Recomendaciones para el uso de fármacos antirretroviral en mujeres embarazadas con VIH-1 para la salud maternal e intervenciones para reducir la transmisión perinatal en los Estados Unidos

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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

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:

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. 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. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed (insert date) [include page numbers, table number, etc. if applicable]

It is emphasized that concepts relevat 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 AIDS*info* website (http://aidsinfo.nih.gov).

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What's New in the Guidelines

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* guidelines are published in an electronic format that can be updated as relevant changes in prevention and treatment recommendations occur. The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission is committed to timely changes in this document because so many health care providers, patients, and policy experts rely on this source for vital clinical information.

Major revisions within the last 12 months are as follows:

October 26, 2016

The Perinatal Guidelines text, appendices, and references were updated to include new data and publications where relevant. Throughout the Perinatal Guidelines, content was revised to refer to expedited HIV testing, preferably using fourth-generation antigen/antibody expedited HIV tests, in accordance with current Centers for Disease Control and Prevention (CDC) recommendations. Major changes are summarized below and all changes are highlighted throughout the guidelines.

1. Preconception Counseling and Care for HIV-Infected Women of Childbearing Age

- Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives was updated and expanded to include new data and additional content (e.g., contraceptive effects on antiretroviral therapy [ART] and HIV, clinical studies, justification/evidence for recommendations). More details can be found in CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016, http://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf.
- Counseling about the potential benefits and risks of starting oral pre-exposure prophylaxis to prevent HIV acquisition was added to the guidance for preconception care of women living with HIV who have uninfected partners.

2. General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

- The Panel now recommends that ART should be initiated as early in pregnancy as possible.
- The Panel added a recommendation that providers should initiate patient counseling during pregnancy about key intrapartum and postpartum considerations, including mode of delivery, maternal lifelong HIV therapy, postpartum contraception, infant feeding, infant antiretroviral (ARV) prophylaxis and timing of infant diagnostic testing and neonatal circumcision.
- The initial assessment of pregnant women with HIV infection was updated to include intimate partner violence-related screening and supportive care and referral of sexual partners for HIV testing and ARV prophylaxis.

3. Teratogenicity

- The Panel now recommends that—based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester compared with later ARV exposures— women can be counseled that ART during pregnancy generally does not increase the risk of birth defects.
- In the past, efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert, review of available data has been reassuring that risks of neural tube defects after first trimester efavirenz exposure are not greater than those in the general population. As a result, the current Perinatal Guidelines do not include the restriction on efavirenz use before 8 weeks' gestation, consistent with both the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy. Importantly, women who become pregnant on suppressive efavirenz-containing regimens

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should continue their current regimens.

4. **Combination Antiretroviral Drug Regimens and Pregnancy Outcome**
   - This section was updated to include new studies, and content was reorganized and presented as a summary with new subsections that discuss the potential mechanism of preterm birth associated with ART and the evidence for additional other pregnancy outcomes potentially associated with ART (i.e., low birth weight, small for gestational age, and stillbirth).

5. **Recommendations for Use of Antiretroviral Drugs during Pregnancy**
   - Although in general, the same regimens recommended for treatment of non-pregnant adults should be used in pregnant women, the Panel has added "if appropriate drug exposure is achieved during pregnancy" to other considerations (e.g., adverse effects for women, fetuses, or infants that outweigh benefits).
   - The Panel recommends that in most cases, women who present for obstetric care on fully suppressive ARV regimens should continue their current regimens unless the regimen includes didanosine, stavudine, or full-dose ritonavir.

6. **Table 6: What to Start: Initial Combination Regimens for Antiretroviral Naive-Pregnant Women was updated with new recommendations for initial therapy.**
   - Zidovudine/lamivudine was changed from a Preferred to an Alternative dual nucleoside reverse transcriptase inhibitor (NRTI) combination for ARV-naive women, because it requires twice-daily dosing and is associated with higher rates of mild-to-moderate adverse effects than Preferred NRTI combinations.
   - The Panel has removed efavirenz from the Preferred agents list; it is now classified as Alternative. The change was principally related to the association of efavirenz with neurological adverse effects. However, the Panel recommends that women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens and notes that efavirenz may be suitable for women who desire a once-daily fixed-dose combination regimen and who tolerate efavirenz without adverse effect.
   - Safety and PK data about the use of tenofovir alafenamide in pregnancy are insufficient to recommend this medication for use in initial regimens for ARV-naive women.

7. **Table 8: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy and Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy**
   - These sections were updated with new data for cobicistat, darunavir, efavirenz, elvitegravir, enfuvirtide, lopinavir, maraviroc, raltegravir, zidovudine. A new section was added for tenofovir alafenamide (TAF), an oral product of tenofovir, based on FDA approval of 3 fixed-dose combination products that contain TAF. No data are currently available about the use of TAF in pregnancy.

8. **HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive)**
   - The section was updated in accordance with changes in Recommendations for Use of Antiretroviral Drugs in Pregnancy (see Table 6: What to Start: Initial Combination Regimens for Antiretroviral Naive-Pregnant Women).
   - The section now includes a statement that zidovudine monotherapy during pregnancy is no longer recommended because of the clear health benefit of ART to the mother and for the prevention of perinatal transmission of HIV.

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9. HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Drugs

- HIV-infected women may present for prenatal care on ART regimens that include ARV drugs that lack significant experience in pregnancy, with limited data on pharmacokinetics and safety. Providers are encouraged to consult with an HIV perinatal specialist before considering altering a regimen that is achieving full viral suppression and is well tolerated.
- Providers should make every effort to report all ART exposures in pregnant women to the Antiretroviral Pregnancy Registry, because little is known about the use of newly approved drugs in pregnancy.

10. Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

- Previous versions of the Perinatal Guidelines have provided guidance for situations in which women stop their ART regimen postpartum. However, the Panel strongly recommends that ART regimens, once initiated, not be discontinued. If a woman desires to discontinue ART after delivery, a consultation with an HIV specialist is strongly recommended.

11. Lack of Viral Suppression

- Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible in pregnancy; both HIV-RNA level and timing of ART initiation have been independently associated with perinatal transmission.
- In the setting of acute HIV infection in pregnancy the rate of viral decline following ART initiation may be significantly slower than among those with chronic HIV infection, after adjustment for baseline CD4 count; strategies to accelerate viral decline may be considered, in consultation with HIV treatment experts.

12. Special Populations: HIV/Hepatitis B Virus Coinfection

- Because all pregnant women newly diagnosed with HIV should begin ART as soon as possible, they should also be screened as soon as possible for hepatitis B virus (HBV) because ART in HIV/HBV-coinfected pregnant women should include tenofovir disoproxil fumarate plus lamivudine or emtricitabine.
- Women should be counseled on the importance of continuing anti-HBV medications indefinitely, both during and after pregnancy.

13. HIV-2 Infection and Pregnancy

- Pregnant women with HIV-1 and HIV-2 coinfection should be treated as per guidelines for HIV-1 mono-infection, but using ARV drugs to which HIV-2 is sensitive.
- A regimen with two NRTIs and an integrase strand transfer inhibitor was added to the prophylactic regimens recommended for all HIV-2-infected pregnant women.
- No randomized clinical trials have been performed to address when to start treatment or what is the optimal treatment for HIV-2 mono-infection.

14. Pregnancy in Women with Perinatal HIV Infection

- The management of prenatal care and general principles of ART and HIV management do not differ between pregnant women who were perinatally infected and those who acquired HIV infection postnatally. With appropriate ART, prenatal management and when optimal viral suppression is attained, the risk of perinatal transmission does not appear to be increased in women who acquired HIV perinatally.
- Optimal ART regimens should be selected on the basis of resistance testing, prior ART history, and minimization of pill burden just as the same guiding principles are used for heavily ART-experienced adults.

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- The benefits from drugs with limited experience for use in pregnancy may be needed due to extensive resistance. Consultation with experts in HIV and pregnancy is recommended.

15. Intrapartum Antiretroviral Therapy/Prophylaxis Care

- The recommendations for testing women who present in labor with unknown HIV status were updated to reflect current CDC testing algorithms.
- The Panel added a bulleted recommendation to emphasize that women testing HIV positive on initial screening during labor should not breastfeed until HIV infection has been ruled out.

16. Transmission and Mode of Delivery

- In women on ART with HIV RNA ≤1,000 copies/ml, duration of ruptured membranes is not associated with an increased risk of perinatal transmission, and vaginal delivery is recommended.

17. Other Intrapartum Management Considerations

- Artificial rupture of membranes (ROM) performed in the setting of ART and virologic suppression is not associated with increased risk of perinatal transmission and can be performed for standard obstetric indications.

18. Postpartum Care

- The Panel added a recommendation that women with a positive rapid HIV antibody test during labor should not breastfeed unless a confirmatory HIV test is negative.

19. Infant Antiretroviral Prophylaxis

- The Panel recommends a 4-week zidovudine prophylaxis regimen for full-term infants when the mother has received a standard combination ART regimen during pregnancy with sustained viral suppression.
- The Panel recommends a 6-week course of combination ARV prophylaxis regimen for all infants at higher risk of HIV transmission including those born to mothers who have received no antepartum or intrapartum ARV drugs, intrapartum ARV drugs only, or who have received combination ARV drugs and do not have sustained viral suppression. The Panel was unable to reach clear consensus on the specific ARV prophylaxis regimen in these infants, but options are listed in an update of Table 7. Neonatal Dosing for Prevention of Perinatal Transmission of HIV.

June 7, 2016

1. Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy and Table 8: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy were revised to incorporate new data and publications, where available, Food and Drug Administration drug label changes, and new fixed dose combination formulations. Updates were made to the following drug sections: Atazanavir, Dolutegravir, Emtricitabine, Fosamprenavir, Indinavir, Lamivudine, Nelfinavir, Nevirapine, Rilpivirine, Ritonavir, Saquinavir, Stavudine, Tenofovir, and Tipranavir. There were no major changes related to management of these drugs during pregnancy.

April 29, 2016

1. Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy and Table 8: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy were revised.

   a. The Abacavir, Etravirine and Didanosine sections were updated to include new data and publications,

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including Food and Drug Administration label updates.

b. The Amprenavir, Delavirdine, and Zalcitabine sections were removed from the guidelines as they are no longer available in the United States. Additional information on these drugs can be found in 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* archives.

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Members of the Panel on Treatment of HIV-Infected Pregnant Woman and Prevention of Perinatal Transmission (Last updated October 26, 2016; last reviewed October 26, 2016)

Revisions to the August 6, 2015, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal Transmission in the United States have been made by the Department of Health and Human Services (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).

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Financial Disclosure List for Members of the Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (Last updated October 26, 2016; last reviewed October 26, 2016)

Name	Panel Status	Company	Relationship
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		Lilly	Stockholder
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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

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Introduction (Last updated October 26, 2016; last reviewed October 26, 2016)

Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal transmission of HIV have evolved considerably in the United States since the mid-1990s, reflecting changes in the epidemic and also in the science of prevention and treatment. 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 2% or less in the United States and Europe.[1,2] In response to this success, the Centers for Disease Control and Prevention has developed a goal of eliminating perinatal HIV transmission in the United States, defined as reducing perinatal transmission to an incidence of <1 infection per 100,000 live births and to a rate of <1% among HIV-exposed infants.[3]

The annual number of pregnancies among HIV-infected women in the United States appears to be increasing, as routine use of antiretroviral therapy (ART) results in HIV-infected women living longer, healthier lives.[4] A focus on appropriate overall medical care for HIV-infected women is the best way to prevent HIV infection of infants, including comprehensive reproductive health, family planning and preconception care services, optimization of HIV treatment, and maintenance of care for HIV-infected women between pregnancies. A critical component of prevention of perinatal HIV transmission is ensuring the use of ART to maximally suppress viral replication as early as possible during pregnancy or, ideally, prior to conception.

