.3%), black/African American female HRHC (22.0%), American Indian/Alaska Native female HRHC (25.0%), and Asian/Pacific Islander female HRHC (30.4%; all comparisons to white female HRHC, \( P < 0.001 \)).

Rates per 100,000 population were calculated for adults/adolescents living with undiagnosed HIV infection in the United States at the end of 2006. Table 2 displays the estimated rates and 95% CI of undiagnosed HIV infection by race/ethnicity and sex for persons aged 13 years and older. Black/African American males had the highest rate of undiagnosed HIV infection (556.5 per 100,000). The next highest rates were among black/African American females (225.7 per 100,000) and Hispanic/Latino males (201.6 per 100,000). Overall, whites represented the greatest percentage of the adult/adolescent population of the United States at the end of 2006, 69.0% overall, but a lower percentage of estimated living HIV cases (34.6% overall; 39.6% of males and 19.7% of females). The estimated rate of undiagnosed HIV among whites was 42.2 per 100,000. In contrast, blacks/African Americans made up 12.0% of the population. Each racial/ethnic minority group had a significantly greater percentage of undiagnosed HIV infection compared with whites. Blacks/African Americans had the highest rates of undiagnosed infection, with black/African American men showing the highest rate overall. These findings demonstrate the differential impact of HIV on racial/ethnic populations. Because race/ethnicity is not itself a risk factor for HIV infection, differences in HIV disease burden across population groups are likely due to differences in other factors, including perception of risk and risk behaviors.

### TABLE 2. Estimated Number and Rate (per 100,000 Population) of Persons Age \( \geq 13 \) Years Living With Undiagnosed HIV Infections, by Race/ethnicity and Sex, 2006–United States

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>72,000</td>
<td>42.2</td>
<td>38.3–46.1</td>
</tr>
<tr>
<td>Male</td>
<td>62,800</td>
<td>75.6</td>
<td>68.3–83.0</td>
</tr>
<tr>
<td>Female</td>
<td>92,000</td>
<td>10.5</td>
<td>7.8–13.3</td>
</tr>
<tr>
<td>Black/African American</td>
<td>113,100</td>
<td>380.3</td>
<td>352.7–407.8</td>
</tr>
<tr>
<td>Male</td>
<td>77,500</td>
<td>556.5</td>
<td>508.0–605.7</td>
</tr>
<tr>
<td>Female</td>
<td>35,700</td>
<td>225.7</td>
<td>196.0–225.4</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>41,900</td>
<td>124.1</td>
<td>111.3–141.5</td>
</tr>
<tr>
<td>Male</td>
<td>34,700</td>
<td>201.6</td>
<td>174.9–228.3</td>
</tr>
<tr>
<td>Female</td>
<td>7,200</td>
<td>45.2</td>
<td>32.0–58.4</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>4,500</td>
<td>38.6</td>
<td>24.9–52.3</td>
</tr>
<tr>
<td>Male</td>
<td>3,700</td>
<td>66.0</td>
<td>39.2–92.8</td>
</tr>
<tr>
<td>Female</td>
<td>800</td>
<td>13.2</td>
<td>6.6–19.9</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>1,200</td>
<td>60.4</td>
<td>51.9–69.5</td>
</tr>
<tr>
<td>Male</td>
<td>848</td>
<td>87.4</td>
<td>46.2–128.6</td>
</tr>
<tr>
<td>Female</td>
<td>336</td>
<td>33.0</td>
<td>18.7–47.3</td>
</tr>
<tr>
<td>Total</td>
<td>232,700</td>
<td>94.2</td>
<td>89.5–98.8</td>
</tr>
</tbody>
</table>

CI, Confidence interval

DISCUSSION

The number of persons in the United States living with HIV infection continues to increase each year. A major factor contributing to this increase is reduced mortality due to the use of highly active antiretroviral therapy among persons diagnosed with HIV. From 1995 to 1998, the estimated number of deaths among persons with AIDS declined 63%, from 51,670 to 18,823,4 from 2002 through 2005, the estimated number of deaths averaged 17,189 per year. 

Additionally, the estimated number of annual HIV infections has remained relatively stable over the past decade,5 and these new infections contribute to the number of persons living with HIV.

The burden of HIV infection, both prevalence and percentage undiagnosed, is disproportionate across population groups. Racial/ethnic minorities made up less than one-third (31.0%) of the adult/adolescent population in the United States at the end of 2006 but accounted for nearly two-thirds (65.4%) of persons estimated to be living with HIV. Blacks/African Americans accounted for slightly less than half (46.1%) of all adults/adolescents living with HIV despite comprising only 12.0% of the population. Each racial/ethnic minority group had a significantly greater percentage of undiagnosed HIV infection compared with whites. Blacks/African Americans had the highest rates of undiagnosed infection, with black/African American men showing the highest rate overall. These findings demonstrate the differential impact of HIV on racial/ethnic populations. Because race/ethnicity is not itself a risk factor for HIV infection, differences in HIV disease burden across population groups are likely due to differences in other factors, including perception of risk and risk behaviors, and relative lack of access to—health care resources, particularly HIV testing and treatment.