These guidelines update the August 6, 2015 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 (Perinatal Guidelines). 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 collaborative informed decision making 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 that influence 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 AIDS*info* website (http://aidsinfo.nih.gov).

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.

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Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in pregnant women for treatment of HIV infection and for prevention of perinatal transmission of HIV and management of HIV-exposed infants in the United States.
Panel Members	The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (e.g., training in obstetrics/gynecology, infectious diseases, or women's health) and interventions for prevention of perinatal transmission (e.g., 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 one representative from each of the following Department of Health and Human Services agencies: the Centers for Disease Control and Prevention (CDC), 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 re-appointment. The Panel may also include liaison members from the Perinatal HIV Hotline, the American Academy of Pediatrics' Committee on Pediatric AIDS, and the American College of Obstetricians and Gynecologists. A list of all Panel members can be found on page ix of the guidelines.
Financial Disclosures	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of antiretroviral drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov).
Users of the Guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Developer	Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—a working group of Office of AIDS Research Advisory Council (OARAC)
Funding Source	Office of AIDS Research, NIH
Evidence for Recommendations	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.
Recommendation Grading	See Table 2.
Method of Synthesizing Data	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 a representative from 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 all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed, with ballots, to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (via email or teleconference) for additional review, discussion and further modification to reach a final version acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines (all available on the AIDS*info* website http://www.aidsinfo.nih.gov) outline the use of ARV agents in non-pregnant HIV-infected adults and adolescents; use of ARV agents in HIV-infected infants and children; treatment and prevention of opportunistic infections (OIs) in HIV-infected adults and adolescents, including pregnant women; treatment and prevention of OIs in HIV-infected and HIV-exposed children; and treatment of people who experience occupational or non-occupational exposure to HIV). 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.

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Guidelines Development Process

Table 1. Outline of the Guidelines Development Process, cont'd

Update Plan	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, and/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 AIDS*info* website until the guidelines can be updated with appropriate changes. Updated guidelines are available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Public Comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* 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 contactus@aidsinfo.nih.gov.

Key to Acronyms: ARV = antiretroviral; FDA = Food and Drug Administration; HRSA = Health Resources and Services Administration; NIH = National Institutes of Health; OARAC = Office of AIDS Research Advisory Council

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

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**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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Preconception Counseling and Care for HIV-Infected Women of Childbearing Age (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations

- Discuss childbearing intentions with all women of childbearing age on an ongoing basis throughout the course of their care **(AIII)**.
- Provide information about effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy **(AI)**.
- During preconception counseling, include information on safer sexual practices and elimination of alcohol, tobacco, and other drugs of abuse; if elimination is not feasible, appropriate treatment (e.g., methadone) should be provided **(AII)**.
- All HIV-infected women contemplating pregnancy should be receiving antiretroviral therapy (ART), and have a plasma viral load below the limit of detection prior to conception **(AII)**.
- When selecting or evaluating ART for HIV-infected women of childbearing age, consider a regimen's effectiveness, a woman's hepatitis B status, teratogenic potential of the drugs in the ART regimen, and possible adverse outcomes for the mother and fetus **(AII)**.
- HIV infection does not preclude the use of any contraceptive method **(AII)**. However, drug-drug interactions between hormonal contraceptives and ART should be taken into account.

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*

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 outcomes, 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 unintended,[2-8] 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.[9-12] Health care providers who routinely care for HIV-infected 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.[13-16] Issues that impact pregnancy should be addressed before conception during their routine medical care for HIV disease because many HIV-infected women are aware of their HIV status before becoming pregnant. In addition to the principles outlined by the CDC Preconception Care Work Group,[17] 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.[18,19]

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- Counsel on safer sexual practices (including condoms) that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted diseases, and reduce the potential to acquire resistant strains of HIV.
- Counsel on eliminating alcohol, tobacco, and other drugs of abuse or appropriately treat when elimination is not feasible.
- Counsel women contemplating pregnancy to take a daily multivitamin that contains 400 mcg 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 infants and the availability of safe and sustainable infant feeding alternatives.
- When prescribing antiretroviral therapy (ART) to women of childbearing age, consider the regimen's effectiveness, an individual's hepatitis B (HBV) status, the potential for teratogenicity, and possible adverse outcomes for mother and fetus.[20-22]
- Use the preconception period in women who are contemplating pregnancy to modify their ART regimen to optimize virologic suppression and minimize potential adverse effects (See Table 6).
- Make a primary treatment goal for women who are on ART and who are planning a pregnancy attainment of sustained suppression of plasma viral load below the limit of detection prior to conception for the health of the woman and to decrease the risk of perinatal transmission and of sexual transmission to an uninfected partner.
- Evaluate and manage therapy-associated side effects (e.g., hyperglycemia, anemia, hepatotoxicity) that may adversely impact maternal-fetal health outcomes.
- Administer all vaccines as indicated (see http://www.cdc.gov/vaccines/acip/committee/guidance/rec-vac-preg.html and 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host) including against influenza, pneumococcus, hepatitis B, and tetanus. All HIV-infected women should also receive Tdap vaccination during each pregnancy.
- All women, including those with HIV infection, should receive Tdap vaccination during each pregnancy.
- Encourage sexual partners to receive counseling and HIV testing and, if infected, to seek HIV care. If partners of HIV-infected women are uninfected, counsel about the potential benefits and risks of starting oral pre-exposure prophylaxis to prevent HIV acquisition.
- 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).[23] 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 ARV drugs 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.[24] There are no data on potential interactions between ARV drugs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is

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predominantly metabolized by CYP3A4, so interactions can be expected.

- Optimize the woman's health prior to conception (e.g., ensure appropriate folate intake, test for sexually transmitted infections and treat as indicated, consider the teratogenic potential of **all** prescribed medications, consider the option of switching to safer medications).

A World Health Organization expert group reviewed all available evidence regarding hormonal contraception and HIV transmission to an uninfected partner and recommended that women living with HIV continue to use all existing hormonal contraceptive methods without restriction.[25] However, drug-drug interactions between hormonal contraceptives and ART should be taken into account (see Table 3).

Data on drug interactions between ARV agents and hormonal contraceptives primarily come from drug labels and limited studies.[24,26-41] Newer data provide some understanding as to the magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy. In a study of 570 HIV-infected women in Swaziland using Jadelle implants, none of the women on nevirapine or lopinavir/ritonavir-based regimens (n = 208 and 13, respectively) became pregnant, whereas 15 women on efavirenz (n = 121; 12.4%) became pregnant.[37] Scarsi et al reported on 3 groups of HIV-infected Ugandan women (not on ART [17 women], nevirapine-based ART [20 women], and efavirenz-based ART [20 women]) who had levonorgestrel implants placed, and had levonorgestrel pharmacokinetic (PK) levels assessed at 1, 4, 12, 36, and 48 weeks post insertion. The geometric mean ratio of efavirenz in ART-naive patients was 0.53 at 36 weeks and 0.43 at 48 weeks. Three pregnancies (3/20, 15%) occurred in the efavirenz group between weeks 36 and 48, whereas no pregnancies occurred in the ART-naive or nevirapine groups.[41] Hormonal contraceptives can be used with ART 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 can be considered since the area under the curve of hormones may be decreased (see Table 3). Implants generally can be used, but providers can consider use of an alternative method or recommend the additional use of a reliable barrier method with efavirenz-based regimens.[37,42,43] Depot medroxyprogesterone acetate (DMPA) can be used without restriction because of its relatively higher dose and limited studies that have shown no significant interaction between DMPA and ARV drugs.[27,29,39,44]

Because no high-quality, definitive studies exist on pregnancy rates among women on different hormonal contraceptives and ARV drugs, the dosing recommendations in Table 3 are based on consensus expert opinion. Whenever possible, the recommendations are based on available data regarding PK interactions between ARV drugs and combined hormonal methods, DMPA, and etonogestrel implants. The smallest decreases in PK for which an alternative method was recommended were 14% in norethindrone (with darunavir/ritonavir) and 19% in ethinyl estradiol (with atazanavir/ritonavir). For women using atazanavir without ritonavir boosting (ethinyl estradiol increase 48%, norethindrone increase 110%), the Panel recommends use of oral contraceptives containing ≤30 µg ethinyl estradiol. The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission did not recommend any change in ethinyl estradiol dose for etravirine (ethinyl estradiol increase 22%), rilpivirine (ethinyl estradiol increase 14%), or indinavir (ethinyl estradiol increase 25%, norethindrone increase 26%).

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Note: All recommendations in the following table are based on consensus expert opinion. More details can be found in the CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016.

Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 1 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
NNRTIs							
EFV	COC: • No effect on EE concentrations • ↓ active metabolites of norgestimate LN AUC ↓ 83%; norelgestromin AUC ↓ 64%[30] • Etonogestrel (in COC) C24 ↓ 61%[36] DMPA: • No effect on DMPA levels[27,29] Etonogestrel Implant: • Etonogestrel AUC ↓ 63%[45] LN Implant: • LN AUC ↓ 47%[41] • LN (emergency contraception) AUC ↓ 58%[24] Changes in ARV Levels and/or Effects on HIV: *COC:* • No effect on EFV concentrations[30] • EFV C12 ↓ 22%; was under therapeutic threshold in 3/16 subjects[36] *DMPA:* • No effect on HIV disease progression[27,46,47] • No effect on EFV concentrations[27] *LN Implant:* • No effect on HIV disease progression[41]	COC: • Pregnancy rates no difference[48] • Pregnancy rate higher (13%) in women using COCs and EFV than COCs alone[43,49] • Progesterone >3 (a surrogate for ovulation) in 3/16[50] • No ovulations[30] DMPA: • No increase in pregnancy[27,43,47,48] • Low progesterone[27,29,47] Etonogestrel Implant: • Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods[43] • Presumptive ovulation in 5%[45] LN Implant: • 12% pregnancy rate[37] • 15% pregnancy rate[41] • Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods[43] • No increase in pregnancy rate[48]	Consider an alternative method or a reliable method of barrier contraception in addition to this method.	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	No additional contraceptive protection is needed.	Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	For COCs, some studies suggest higher pregnancy rate and ovulation and decreased progestin levels. EFV may decrease, but clinical significance unclear. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also no effect on HIV disease progression or EFV levels. For implants, some studies suggest higher pregnancy rate and decreased hormone levels.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 2 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
ETR	EE AUC ↑ 22%[51] NE: • No significant effect[51]	COC: • No ovulations[51]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, one study found no ovulations and no significant change in progestin levels. No evidence on POCs.
NVP	EE AUC ↓ 29%;[52] EE AUC no change[53] NE AUC ↓ 18%[52] Etonogestrel (in COC) AUC decreased 22%[36] DMPA: • No significant change[27] LN Implant: • LN AUC ↑ 35%[41] Changes in ARV Levels and/or Effects on HIV *COC:* • NVP no significant effect[50,52,54] *DMPA:* • No effect on HIV disease progression[27,46,47,55] *LN Implant:* • No effect on HIV disease progression[41,56]	COC: • No increase in pregnancy rate[43,48,49,57,58] • No ovulations[50,53,58] DMPA: • No increase in pregnancy rate[43,47,48,57] • No ovulations[27] Etonogestrel Implant: • No increase in pregnancy rate[43] LN Implant: • No increase in pregnancy rate[37,41,43,48,56]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed	For COCs, evidence does not show effects on pregnancy rate or ovulations and demonstrated small decrease in progestin levels. Also no effect on NVP levels. For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also no effect on HIV disease progression. For implants, evidence does not show effects on pregnancy rate or HIV disease progression.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 3 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
RPV	EE AUC ↑ 14%[35] NE: • No significant change[35] Changes in ARV Levels and/or Effects on HIV *COC:* • No change in RPV levels compared to historical controls[35]	COC: • No change in progesterone[35]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, evidence does not show effects on ovulation or progestin levels. Also no change in RPV levels. No evidence on POCs.
RTV-Boosted PIs							
ATV/r	EE AUC ↓ 16%[59] Norgestimate AUC ↑ 85%[59] POP: • NE AUC ↑ 50%[60]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	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.	For COCs, increase in progestin levels but only one study. For POPs, increase in progestin levels but only 1 study. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.
DRV/r	EE AUC ↓ 44%[61] NE AUC ↓ 14%[61]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	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.	For COCs, small decrease in progestin levels. No evidence on POCs.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 4 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
FPV/r	EE AUC ↓ 37%[62] NE AUC ↓ 34%[62] FPV/r level: no change[62]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	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.	For COCs, decrease in progestin levels. No evidence on POCs.
LPV/r	EE AUC ↓ 55%%[26] NE AUC ↓ 17% Patch: • EE AUC ↓ 45%[26] • Norelgestromin AUC ↑ 83%[26] DMPA: • DMPA AUC ↑ 46%[39] Etonogestrel Implant: • Etonogestrel AUC ↑ 52%[45] Changes in ARV Levels and/or Effects on HIV Patch: • LPV/r level ↓ 19%[26] DMPA: • No effect on HIV disease progression[39] • LPV/r no change[39]	COC: • Increase pregnancy rate, but CIs overlap[43] Patch: • No ovulations[26] DMPA: • No pregnancies, no ovulations[39] • Increased pregnancy rate, but CIs overlap[43] Etonogestrel Implant: • No increase in pregnancy rate[43] LN Implant: • No increase in pregnancy rate[37,43]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, nonsignificant increase in pregnancy rate. Small decrease in progestin level. For patch, no ovulations and progestin levels increase. For DMPA, evidence shows no effect on pregnancy rate or ovulations and progestin levels increased. For implants, evidence shows no effect on pregnancy rate and progestin levels increased.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 5 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
SQV/r	↓ EE[63] Changes in ARV Levels and/or Effects on HIV: COC: • SQV/r no change[64]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	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.	No information on progestin levels for CHCs or POCs. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.
TPV/r	Ethinyl estradiol AUC ↓ 48%[65] Norethindrone: • No significant change[65] Changes in ARV Levels and/or Effects on HIV • TPV no change[65]		Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	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.	For COCs, no significant change in progestin levels but only from product label. No evidence on POCs. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 6 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
PIs without RTV							
ATV	COC: EE AUC ↑ 48%[66] NE AUC ↑ 110%[66]		Can consider an alternative method based on safety concerns (i.e., increased estrogen).	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, increased concentrations of estrogen and progestin, but only data available are from the product label. No evidence on POCs.
ATV/ COBI	Progestin and estrogen effects unknown[67] COBI may increase steroid hormone (E/P) as COBI is a strong 3A4 inhibitor (inhibition could lead to ↑ concentrations of E and possibly P)		Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	No evidence on POCs or COCs.
DRV/ COBI	Progestin and estrogen effects unknown[68] COBI may increase steroid hormone (E/P) as COBI is a strong 3A4 inhibitor (inhibition could lead to ↑ concentrations of E and possibly P)		Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	Can consider an alternative method based on safety concerns.	No evidence on POCs or COCs.
FPV	COC: *APV:* • EE AUC no change, C_{min} ↑ 32% • NE AUC ↑ 18%, C_{min} ↑ 45%[62] FPV with EE/Norethindrone: • ↓ APV (AUC 22%, C_{min} 20%)[62]		Use alternative contraceptive method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	Use of fosamprenavir alone with ethinyl estradiol/ norethindrone may lead to loss of virologic response. No evidence on POCs.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 7 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
IDV	COC: • EE AUC ↑ 22% • NE AUC ↑ 26%[69]	COCs: • No pregnancies among women taking IDV and COCs[49]	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, small increases in EE and progestin, and one clinical study did not suggest any efficacy concerns. No evidence on POCs.
NFV	COC: • EE AUC ↓ 47%; NE AUC ↓ 18%[70] DMPA: No change[27] NFV: AUC ↓ 18%	COCs: • One small study suggested that women using COCs and NFV may have had higher pregnancy rates than those using COCs alone[49] DMPA: • No pregnancies, no ovulations[27,47] • CD4 count/HIV RNA: no change[27,47]	Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method.	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.	For COCs, small decrease in progestin and decrease in estrogen; one small clinical study suggests possible higher pregnancy rate with COC and NVP use. DMPA, PK, and clinical data demonstrate no change. However, NFV AUC slightly decreased. No evidence on POPs or implants.
CCR5 Antagonist							
MVC	COC: • No significant effect on EE or LN[71]		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, no change in EE or progestin. No clinical data. No evidence on POCs.

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Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 8 of 8)

ARV Drug	Effect on Contraceptive Drug Levels and Contraceptive's Effects on ART and HIV	Clinical Studies	Dosing Recommendation/ Clinical Comment for COC/P/R	Dosing Recommendation/ Clinical Comment POPs	Dosing Recommendation/ Clinical Comment for DMPA[a]	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
Integrase Inhibitors							
RAL	COC: • EE no change • Norgestimate AUC ↑ 14%[72]		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	For COCs, no change in EE and small increase in progestin. No clinical data. No evidence on POCs.
DTG	COC: • No significant effect on norgestimate or EE • DTG AUC no change[40]		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	COCs, no change in EE or progestin. No clinical data No evidence on POCs.
EVG/ COBI	EVG/COBI/FTC/TDF *COC:* • Norgestimate AUC ↑ 126% EE AUC ↓ 25%		No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	When administered as the 4-drug regimen EVG/COBI/FTC/TDF, increases in P and small decrease in E was observed. No clinical data. No evidence on POCs.

[a] 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: ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; CHC = combination hormonal contraceptives; C_{min} = minimum plasma concentration; COBI = cobicistat; DMPA = depot medroxyprogesterone acetate; COC/P/R =combined oral contraceptives/patch/ring; DRV/r = darunavir/ritonavir; DTG = dolutegravir; e = estrogen; EE = ethinyl estradiol; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = IDV = indinavir; LN =levonorgestrel; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; P = progestin; PI = protease inhibitor; PI/r = ritonavir boosted-protease inhibitor; POP = progesterone-only oral contraceptive pills; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TPV/r = tipranavir/ritonavir

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Tables 15a, 15b, and 15d. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed July 27, 2016.

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Reproductive Options for HIV-Concordant and Serodiscordant Couples (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations

For Couples Who Want to Conceive

For Concordant (Both Partners are HIV-Infected) and Discordant Couples:

- Expert consultation is recommended so that approaches can be tailored to couples' specific needs **(AIII)**.
- Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- Both partners should attain maximum viral suppression before attempting conception **(AIII)**.

For Discordant Couples:

- The couple should be counseled and only attempt conception after the HIV-infected partner has initiated antiretroviral therapy and have achieved sustained suppression of plasma viral load below the limits of detection **(AI)**.
- Administration of antiretroviral pre-exposure prophylaxis 30 days before and 30 days after conception for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission, particularly if the HIV-infected partner's plasma viral load is unknown or detectable **(BII)**. It is not known whether pre-exposure prophylaxis for the uninfected partner confers additional benefit when the infected partner receiving antiretroviral therapy has demonstrated sustained viral suppression.

Discordant Couples with HIV-Infected Women:

- The safest conception option is assisted insemination at home or in a provider's office with a partner's semen during the peri-ovulatory period **(AIII)**.

Discordant Couples with HIV-Infected Men:

- The use of donor sperm from an HIV-uninfected man with artificial insemination is the safest option **(AIII)**.
- When the use of donor sperm is unacceptable, the use of semen preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization should be considered **(BII)**.
- Semen analysis is recommended for HIV-infected men before conception is attempted to prevent unnecessary exposure to infectious genital fluid. Semen abnormalities appear to be more common among HIV-infected men than HIV-uninfected men **(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*

The objective of this section is to provide guidance for safe conception and pregnancy while maximing efforts to prevent transmission to an HIV-uninfected partner and perinatal transmission of HIV.

For couples in which one or both partners are HIV-infected, optimal health should be attained before attempting conception; couples should be counseled to only attempt conception after HIV-infected partners have initiated antiretroviral therapy (ART) and have achieved sustained suppression of plasma viral load below the limits of detection. For concordant or serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs.

Before attempting to conceive, both partners should be screened for genital tract infections. Treatment of such infections is important because genital tract inflammation is associated with genital tract shedding of HIV.[1-5]

Serodiscordant Couples

Before conception is attempted, the HIV-infected partner should be receiving ART and have achieved sustained suppression of plasma viral load below the limits of detection. 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/mm^3 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. This study showed that earlier initiation of ART led to a 96% reduction in transmission of HIV to the uninfected partner. Of 28 cases of HIV infection

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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/mm^3, whereas only one case of HIV infection occurred in the 886 couples with an HIV-infected partner who began immediate ART; 17 of the 27 transmissions in the delayed-therapy group occurred in individuals with CD4 cell counts >350 cells/mm^3. The majority of transmissions (82%) were observed in participants from Africa. Thus this randomized trial clearly demonstrated that provision of treatment to infected individuals can reduce the risk of transmission to their uninfected sexual partners.[6]

It is important to recognize that no single method (including treatment of the infected partner) is fully protective against transmission of HIV. Effective ART that decreases plasma viral load to undetectable levels is also associated with decreased concentration of virus in genital secretions. However, discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus.[7-9] In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.[10] 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.[11] Each $\log_{10}$ increase in genital HIV-1 RNA levels increased the risk of female-to-male or male-to-female HIV transmission by 1.7-fold.[11] Hence, the use of ART reduces but does not completely eliminate the risk of HIV sexual transmission in couples who have decided to conceive through condomless intercourse.[12]

In addition to reducing the risk of HIV transmission between partners, starting ART before conception in HIV-infected women may also reduce the risk of perinatal transmission.[13] Data suggest that early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission,[14,15] but not complete elimination of the risk of perinatal transmission.[15] In addition, reports are mixed on the possible effects of ART 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.[16-18]

The implications of initiating therapy before conception and the need for strict adherence to achieve plasma viral load below the limits of detection should be discussed with the couple. Consultation with an expert in HIV care is strongly recommended.

Periconception pre-exposure prophylaxis (PrEP) can be used to minimize risk of transmission of HIV within discordant couples. PrEP is the 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. Other trials failed to demonstrate PrEP efficacy, likely related to suboptimal levels of adherence.[6,19-24] Table 4 summarizes clinical trials of PrEP.[25]

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Table 4. Clinical Trials of Pre-Exposure Prophylaxis

Trial.	Study Population	Location	Intervention	Outcome	Comments
TDF2	1,219 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% aged 21–29	Botswana	Daily oral TDF/ FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately.
PIP	4,758 heterosexual serodiscordant couples; 38% HIV-negative female, 68% HIV-negative male partner; 98% married; median age 33	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	67% protection with TDF alone; 75% protection with TDF/FTC	Discordant couples may be a distinct, unique population.
FEM-PrEP	1,951 heterosexual women aged 18–35 at high risk of infection	Kenya, South Africa, Tanzania	Daily oral TDF/ FTC	Trial discontinued for futility in April 2011.	Adherence assessment with monthly clinical samples to measure drug concentration is pending.
VOICE MTN-003	5,029 heterosexual women aged 18–45 in high-prevalence areas	Uganda, South Africa, Zimbabwe	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	No study drug significantly reduced the risk of HIV acquisition. Estimates of effectiveness were less than 0 for TDF and TDF/ FTC daily oral dosing (negative 48.8% and negative 4.2% TDF/FTC respectively), and reduced risk of HIV infection of 14.7% for TDF gel.	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.