We also observed differences in HIV prevalence and percent undiagnosed by behavioral risk factor. Sexual contact is the main behavioral risk for both men and women diagnosed with HIV. Our analysis found that men with a behavioral risk factor of male to male sex comprise nearly half (48.1%) of the estimated adults/adolescents living with HIV at the end of 2006. Although not precisely known, the percentage of MSM in the general population is estimated to be much lower. Data from CDC’s National Survey of Family Growth indicate that among males aged 15–44 years, 3.7% ever had anal sex with another male and the percentage of men who had a male sexual partner in the past 12 months was 2.9%.32 MSM also had a significantly greater percentage of undiagnosed HIV infection (23.5%) compared with the overall percentage undiagnosed (21.0%). Again, there were differences in the percentage of undiagnosed HIV infection among MSM by race, with minority MSM having significantly higher percentages undiagnosed compared with white MSM.
A similar pattern was seen in a study among MSM in 5 US cities.\textsuperscript{27} That study also found 48% of MSM diagnosed with HIV were unaware of their infection, twice the undiagnosed percentage of MSM from our national estimate. This finding is likely due to differences in the analysis populations. Persons whose HIV behavioral risk factor was HRHC made up over one-quarter (27.6\%) of estimated prevalent HIV cases. Two-thirds (66.0\%) of the estimated living HIV cases attributed to HRHC were among women, with two-thirds of those being black/African American women.

Interestingly, our analysis found that persons exposed to HIV through IDU had significantly lower percentages of undiagnosed HIV infection. This may be the result of injection drug users interacting with the health care system through the use of emergency departments, needle exchanges, drug treatment facilities, or community outreach programs;\textsuperscript{34,37} in such settings, IDUs may have a greater chance of being offered an HIV test. Also, it may be that injection drug users are more likely to acknowledge their exposure risk for HIV and thus have a greater predilection to accept HIV testing when it is offered.\textsuperscript{35–38}

Our analysis is subject to some limitations. HIV data from the 40 states used in the extended back-calculation model represent only a portion of persons in the United States who are diagnosed with HIV infection. Several high-morbidity areas did not contribute HIV surveillance data, including California, Illinois, Maryland, and the District of Columbia. Thus, the national data on diagnosed cases of HIV infection are incomplete. Additionally, the data presented here have been statistically adjusted to account for reporting delays for new cases and for deaths, and cases reported without risk factor information have been redistributed among other transmission categories. These adjustments are based on assumptions (eg, reporting delays have not changed over time) that may no longer be accurate.\textsuperscript{12,13}

The continued increase in the prevalence of persons living with HIV infection, both diagnosed and undiagnosed, is an ongoing challenge for providing medical and social services. The financial costs of care for persons diagnosed with HIV continue to grow, with most of the care dollars provided by the federal government. The federal budget request for fiscal year 2007 included $13.2 billion for medical care for persons with HIV.\textsuperscript{39} The discounted lifetime cost for treating a person entering HIV care with a CD4 count less than 350 has been estimated to be $385,000 in 2004, with most of the cost attributed to HIV-related medications.\textsuperscript{40} That figure reflects the substantial costs associated with treating HIV infection for a projected period of 24.2 years after initiation of antiretroviral therapy. As the number of diagnosed cases of HIV infection increases, those dollar amounts will continue to grow ever larger.

Persons living with HIV infection who are not yet diagnosed are not able to benefit from early monitoring and appropriate treatment of their disease condition, which have been shown to reduce morbidity and mortality.\textsuperscript{31,42} Persons who are unaware of their positive HIV status are also more likely to engage in HIV transmission risk behaviors compared with infected persons who have been diagnosed: Studies have shown that transmission risk behavior decreases among persons newly diagnosed with HIV infection.\textsuperscript{7,43,44} Thus, recent national HIV prevention strategies have focused efforts on routinizing HIV testing and working with HIV-positive persons to initiate and maintain HIV risk reduction behaviors, with the goal of reducing new HIV infections in the United States.\textsuperscript{2,45}

The epidemic of HIV infection in the United States is now in its third decade. Better treatments are allowing many infected people to live longer; however, there is still no cure for HIV disease. Despite major advances in the scientific understanding of HIV, development of a safe and effective vaccine against HIV remains elusive.\textsuperscript{46,47} Thus, prevention will continue to be the main component of HIV disease control activities. Innovative approaches to reduce transmission risk behaviors are needed to decrease the number of new HIV infections. Additionally, new and creative public health programs that include sufficient and sustained funding are necessary to increase the percentage of persons with HIV infection who are diagnosed and provided appropriate care and prevention services.

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4. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS. 2006;20:1447–1450.