Key to Acronyms: TDF = tenofovir disoproxil fumarate; TFV = tenofovir; FTC = emtricitabine

Source: Adapted from: Kashuba et al., Pre-exposure prophylaxis for HIV prevention: how to predict success: Table Antiretroviral-based HIV prevention studies. *Lancet.* 2012;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 the fertile period. Several studies evaluating the efficacy of PrEP in heterosexual discordant couples planning pregnancy are ongoing, but complete data are not yet available.

Only daily dosing of combination tenofovir disoproxil fumarate (TDF) and emtricitabine is currently Food and Drug Administration-approved for use as PrEP. Adherence is critical. The use of continued PrEP is recommended for anyone who is at ongoing risk of HIV acquisition.

Pregnancy and breastfeeding are not contraindications to PrEP.[26-30] Currently, there is no reported increase in congenital anomalies among children born to women exposed to TDF (2.3%) or to emtricitabine (2.4%) during the first trimester.[31] Data from studies of infants born to HIV-infected mothers and exposed to TDF through breast milk suggest limited drug exposure.[32-34] 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.

Periconception administration of ARV pre-exposure prophylaxis for HIV-uninfected partners whose HIV-infected partner's plasma viral load is unknown or detectable may offer an additional tool to reduce the risk of sexual transmission. The additional benefit of daily oral PrEP when the HIV-infected partner is receiving ARTis unknown. Several modeling studies have analyzed the utility of PrEP under different conditions. Hoffman's analysis shows that PrEP provides little added benefit when the HIV-infected male partner is on ART with suppressed viral load, condomless sex is limited to the ovulation window, and other modifiable

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transmission risks are optimized.[35] In another modeling study by Mabileau et al to assess the residual risk of HIV transmission, cost and cost-effectiveness of various options for discordant couples where the male partner is HIV-infected and is on suppressive therapy with viral load below detectable:

- Treatment as prevention (TaP)
- Treatment as prevention limited to fertile days;
- Treatment as prevention with pre-exposure prophylaxis;
- Treatment as prevention and pre-exposure prophylaxis limited to fertile days; or
- Medically assisted procreation (MAP).

In the modeling studies HIV transmission was highest with TaP and lowest with MAP. Targeting fertility days with TaP was more effective than pre-exposure prophylaxis and TaP and cost less. The risk of HIV transmission was lower with TaP and pre-exposure prophylaxis limited to fertile days and MAP but cost more.[36]

Pre-exposure Prophylaxis Use and Monitoring in HIV-Serodiscordant Couples

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. The Centers for Disease Control and Prevention (CDC) recommends that an HIV-uninfected partner planning pregnancy with an HIV-infected partner start daily oral TDF plus emtricitabine beginning 1 month before conception is attempted and continued for 1 month after conception is attempted.[37] Recommended laboratory testing should include HIV diagnostic testing at baseline then every 3 months, renal function testing at baseline and then every 6 months, and pregnancy testing at baseline and every 3 months. Testing for hepatitis B virus (HBV) infection should be performed when initiating PrEP. HBV-uninfected individuals should be vaccinated if they have not received HBV vaccination or they lack immunity to HBV. Individuals receiving PrEP 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, measures should be instituted to prevent perinatal transmission if pregnancy has occurred and attempts at conception stopped if pregnancy has not occurred, and the patient should be referred to an HIV specialist immediately. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.[38] Clinicians are strongly encouraged to register HIV-uninfected women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

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 ART and had undetectable plasma HIV RNA levels. One dose of oral TDF disoproxil fumarate (TDF) 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.[39] Another study from England reported the use of TDF with or without emtricitabine for PrEP by the HIV uninfected female partner with timed intercourse in 13 serodiscordant couples; PrEP was well tolerated and no HIV transmissions occurred.[40]

Additional Options for Safer Conception

For HIV-discordant couples in which the woman is the HIV-infected partner, the safest form of conception is assisted insemination, including the option to self-inseminate with the partner's semen during the fertile period. Condom use should be advised at all times.

For HIV-discordant couples in which the man is the HIV-infected partner, the use of donor sperm from an HIV-uninfected man 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 with intracytoplasmic sperm injection has been reported to be effective in avoiding seroconversion in uninfected women and offspring in several studies.[41-43]

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These sperm preparation techniques were largely developed prior to the studies demonstrating the efficacy of PrEP and ART in decreasing transmission to HIV-uninfected sexual partners. Therefore, the appropriate role of semen preparation techniques in the current context is unclear, particularly given their expense and technical requirements. Semen 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 that there may be a small risk of transmission of HIV to the uninfected partner and to their offspring.[42] Semen analysis is recommended for HIV-infected men before conception is attempted because HIV, and possibly ART, may be associated with a higher prevalence of sperm 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 conceiving naturally is low or nonexistent.[44-47]

Discordant couples who do not have access to these reproduction services (i.e., artificial insemination, sperm preparation, *in vitro* fertilization) and who still want to try to conceive after comprehensive counseling should be advised that timed, periovulatory unprotected intercourse after the infected partner has achieved a plasma viral load below the limits of detection (with use of condoms at all other times) may reduce but not completely eliminate the risk of sexual transmission.[42] 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).

Concordant Couples

Both partners should be on ART 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 ART and have fully suppressed plasma viral loads.[48]

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 CDC has issued guidelines for the use of PrEP in sexually active heterosexual adults.[37]

Monitoring of HIV-Uninfected Pregnant Women with Partners Known to Be HIV-Infected

HIV-uninfected women who present during pregnancy and indicate that their partners are HIV-infected, 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. HIV-uninfected pregnant women should also be counseled to always use condoms to reduce the risk of HIV acquisition and their HIV-infected partners should be virological suppressed on ART. These women also should receive a second HIV test during the third trimester, preferably before 36 weeks' gestation, as is recommended by CDC. Furthermore, pregnant women who present in labor without results of third-trimester testing should be screened on the labor and delivery unit with an expedited serum HIV test, preferably a fourth-generation antigen/antibody expedited HIV test. 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 antigen/antibody fourth-generation test. If the plasma HIV RNA is negative, it should be repeated in 2 weeks. 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, and headache) and the importance of seeking medical care and testing if they experience such symptoms.

Pregnancy and breastfeeding are not contraindications to PrEP, and PrEP should be considered in HIV-seronegative pregnant women who are at ongoing risk of HIV acquisition. However, the use of daily oral PrEP

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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 ART 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 HIV seronegative 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.[49,50]

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Antepartum Care (Last updated October 26, 2016; last reviewed October 26, 2016)

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 antiretroviral therapy (ART) or the need for any modification if currently receiving ART **(AIII)**. The National Perinatal HIV Hotline (888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.
• All pregnant HIV-infected women should receive ART, initiated as early in pregnancy as possible, to prevent perinatal transmission regardless of plasma HIV RNA copy number or CD4 T lymphocyte count **(AI)**. Maintainenance of a viral load below the limit of detection throughout pregnancy and lifetime of the HIV-infected individual is recommended.
• Combined maternal antepartum and intrapartum (ARV) treatment/prophylaxis as well as infant 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 all medication use, including ARV drug use during pregnancy, should be discussed with all HIV-infected women **(AIII)**.
• The importance of adherence to ARV drug regimens should be emphasized in patient counseling **(AII)**.
• 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)**. In pregnant women not already receiving ART, ART should be initiated before results of drug-resistance testing are available because earlier viral suppression has been associated with lower risk of transmission. If ART is initiated before results are available, the regimen should be modified, if necessary, based on resistance assay results **(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, intimate partner violence support services, and public assistance programs, is essential to help ensure that infected women adhere to their ARV drug regimens **(AII)**.
• Providers should also initiate counseling during pregnancy about key intrapartum and postpartum considerations, including mode of delivery, maternal lifelong HIV therapy, postpartum contraception, infant feeding, infant ARV prophylaxis and timing of infant diagnostic testing and neonatal circumcision **(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 level;
- 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 A virus (HAV), hepatitis C virus, and tuberculosis in addition to standard screening for hepatitis B virus (HBV) infection;

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- Assessment of the need for immunizations per guidelines from the American College of Obstetricians and Gynecologists, the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America with particular attention to HAV, HBV, influenza, pneumococcus, and Tdap immunizations;[1,2]
- Complete blood cell count and renal and liver function testing;
- HLA-B*5701 testing if abacavir use is anticipated (see Table 8);
- 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 ARV drug-resistance studies;
- History of adverse effects or toxicities from prior ARV regimens;
- Assessment of supportive care needs (e.g., mental health services, substance abuse treatment, smoking cessation) as well as support to help ensure lifelong ART;
- Intimate partner violence-related screening and supportive care needs; and
- Referral of sexual partner(s) for HIV testing and ARV prophylaxis

The National Perinatal HIV Hotline

The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation to providers caring for HIV-infected women and their infants.

How Antiretrovirals Prevent Perinatal 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. ARV drugs can reduce perinatal transmission through a number of mechanisms. Antenatal drug administration decreases maternal viral load in blood and genital secretions. Although the risk of perinatal transmission in women with undetectable plasma HIV RNA levels appears to be extremely low, it has been reported even among women on antiretroviral therapy (ART).[3-5] Low-level cervicovaginal HIV RNA and DNA shedding has been detected even in women treated with ART who have undetectable plasma viral load.[6-8] Penetration of ARV drugs into the female genital tract has been shown to vary between drugs.[9-11] Because maternal viremia is not the only risk factor for HIV transmission, another important mechanism of protection is infant pre-exposure prophylaxis achieved by administering ARV drugs that cross the placenta and produce adequate systemic drug levels in the fetus. In addition, infant post-exposure prophylaxis is achieved by administering drugs 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 reduced efficacy of interventions that involve administration of ARVs only during labor and/or to the newborns.[12-18] Therefore, combined preconception ART, confirmation of antepartum viral load suppression, intrapartum continuation of current regimen with intravenous zidovudine added if the plasma viral load is >1,000 copies/mL, and infant ARV prophylaxis are recommended to prevent perinatal transmission of HIV.

General Principles of Drug Selection

In general, guidelines for the use of ART 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 or limited experience with newer drugs during pregnancy, where the perinatal guidelines may differ from the adult guidelines.

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The known benefits and known and unknown risks of ARV drug use during pregnancy should be considered and discussed with women (see Table 8 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 directive but non-coercive, and providers should help them make informed decisions regarding use of ARV drugs.

Discussions with women about initiation of ART regimens should include information about:

- Maternal risk of disease progression and benefits and risks of initiation of therapy for maternal health and lifelong treatment and viral suppression with ART;
- Benefit of ART for preventing perinatal transmission of HIV;[4]
- Benefits of therapy for reducing sexual transmission to discordant partners when viral suppression is maintained;[19]
- 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 (see Recommendations for use of ARVs during pregnancy); and
- The limited long-term outcome data for infants after *in utero* drug exposure.

Transplacental passage of ARV drugs 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 ART regimen (see Table 8).[20-24]

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 ART. However, in pregnant women not already receiving ART, ART should be initiated while awaiting results of genotype resistance testing because earlier viral suppression is associated with lower risk of perinatal transmission.[25] The ART regimen can be modified, if necessary, based on resistance assay results[26] (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.

All HIV-infected pregnant women should initiate or continue on ART during pregnancy to minimize the risk of transmission of HIV to their infant and partner(s). Providers should begin to counsel HIV-infected women about what they can expect during labor and delivery and the postnatal period. This includes discussions about the mode of delivery and possible intrapartum zidovudine, lifelong ART recommendation for all HIV-infected individuals and therefore continuing ART postpartum and possible changes in maternal ARV therapy postpartum and beyond, and discussion of family planning and available contraception. In addition, recommendations regarding the avoidance of both breastfeeding and premastication of food to prevent postnatal HIV transmission and the importance of neonatal ARV prophylaxis and infant diagnostic HIV testing should be discussed.

Medical care of HIV-infected pregnant women requires coordination and communication between HIV specialists and obstetric 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. 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. Additional support services such as mental health services and intimate partner violence assessment may be required, depending on a woman's

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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.

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Teratogenicity (Last updated October 26, 2016; last reviewed October 26, 2016)

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)**.
• Based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester compared with later ARV exposures, women can be counseled that antiretroviral therapy during pregnancy generally does not increase the risk of birth defects. **(BIII)**.
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*

First-Trimester Exposure and Birth Defects

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. 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 in exposed infants of Food and Drug Administration-approved antiretroviral (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.[2-5] In the primary analysis by the Antiretroviral Pregnancy Registry of prospective cases of ARV exposure during pregnancy provided by health care providers, prevalence of birth defects was 2.9 per 100 live births among women with a first-trimester exposure to any ARV (221 of 7,738 exposures; 95% confidence interval [CI], 2.5–3.3). The prevalence of defects is not significantly different from that in women with an initial exposure during the second and/or third trimester (2.8 per 100 live births) (prevalence ratio 1.02; 95% CI, 0.86–1.22).[6]

Some individual reports have raised concerns regarding specific ARV agents. Most studies evaluating a possible association between ARV exposure and birth defects do not evaluate maternal folate use or levels. Folate antagonists (e.g., trimethoprim-sulfamethoxazole), which have been associated with an increased risk of birth defects with first-trimester use in some, but not all, studies, may be prescribed to women with advanced HIV disease.[7] 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.[8] Maternal tobacco and alcohol use may also serve as confounders.[9]

Specific Drugs

Efavirenz

Efavirenz use during pregnancy has received increased scrutiny because of the results of a small study in non-human primates. Significant malformations were observed in 3 of 20 infant cynomolgus monkeys

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receiving efavirenz from gestational days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human exposure at therapeutic dosage.[10] The malformations included anencephaly and unilateral anophthalmia in one, microphthalmia in another, and cleft palate in the third. In humans, sufficient numbers of first trimester exposures to efavirenz have been monitored in the Antiretroviral Pregnancy Registry to detect at least a two-fold increase in the risk of overall birth defects, without any such increase detected; a single case of myelomeningocoele and one case of anopthalmia have been prospectively reported in live births.[6] In retrospective reports to the Antiretroviral Pregnancy Registry, there have been six cases of central nervous system defects, including meningomyelocoele, with first trimester exposure. 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.

Two publications have reported higher rates of congenital birth defects with first trimester efavirenz exposure. The PACTG protocols 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 (AOR 4.31; 95% CI, 1.56–11.86). However, only 32 infants had efavirenz exposure.[11] 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,[3] there is overlap in the defect cases between the two studies and only 41 infants with efavirenz exposure are included in this analysis. There was no specific pattern of anomalies specific to efavirenz described by these studies: patent forman ovale (N = 1), gastroschisis (N = 1), polydactyly (N = 1), spina bifida cystica (N = 1), plagiocephaly (N = 1), Arnold Chiari malformation (N = 1) and talipes (N = 1).

In a report from the French Perinatal Cohort on 5,388 births with first-trimester exposure to ARV drugs, first-trimester efavirenz use was not associated with an increase in defects in the primary analysis using the European Surveillance of Congenital Abnormalities birth defect classification system.[12] However, in a secondary analysis using the Metropolitan Atlanta Congenital Defects Program (MACDP) birth defect classification (the system used by the Antiretroviral Pregnancy Registry), an association was found between first-trimester efavirenz exposure and neurologic defects. However, none of the four defects were neural tube defects, and none of the defects had common embryology.[13] A meta-analysis including data from 23 studies reporting on 2,026 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 0.78; 95% CI, 0.56–1.08). One neural tube defect was observed, giving an incidence of 0.05% (95% CI, <0.01 to 0.28).[14] The number of reported first-trimester efavirenz exposures is currently sufficient to rule out a 2-fold increase in low-incidence birth defects such as neural tube defects (incidence of neural tube defects in the general U.S. population is 0.02% to 0.2%).[15]

In prior 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 (Perinatal Guidelines), efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert, the large meta-analysis above has been reassuring that risks of neural tube defects after first trimester efavirenz exposure are not greater than those in the general population.[7,10,16] As a result, the current Perinatal Guidelines do not include the restriction of use before 8 weeks' gestation, consistent with both the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy (which note that efavirenz can be used throughout pregnancy).[17,18] Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) has not demonstrated teratogenicity in rodents or monkeys. Data from the Antiretroviral Pregnancy Registry show a birth defect incidence of 2.3% (60/2608) women with first-trimester TDF exposure, similar to that in the general population.[6]

Administration of TDF at high doses to pregnant monkeys (exposure resulting in drug levels 25 times the

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area under the curve achieved with therapeutic dosing in humans), was associated with maternal toxicity, resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights in infant monkeys. A slight reduction in fetal bone porosity was also observed. In human neonates, a study evaluated whole body dual-energy X-ray absorptiometry scans within 4 weeks of birth among 74 infants exposed to more than 8 weeks of TDF *in utero* and 69 infants with no TDF exposures. The adjusted mean whole body bone mineral content (BMC) was significantly lower in the TDF group by 6.3 g ($P = 0.004$) as was the whole-body-less-head BMC (-2.6 g, $P = 0.056$). However, the duration and clinical significance of these findings require further longitudinal evaluation. In contrast, in a study evaluating fetal long bone (femur and humerus) growth by serial ultrasound in women who received different durations of TDF antiretroviral therapy during pregnancy (<10 weeks, 10–24 weeks, >25 weeks) found no association between duration of *in utero* TDF disoproxil fumarate exposure per week and change in femur and humerus length *z*-score ($P = 0.51$ and $P = 0.40$, respectively).[19] No clinical studies have examined the clinical outcomes of maternal usage of tenofovir alafenamide (TAF) on newborn outcomes.

Other Drugs

In a study from France that included 13,124 live births that occurred between 1994 and 2010; 5,388 (42%) had first-trimester exposure to ARV drugs. The authors reported a significant adjusted association between first-trimester zidovudine exposure and congenital heart defects, primarily ventricular (58%) and atrial (18%) septal defects (adjusted odds ratio [AOR] 2.2; 95% CI, 1.3–3.7). Because fetal ultrasounds were conducted on all HIV-exposed infants, and spontaneous closure of ventricular septal defects after birth is common, the clinical significance of the cardiac findings is uncertain.[13] In contrast to the French study, an analysis of 16,304 prospectively reported pregnancies to assess the risk of ventricular septal defects and congential heart defects comparing exposure between zidovudine-containing regimens and non-zidovudine ART regimens did not find significant differences between the two groups.[20] Additionally, in a comparison between 417 HIV- and ARV-exposed, uninfected infants and unexposed controls tested at ages 2 to 7 years, no clinically significant differences were found in echocardiographic parameters of left ventricular function and structure.[9]

In an analysis from PHACS that included 2,580 live births, first-trimester ARV exposure overall was not associated with an increased risk of birth defects.[21] In adjusted analyses, the only individual ARV drug for which first-trimester exposure was associated with birth defects was atazanavir, primarily skin and musculoskeletal defects. However, in the Antiretroviral Pregnancy Registry, there was no increase in birth defects with first-timester atazanavir exposure among 1,093 births.[6]

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures have been monitored to detect at least a 2-fold increase in risk of overall birth defects for abacavir, darunavir, didanosine, efavirenz, indinavir, and stavudine; no such increases have been detected to date. For atazanavir, emtricitabine, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, TDF, and zidovudine, sufficient numbers of first-trimester exposures have been monitored 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 the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. 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) surveillance data.[6] The lower bounds of the confidence intervals for didanosine and nelfinavir (2.9% and 2.8%, 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 Antiretroviral Pregnancy Registry will continue to monitor didanosine and nelfinavir for any signal or pattern of birth defects.

See Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy for detailed information on individual drugs.

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Antiretroviral Pregnancy Registry Reporting

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 as early in pregnancy as possible. This registry is an epidemiologic project to collect observational, nonexperimental 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:

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

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Combination Antiretroviral Drug Regimens and Pregnancy Outcome

(Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• Clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving antiretroviral therapy. However, given the clear benefits of such regimens for both a woman's health and the prevention of perinatal transmission, HIV treatment should not be withheld for fear of altering pregnancy outcome **(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*

Women taking antiretroviral therapy (ART) may be at increased risk for adverse pregnancy outcomes, including preterm birth or delivery (PTD) (delivery before 37 weeks' gestation), low birth weight (LBW) infants (<2,500 g), and small-for-gestational-age (SGA) infants (birth weight <10th percentile expected for gestational age). In this section, we provide a brief summary of the published data regarding ART and adverse pregnancy outcomes.

We have reviewed and summarized studies from 1986 to 2015 reporting on birth outcomes in HIV-infected women. These studies are conducted in Europe (11), North America (8), sub-Saharan Africa (6), and Latin America (2). Study size and designs vary significantly; the total study participant numbers range from 183 to 9,504. The ART regimens evaluated in these studies differ and may include no ART (8), monotherapy (single antiretroviral [ARV] drug) (19), dual therapy (2 ARV drugs) (13), and multi-ARV drugs (at least 3 ARV drugs) [protease inhibitor (PI)-based (22) or non-PI-based (26)]. Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery lists the published, high-quality studies reporting potential effects of ART use on pregnancy outcomes. The studies' conclusions regarding PTD, LBW, and SGA are provided. These data are weighted heavily regarding PTD (26), and fewer studies report outcomes of LBW (12), SGA (7), and stillbirth (10).

Preterm Delivery

All of the studies reviewed in this section (27) have reported outcomes related to PTD. Among the 16 studies that report an association between ART use and PTD, the relative risks/odds ratios for PTD range from 1.2 to 3.4.[1-16] Conflicting findings regarding PTD and ART use may be influenced by variability in the data available for analysis. For example, some studies have reported increased rates of PTD when ART is initiated before or in early pregnancy compared to later in pregnancy. Maternal factors, such as HIV disease severity, may affect the timing of ART initiation during pregnancy. These variables may be associated with PTD independent of ART use.[17,18] In order to control for medical or obstetrical factors associated with PTD, two studies have assessed spontaneous PTD alone. One study included women initiating ART during pregnancy. Neither study reported an association between ART use and PTD.[19,20] In general, none of the studies reviewed in this section have comprehensively controlled for all potential factors that may be associated with PTD.

Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Six of the 27 studies in Table 5 report an association between ART initiation prior to pregnancy and PTD.[1] The relative risks and odds ratios reported range from 1.20 to 2.05; the risk is attenuated in multivariate analysis.[14] These studies were conducted in Europe (3), Latin America (1), and Africa (2) and included various ART regimens (including single-drug, two-drug and multi-drug regimens). A large meta-analysis of 11,224 women in 14 European and American studies did not demonstrate an increased rate of PTD among women using ART during pregnancy.[4]

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Antiretroviral Therapy Regimens Associated with Preterm Delivery

PI-Based

Thirteen of the 27 studies in Table 5 investigate an associated risk between PI-based ART and PTD. These studies include populations in Europe (4), North America (7), and Africa (2). The risk of PTD ranges from 1.2 to 3.4.[1,3-6,8,15,19,21,22] Four of these studies did not demonstrate a significant association between PI-based ART and PTD.[15,19,21,22] The use of ritonavir to boost a PI-based regimen may be associated with PTD compared to non-boosted PI regimens. In a small, retrospective Canadian study, women taking non-boosted PI regimens did not have increased rates of PTD.[15]

Non-PI-Based

Exposure to nucleoside reverse transcriptase inhibitor single-drug prophylaxis (primarily zidovudine) was not associated with PTD.[1] Other reports have found increased rates of PTD when ART is compared with dual-ARV regimens[9] and when non-nucleoside reverse transcriptase inhibitor-based ART regimens were compared with other forms of ART.[18]

Mechanism for Preterm Delivery

The potential mechanism of action by which protease inhibitors (PIs) may increase a woman's risk of PTD is unknown. Papp et al demonstrated in cell culture, mouse models, and in HIV-infected pregnant women that exposure to PI, with the exception of darunavir, can decrease plasma progesterone levels. Low levels of plasma progesterone during pregnancy may potentially be associated with fetal loss, PTD, and LBW.[23] Papp et al subsequently demonstrated that HIV-infected pregnant women exposed to PI-based ART with low serum progesterone have elevated levels of human placental 20-α-hydroxysteroid dehydrogenase levels, an enzyme that inactivates serum progesterone. These women were also noted to have lower prolactin levels in comparison to controls.[24]

Other Pregnancy Outcomes: Low Birth Weight, Small-for-Gestational-Age, and Stillbirth

Fewer studies included in Table 5 have evaluated the effects of ART use on outcomes of LBW, SGA, and stillbirth. Reported rates of LBW range from 7.4% to 36%.[8,14,16,21,22,25,26] Of the 13 studies that address effects of ART on birth weight, only 3 demonstrate a significant association between any ART use and LBW.[16,26,27] Five studies report the rates of SGA, which range from 7.3% to 31%.[11,14,16,28,29] When comparing the initiation of monotherapy in pregnancy versus ART initiated before pregnancy and continued during pregnancy, ART was associated with SGA (1.34 [95% CI, 1.05–1.7]).[16] Two studies in Botswana report a positive association with ART use (both non-PI-based and PI-based) and SGA.[11,30] Continuation of ART initiated before pregnancy and initiation of ART during pregnancy may be associated with SGA (1.8 [95% CI, 1.6–2.1] and 1.5 [1.2–1.9]).[11] Seven studies report rates of stillbirth ranging from 0.5% to 11.4%.[7,11,12,14,22,26] Only 1 study reported a positive association between continuation of ART, both non-PI-based and PI-based, or starting ART during pregnancy and a risk of stillbirth (1.5 [95% CI, 1.2–1.8] and 2.5 [95% CI, 1.6–3.5]).[11]

Unknown Effects of Newer Antiretroviral Drugs on Pregnancy Outcomes

Data are insufficient regarding the effects of newer ARV drug classes on adverse pregnancy outcomes. Therefore, potential adverse pregnancy outcomes associated with these drug classes, which include integrase inhibitors, fusion inhibitors, and CCR5 antagonists, are not addressed in this section.

Summary

Clinicians should be aware of a possible increased risk of PTD with use of ART. Given the clear benefits for maternal health and reduction in perinatal transmission, these agents should not be withheld due to concern for increased risk of PTD. Until more information is available, HIV-infected pregnant women receiving ART should continue their provider-recommended regimens and receive regular monitoring for pregnancy complications, including PTD.[31]

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
European Collaborative Study and Swiss Mother and Child HIV Cohort Study; 1986–2000[1]	3,920/896	• Mono (573) • Multi, no PI (215) • Multi-PI (108)	• YES (compared with no ARV) • Multi: 1.82 (1.13–2.92) • Multi-PI: 2.60 (1.43–4.7)	• Increase in PTD if ARV begun before pregnancy versus in third trimester
United States; 1990–1998[21]	3,266/2,123	• Mono (1,590) • Multi (396) • Multi-PI (137)	• NO (compared with mono) • Multi: 0.95 (0.60–1.48) • Multi-PI: 1.45 (0.81–2.50)	• 7 prospective clinical studies
European Collaborative Study; 1986–2004[32]	4,372/2,033	• Mono (704) • Dual (254) • Multi (1,075)	• YES (compared with mono/dual) • Multi in pregnancy: 1.88 (1.34–2.65) • Multi pre-pregnancy: 2.05 (1.43–2.95)	N/A
United States; 1990–2002[27]	2,543/not given	Early (<25 Weeks): • Mono (621) • Multi (≥2 without PI or NNRTI) (198) • Multi (with PI or NNRTI) (357) Late (≥32 Weeks): • Mono (932) • Multi (≥2 without PI or NNRTI) (258) • Multi (with PI or NNRTI) (588)	• NO (compared with mono) • No association between any ARV and PTD	• PTD decreased with ARV compared with no ARV.
United States; 1990–2002[3]	1,337/999	• Mono (492) • Multi (373) • Multi-PI (134)	• YES (compared with other multi) • Multi-PI: 1.8 (1.1–3.03)	• Multi-PI reserved for advanced disease, those who failed other multi-ARV regimens.
Brazil, Argentina, Mexico, Bahamas; 2002–2005[25]	681/681	• Mono/dual NRTI (94) • Multi-NNRTI (257) • Multi-PI (330)	• NO (compared with mono/ dual NRTI) • No association between any ARV regimen and PTD	• All on ARV for at least 28 days during pregnancy • Preeclampsia/eclampsia, cesarean delivery, diabetes, low BMI associated with PTD
Meta-Analysis, Europe and United States; 1986–2004[4]	11,224/not given	• Multi-no PI (including dual) or multi-PI (2,556)	• YES (only comparing PI with multi) • PI versus multi-no PI: 1.35 (1.08–1.70)	• 14 studies, 5 in PTD-ARV comparison • No overall increase in PTD with antepartum ARV • PTD increased in those on ARV pre-pregnancy and in first trimester compared with later use.
Italy; 2001–2006[5]	419/366	• Multi-PI second trimester (97) • Multi-PI third trimester (146)	• YES • Multi-PI second trimester: 2.24 (1.22–4.12) • Multi-PI third trimester: 2.81 (1.46–5.39)	• Multivariate association also with hepatitis C

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
United States; 1989–2004[6]	8,793/6,228	• Mono (2,621) • Dual (1,044) • Multi-no PI (1,781) • Multi-PI (782)	• YES (compared with dual) • Multi-PI associated with PTD: 1.21 (1.04–1.40)	• Lack of antepartum ARV also associated with PTD • PTD and LBW decreased over time.
United Kingdom, Ireland; 1990–2005[7]	5,009/4,445	• Mono/dual (1,061) • Multi-NNRTI or multi-PI (3,384)	• YES (compared with mono/dual) • Multi: 1.51 (1.19–1.93)	• Similar increased risk with PI or no-PI multi • No association with duration of use
Germany, Austria; 1995–2001[8]	183/183	• Mono (77) • Dual (31) • Multi-PI (21) • Multi-NNRTI (54)	• YES (compared with mono) • Multi-PI: 3.40 (1.13–10.2)	N/A
United States; 2002–2007[19]	777/777	• Mono (6) • Dual (11) • Multi-no PI (202) • Multi-PI (558)	• NO (compared PI with all non-PI) • Multi-PI: 1.22 (0.70–2.12)	• All started ARV during pregnancy. • Analyzed only spontaneous PTD
Swiss Mother and Child HIV Cohort Study; 1985–2007[9]	1,180/941	• Mono (94) • Dual (53) • Multi (PI or no PI) (409) • Multi-PI (385)	• YES (compared with no ARV) • Multi: 2.5 (1.4–4.3)	• No association of mono/dual with PTD compared with no ARV • No confounding by duration of ARV or maternal risk factors
Botswana; 2006–2008[10]	530/530	• LPV/r plus ZDV plus 3TC (267) • ABC plus ZDV plus 3TC (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^3
Botswana; 2007–2010[30]	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; 1986–2010[20]	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-ARV or multi-PI before or during pregnancy	• PTD associated with multi-ARV given in second half of pregnancy and with prior PTD
Botswana; 2009–2011[11]	9,504/7,915	• Mono (4,625) • All multi (3,290) • Multi-PI (312)	• YES (multi-ARV before and during pregnancy compared to mono) 1.2 (1.1–1.4) and 1.4 (1.2–1.8) • YES (multi-PI compared to multi-no PI before pregnancy 2.0 (1.1–3.6)	• ART group classified by initiation before and during pregnancy

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 3 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
France; ANRS French Perinatal Cohort 1990–2009[12]	8,696/8,491	• Mono (950) • Dual (590) • Multi-PI (2,414)	• YES (multi-ARV compared to mono) 1.69 (1.38–2.07) • YES (before conception compared to during pregnancy) 1.31 (1.11–1.55)	• Patients on ART before and during pregnancy had increased rates of PTD
United States; 2000–2011[29]	183/183	• Multi-PI (183)	• NO (no control group without ART) • Rate of PTD 18.6%	• SGA rate 31.2% • NNRTI-based ART less likely to have SGA 0.28 (0.1–0.75)
United States; 2007–2010[13]	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
Latin America; 2002–2012[14]	1,512/1,446	• Multi-PI (907) • Multi-non-PI (409) • Mono/dual (130) • No ART or ART <28 days (66)	• YES (when on ARVs at conception), PTD 1.53 (1.11–2.09)	• ART for treatment rather than prophylaxis associated with increased rates of LBW (<2,500 gm) infants, LBW 1.8 (1.26–2.56) • Multi-non-PI associated with decreased risk of LBW 0.33 (0.14–0.74) and stillbirth 0.11 (0.04–0.34) • Multi-PI associated with decreased risk of stillbirth 0.14 (0.05–0.34)
Uganda; 2009–2012[33]	356/356	• Multi-PI (LPV/r) (179) • Multi-non-PI (EFV) (177)	• NO (no control group without ART)	• Trend in increased PTD among women starting ART 24–28 week GA was NS, aOR 1.76 (0.96–3.23)
Italy; 1997–2013[34]	158/158	• Mono/dual (27) • Multi-PI (114) • Multi-non-PI (17)	• NO (no control group without ART)	• PTD rate was 17% for this cohort, trend towards association with longer duration of ART 2.82 (0.35–8.09)
Canada; 1988–2011[15]	589/530	• Multi-non-boosted PI (220) • Multi-boosted PI with ritonavir (144) • Multi-non-PI (166) • Mono (77) • No ART (59)	• YES (compared to multi-non boosted PI) 2.01 (1.02–3.97) • NO (non-PI compared to non-boosted PI) 0.81 (0.4–1.66)	• Highest risk of PTD among women not taking ART compared to non-boosted PI group, 2.7 (1.2–6.09)

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 4 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
United Kingdom; 2007–2012[22]	493/493	• Multi-PI LPV/r • Multi-PI ATV/r	• NO (comparing two PI-based regimens) aOR 1.87 (0.93–3.75)	• Rate of PTD 13% among women who conceived on ART and 14% among women who started ART during pregnancy. • In multivariate analysis, a history of PTD was associated with recurrent PTD, aOR 5.23 (1.91–14.34)
Republic of the Congo; 2007–2012[26]	188/188	• Multi-non-PI, EFV-based (31) • Multi-non-PI, NVP-based (146)	• NO (comparing EFV 13% vs NPV 10%)	• Rate of PTD 11%, no difference between study groups • LBW increased in EFV group (33% vs 16%, *P* = 0.04). • Stillbirth rate 4% (8/188)
Tanzania; 2004–2011[16]	3,314/2,862	• Multi (1,094) • Mono (1,768) • No ART (452-excluded)	• YES (Multi before pregnancy vs Mono, 1.24 (1.05–1.47)) • VPTD, YES (Multi before pregnancy vs Mono, 1.42 (1.02–1.99) • NO (Multi during pregnancy compared to Mono, 0.85 (0.7–1.02)	• Rate of PTD 29%; women who conceived on ART more likely to have PTD compared to women on AZT monotherapy. • Pregnancy-induced hypertension associated with PTD, 1.25 (1.03–1.51)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; dual = two ARV drugs; LBW = low birth weight; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PTD = preterm delivery; VPTD= very preterm delivery

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Recommendations for Use of Antiretroviral Drugs during Pregnancy: Overview (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• Multiple factors must be considered when choosing an antiretroviral (ARV) drug regimen for a pregnant woman, including comorbidities, convenience, adverse effects, drug interactions, resistance testing results, pharmacokinetics (PK), and experience with use in pregnancy **(AIII)**.
• In general, the same regimens as recommended for treatment of non-pregnant adults should be used in pregnant women if appropriate drug exposure is achieved in pregnancy, unless there are known adverse effects for women, fetuses, or infants that outweigh benefits **(AII)**.
• In most cases, women who present for obstetric care on fully suppressive ARV regimens should continue their current regimens **(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*

This section provides an overview of the key clinical and pharmacokinetic (PK) issues relevant to the selection of specific antiretroviral (ARV) drugs for use in pregnancy. Specific recommendations for women who have never received ARV drugs (ARV-naive women), for women who are currently receiving ARV drugs, and for women with previous (but not current) ARV use are listed in the three sections that follow this overview. Table 6 provides specific information about recommended ARVs when **initiating** ART in treatment-naive pregnant women, and Table 8 provides dosing and PK data.

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** these adverse effects outweigh the benefits to the woman (or unless adequate drug levels are not likely to be attained during pregnancy).[1] Pregnancy should not preclude the use of optimal drug regimens. The decision about which ARV drug to use 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:

- Potential teratogenic effects and other short- and long-term adverse effects on fetuses or newborns including preterm birth, mutagenicity, and carcinogenicity,
- Experience with use in pregnancy,
- Potential drug interactions with other medications,
- Results of genotypic resistance testing and prior ARV exposure,
- PK changes in pregnancy,
- Potential adverse maternal drug effects, especially those that may be exacerbated during pregnancy,
- Comorbidities,

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- Ability of patient to adhere to regimen, *and*
- Convenience.

Information used by the Panel for recommendations on specific drugs or regimens for pregnant women includes:

- Data from randomized clinical trials and prospective 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;
- Known efficacy of ARV drug regimens in reducing perinatal transmission of HIV;
- PK (drug exposure) data during the pregnancy;
- Data from animal teratogenicity studies; and
- Antiretroviral Pregnancy Registry (and other post-marketing surveillance) data.[2]

Categories of ARV regimens include:

- **Preferred:** Drugs or drug combinations are designated as preferred for initiating ART 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 (from animal and/or human studies) or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported. Drugs in the preferred category may have toxicity or teratogenicity 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 Perinatal Guidelines before administering any of these medications to your patients (also see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy).
- **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 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, tolerability, 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 initiating ART in ARV-naive pregnant women.
- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for initial 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. While this section pertains primarily to initiating ARVs, Table 6 also includes information on medications that should be stopped due to toxicity in women who become pregnant.

In pregnant women, as in non-pregnant adults, ART 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, the results of drug-resistance assays, and the presence of comorbidities. Women receiving ART may become pregnant and present for obstetric care. In general, women who are already on a fully suppressive regimen should continue their regimens. Key exceptions include medications with high risk for toxicity in pregnancy (didanosine, stavudine, and treatment-dose ritonavir;

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see Table 6). Other HIV-infected women may not be receiving ART at the time they present for obstetrical care. Some women have never received ARV drugs in the past and some may have been treated in previous pregnancies. Specific recommendations for each type of patient are described in the following three sections: HIV-Infected Women Who Have Never Received Antiretroviral Drugs (ARV-naive); HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy; and HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications.

For ARV-naive women, an ART regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a ritonavir-boosted protease inhibitor (PI) or an integrase inhibitor is preferred (Table 6).

Nucleoside Reverse Transcriptase Inhibitors and Pregnancy

There are two preferred NRTI combinations for use in ARV-naive pregnant women: abacavir in combination with lamivudine, and tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (or with lamivudine).

Abacavir/lamivudine is the NRTI component in some Preferred regimens for non-pregnant adults. It offers the advantage of once-daily dosing and is well tolerated in pregnancy.[3] 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.

TDF with emtricitabine or lamivudine is the NRTI component in some Preferred regimens for non-pregnant adults. Based on extensive experience with use in pregnancy, once-daily dosing, enhanced activity against hepatitis B, and less frequent toxicity compared to zidovudine/lamivudine, it is considered a Preferred combination in pregnancy. Although there have been concerns about bone and growth abnormalities in infants exposed to TDF *in utero*, the duration and clinical significance of study findings require further evaluation (see Tenofovir Disoproxil Fumarate).[4]

Zidovudine/lamivudine is now an Alternative NRTI regimen for ARV-naive women, despite efficacy studies in preventing perinatal transmission and extensive experience with safe use in pregnancy. This is because it requires twice-daily dosing and is associated with higher rates of mild-to-moderate adverse effects, including nausea, headache, and reversible maternal and neonatal anemia and neutropenia.

Women receiving **didanosine** or **stavudine** in pregnancy should be switched to Preferred or Alternative NRTI regimens.

Safety and PK data about the use of **tenofovir alafenamide** in pregnancy are insufficient to recommend initiation of this medication in pregnant women.

Mitochondrial Toxicity with Nucleoside Reverse Transcriptase Inhibitors

NRTIs are well-tolerated medications in general. However, NRTIs are known to induce some level of 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.[5-7] Mitochondrial dysfunction is less common with currently recommended NRTI agents than with older medications (didanosine, stavudine). Although several syndromes linked to mitochondrial toxicity have been reported in ARV-exposed infants, their clinical significance remains uncertain, and they are very likely to be outweighed by the importance of maternal and infant ARV use to prevent perinatal HIV transmission.[8,9] For pregnant women, uncommon but important clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis; the latter two may be more common in women than in men.[10,11] These syndromes have similarities to two life-threatening syndromes that occur during pregnancy, most often during the third trimester: the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and acute hepatic steatosis (with or without lactic acidosis). The frequency of HELLP syndrome or lactic

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acidosis and hepatic steatosis in pregnant HIV-infected women receiving NRTI drugs is unknown, but a small number of cases have been reported, including several in which didanosine and stavudine were used in combination during pregnancy. Nonfatal cases of lactic acidosis also have been reported in pregnant women receiving combination didanosine/stavudine.[12] Thus, clinicians should not prescribe combination didanosine/stavudine for pregnant (or even non-pregnant) adults, and women becoming pregnant while receiving these medications should switch to safer options (see above) (see Adult and Adolescent Guidelines).

Non-Nucleoside Reverse Transcriptase Inhibitors and Pregnancy

There are no preferred non-nucleoside reverse transcriptase inhibitors (NNRTIs) for use in ARV-naive pregnant women.

Efavirenz is now an Alternative NNRTI for both pregnant and non-pregnant ARV-naive adults. Although increasing data on use of efavirenz in pregnancy are reassuring with regard to neural tube defects, and it is increasingly used in pregnancy worldwide, it is associated with dizziness, fatigue, vivid dreams and/or nightmares, and increased suicidality risk.[13,14] Efavirenz remains an Alternative agent for use in pregnancy, and may be suitable for women who desire a once-daily fixed-dose combination regimen and who tolerate efavirenz without adverse effect.

In prior guidelines, efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert information, recent large meta-analyses have been reassuring that risks of neural tube defects after first-trimester efavirenz exposure are not greater than those in the general population.[13-15] Both British and World Health Organization guidelines note that efavirenz can be used throughout pregnancy (see Teratogenicity and HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment). Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

As for all women, screening for both antenatal and postpartum depression is recommended; because efavirenz may increase risk of depression and suicidality, this is particularly critical for women on efavirenz-containing regimens.[16]

Rilpivirine may be used as part of an Alternative regimen for non-pregnant adults with pretreatment HIV RNA <100,000 copies/mL and CD4 T lymphocyte (CD4) cell count >200 cells/mm^3. There are sufficient data from use in pregnancy to recommend it as an Alternative agent for ARV-naive pregnant women who meet these same CD4 and viral load criteria. **Nevirapine** is not recommended for initial ART in ARV-naive pregnant women or for non-pregnant adults because of greater potential for adverse events, complex lead-in dosing, and low barrier to resistance. **Etravirine** is not recommended for ARV-naive non-pregnant patients, and safety and PK data on etravirine in pregnancy are insufficient to recommend use of this NNRTI drug in ARV-naive pregnant women.

Protease Inhibitors and Pregnancy

Atazanavir/ritonavir and **darunavir/ritonavir** are the Preferred PI drugs for use in ARV-naive pregnant women, based on efficacy studies in adults and experience with use in pregnancy (see Table 8 for dosing considerations). The Alternative PI is **lopinavir/ritonavir**, for which there are extensive clinical experience and PK data in pregnancy, but which requires twice-daily dosing in pregnancy and frequently causes nausea and diarrhea. PK data and extensive clinical experience exist for **nelfinavir** in pregnancy, but the rate of virologic response to nelfinavir-based regimens was lower than lopinavir/ritonavir 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 for initial ART in pregnancy. **Saquinavir** is not recommended for initial ART in ARV-naive pregnant women because it requires a baseline electrocardiogram due to potential PR and QT prolongation, has a high pill burden, and is not recommended for use in initial therapy for non-pregnant adults. **Indinavir** may be associated with nephrolithiasis and has a higher pill burden than many other PI drugs; therefore, it is also not recommended for initial ART in ARV-naive pregnant women. Both atazanavir and indinavir are associated with

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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.[17] 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 this finding was no longer significant at 24 months.[18,19] Data on use in pregnancy are too limited to recommend routine use of **fosamprenavir** and **tipranavir/ritonavir** in pregnant women.

Entry and Fusion Inhibitors and Pregnancy

Safety and PK data in pregnancy are insufficient to recommend use of the entry inhibitors **enfuvirtide** and **maraviroc** for initial ART 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.

Integrase Inhibitors and Pregnancy

Raltegravir is the Preferred integrase inhibitor for use in ARV-naive pregnant women. PK, safety, and other data on the use of raltegravir during pregnancy are available and increasing; ART regimens including raltegravir can be considered as Preferred regimens in ARV-naive pregnant women as they are for ARV-naive non-pregnant adults.[20-25] Clinical trial data from non-pregnant adults suggest a more rapid viral decay with the use of raltegravir compared to efavirenz.[26] Case series have reported rapid viral decay with the use of raltegravir initiated late in pregnancy to achieve viral suppression and reduce the risk of perinatal HIV transmission, but no comparative data are available in pregnancy.[20,22,27-32] The rate of viral decay with raltegravir compared to efavirenz in late-presenting pregnant women is currently under investigation.[33] 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.[34]

There are currently limited data on the use of **dolutegravir** or **elvitegravir/cobicistat** in pregnancy; thus these drugs cannot be recommended for initial ART in ARV-naive pregnant women at this time.[31,35]

Pharmacologic Boosters

There are currently limited data on the use of **cobicistat** in pregnancy; thus this drug cannot be recommended for ARV-naive pregnant women at this time. Low-dose **ritonavir** as a pharmacologic booster for other PIs is described above.

Pharmacokinetic Considerations for Antiretrovirals

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.[36,37] 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 8. In general, the PKs of NRTIs and NNRTIs are similar in pregnant and non-pregnant women (although data on etravirine are limited), whereas PI PKs are more variable, particularly in later pregnancy. Current data suggest that with standard adult dosing, plasma concentrations of nelfinavir and lopinavir/ritonavir, atazanavir, and darunavir are reduced during the second and/or third trimesters (see Table 8). 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.[38-45] Raltegravir levels in the third trimester were quite variable but not significantly different than postpartum or historical data in non-pregnant individuals.[24,25] Data on enfuvirtide

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and maraviroc in pregnancy are too limited to allow recommendations on dosing. Limited data exist about dolutegravir and elvitegravir/cobicistat PK during pregnancy, but available data suggest that levels of both integrase inhibitors are lower in pregnancy compared to the postpartum period.[46,47]

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 initiating ART in pregnant antiretroviral-naive women are shown in Table 6.

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Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated December 15, 2016; last reviewed December 15, 2016)

Panel's Recommendations

- Combination antiretroviral therapy (ART) should be recommended to all pregnant women living with HIV to reduce the risk of perinatal transmission of HIV and also to optimize the health of the mother **(AI)**. Initiation of ART as soon as HIV is diagnosed during pregnancy is recommended based on data demonstrating that earlier virologic suppression is associated with lower risk of transmission **(AII)**.
- Antiretroviral (ARV) drug-resistance studies should be performed to guide selection of regimens in women whose HIV RNA levels are 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 ART is initiated before the results of the drug-resistance assays are available, the ARV regimen should be modified, if necessary, based on the resistance assay results **(BIII)**.
- The choice of regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy and risk of teratogenicity (Table 6 and Table 8) and maternal factors such as nausea and vomiting and comorbid conditions. ART regimens that are preferred for the treatment of pregnant women living with HIV who are ARV-naive include: a dual nucleoside reverse transcriptase inhibitor combination (abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine) and either a ritonavir-boosted protease inhibitor (atazanavir/ritonavir or darunavir/ritonavir) or an integrase inhibitor (raltegravir) (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 living with HIV infection should receive standard clinical, immunologic, and virologic evaluation. They should be counseled about and offered combination antiretroviral therapy (ART) containing at least three drugs for their own health and for the prevention of perinatal transmission of HIV, consistent with the principles of treatment for non-pregnant adults.[1] Use of an ART 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 antiretroviral (ARV) drug resistance in the mother. In an analysis of perinatal transmission in a total of 12,486 infants delivered by women living with HIV between 2000 and 2011 in the United Kingdom and Ireland, the overall perinatal transmission rate declined from 2.1% in 2000–2001 to 0.46% in 2010–2011. The transmission risk was significantly lower (0.09%) in women with viral loads <50 copies/mL compared with a risk of 1.0% in women with viral loads of 50–399 copies/mL, regardless of the type of ARV regimen or mode of delivery.[2] The continued decline in perinatal transmission rates was attributed to the increasing number of women on ART at the time of conception and reductions in the proportion of women either initiating ART late in pregnancy or never receiving ART prior to delivery. Similar data from Canada in 1,707 pregnant women living with HIV followed between 1997 and 2010 showed perinatal transmission was 1% in all mothers receiving ART and 0.4% if more than 4 weeks of ART was received.[3]

ARV drug-resistance testing should be performed before starting an ARV regimen if plasma HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL). For details regarding genotypic and phenotypic resistance testing, see Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Adult and Adolescent Guidelines). Given the association of earlier viral suppression with lower risk of transmission as discussed above, during pregnancy, ART should be initiated as soon as HIV is diagnosed without waiting for the results of resistance testing, with modification of the regimen, if required, when test results return. A PI-based ART regimen generally should be considered when the results of resistance testing are not available to inform selection of ARVs because clinically significant resistance to protease inhibitors (PI) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in ARV-naive individuals.

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Table 6 outlines the ARV regimens that are preferred for treatment of pregnant women living with HIV who have never received ARV drugs. These recommendations are 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 outcomes for mother, fetus or newborn in addition to optimal ARV efficacy and durability. Preferred regimens include a dual nucleoside reverse transcriptase inhibitor (NRTI) combination (abacavir/lamivudine, tenofovir disoproxil fumarate [TDF]/emtricitabine or lamivudine, or zidovudine/lamivudine) in combination with either a ritonavir-boosted PI (atazanavir/ritonavir or darunavir/ritonavir), or an integrase inhibitor (raltegravir). 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 8).

Susceptibility of fetuses to the potential teratogenic effects of drugs is dependent on multiple factors, including the gestational age of the fetus at exposure (see the Teratogenicity section). Although fetal effects of ARV drugs are not fully known, in general, reports of birth defects in fetuses/infants of women enrolled in observational studies who receive ARV regimens during pregnancy have been reassuring. There have been no differences in the rates of birth defects for first-trimester compared with either later gestational exposures or with rates reported in the general population.[4-7] The decision about when to initiate ART 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 and the potential risks and benefits to the fetus.

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 the prospective multicenter French Perinatal Cohort, maternal viral load at delivery and timing of ART initiation were both independently associated with perinatal transmission rate. The perinatal transmission rate increased from 0.2% for women starting ART before conception to 0.4%, 0.9% and 2.2% for those starting in the first, second or third trimester (respectively). Regardless of when ART was initiated, the perinatal transmission rate was higher for women with viral loads of 50 to 400 copies/mL near delivery than for those with <50 copies mL.[8] In an earlier publication involving the same cohort, lack of early and sustained control of maternal viral load appeared strongly associated with residual perinatal transmission of HIV.[9] 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 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 ART 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 ART would be particularly important in pregnant women who have high baseline viral loads.[10-12] However, the potential benefits of earlier initiation of ART must be balanced against the unknown long-term outcome of first-trimester ARV exposure to the fetus.

ART is recommended for all pregnant women living with HIV, 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.[13-15] 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.[16-20] Additional mechanisms of protection include pre-exposure prophylaxis (PrEP) and

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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, ART regimens initiated during pregnancy should include an NRTI with high transplacental passage, such as lamivudine, emtricitabine, tenofovir, or abacavir (see Table 8).[21-24] With post-exposure prophylaxis, ARV drugs are administered to the infant after birth.

The use of zidovudine monotherapy during pregnancy is no longer recommended because of the clear health benefit of ART to the mother and for the prevention of perinatal transmission of HIV. In the past, use of zidovudine alone during pregnancy for prophylaxis of perinatal transmission was considered to be an option for women with low viral loads (i.e., <1,000 copies/mL) on no ARV drugs. Zidovudine single-drug prophylaxis is still recommended in the British HIV Association guidelines for women with CD4 T lymphocyte counts >350 cells/mm^3 *and* HIV RNA levels <10,000 copies/mL *and* wild-type virus who do not require treatment for their own health.[25]

All pregnant women living with HIV should be counseled that ART is recommended, regardless of viral load, to optimally reduce the risk of perinatal transmission. However, after counseling, women's choices 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).[26-29] Two recent case series have reported the effect of adding raltegravir to ART regimens. In one, 4 women diagnosed with HIV infection in the third trimester experienced a mean viral load decline per week of 1.12 log after raltegravir was added to a standard ARV regimen.[30] In the second publication, raltegravir was either initiated as part of a combination ARV regimen in nine ARV-naive women or added to an existing ARV regimen in five women who conceived on ART but had persistent viremia. Raltegravir was initiated at a gestational age of 34 weeks or later.[31] The median exposure time to raltegravir was 17 days and the mean viral load decline was 2.6 log. Although no raltegravir-related adverse effects were noted in these reports, marked elevations in hepatic transaminases were reported in a single pregnant woman living with HIV when raltegravir was added to an ARV regimen.[32] 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 ART 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).

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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., antiretroviral-naive) and who have no evidence of significant resistance to regimen components. See Table 8 for more information on specific drugs and dosing in pregnancy. Within each drug class and recommendation category, 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 ART regimen with viral suppression remain on that same regimen, with the exception of regimens containing didanosine, stavudine, or treatment-dose ritonavir.

Drug	Comments
Preferred Initial Regimens in Pregnancy: • Drugs or drug combinations are designated as Preferred for initiating ART 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 (from animal and/or human studies) or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported.	
Preferred Two-NRTI Backbones	
ABC/3TC	Available as FDC. Can be administered once daily. ABC **should not be used** in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction. ABC/3TC with ATV/r or with EFV is not recommended if pretreatment HIV RNA is >100,000 copies/mL.
TDF/FTC or TDF/3TC	TDF/FTC available as FDC. Either TDF/FTC (coformulated) or TDF with separate 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.
Preferred PI Regimens	
ATV/r plus a Preferred Two-NRTI Backbone	Once-daily administration. Extensive experience in pregnancy. Maternal hyperbilirubinemia; no clinically significant neonatal hyperbilirubinemia or kernicterus reported, but neonatal bilirubin monitoring recommended.
DRV/r plus a Preferred Two-NRTI Backbone	Better tolerated than LPV/r. PK data available. Increasing experience with use in pregnancy. Must be used twice daily in pregnancy.
Preferred Integrase Inhibitor Regimen	
RAL plus a Preferred Two-NRTI Backbone	PK data available and increasing experience in pregnancy. Rapid viral load reduction (potential role for women who present for initial therapy late in pregnancy). Useful when drug interactions with PI regimens are a concern. Twice-daily dosing required. If there are concerns about adherence or medication discontinuation postpartum, a PI regimen is preferred instead of an integrase inhibitor regimen, to minimize the risk of resistance.
Alternative Initial Regimens in Pregnancy: • 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.	
Alternative Two-NRTI Backbones	
ZDV/3TC	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 toxicities.
PI Regimens	
LPV/r plus a Preferred Two-NRTI Backbone	Abundant experience and established PK in pregnancy. More nausea than with preferred agents. Twice-daily administration. Dose increase recommended in third trimester (see Table 8). Once-daily LPV/r is not recommended for use in pregnant women.
NNRTI Regimen	
EFV plus a Preferred Two-NRTI Backbone	Concern because of birth defects seen in primate study; data not borne out in human studies, but cautionary text remains in package insert (see Teratogenicity and Table 8). Preferred regimen in women who require coadministration of drugs with significant interactions with PIs or the convenience of coformulated, single-tablet, once-daily regimen. Screening for antenatal and postpartum depression is recommended.
RPV/TDF/FTC (or RPV plus a Preferred Two-NRTI Backbone)	RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4 cell count <200 cells/mm^3. Do not use with PPIs. PK data available in pregnancy but relatively little experience with use in pregnancy. Available in coformulated single-pill, once-daily regimen.

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Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 2 of 2)

Drug	Comments
Insufficient Data in Pregnancy to Recommend Routine Use in Initial Regimens for ART-Naive Women: • Drugs that are approved for use in adults but lack adequate pregnancy-specific PK or safety data	
COBI	Limited data on use of COBI (including coformulations with ATV or DRV) in pregnancy.
DTG	Limited data on use of DTG in pregnancy.
EVG/COBI/TDF/FTC Fixed Drug Combination	Limited data on use of EVG/COBI component in pregnancy.
FPV	Limited data on use in pregnancy.
MVC	MVC requires tropism testing before use. Few case reports of use in pregnancy.
EVG/COBI/TAF/FTC Fixed Drug Combination	Limited data on use of EVG/COBI; no data on use of TAF in pregnancy
TAF/FTC Fixed Drug Combination	No data on use of TAF in pregnancy.
RPV/TAF/FTC Fixed Drug Combination	No data on use of TAF in pregnancy.
Not Recommended for Initial ART in Pregnancy: • Drugs whose use is not recommended as part of initial regimens in pregnancy because of toxicity, lower rate of viral suppression or because not recommended in ART-naive populations.	
Note: Drugs not recommended for initial use because of toxicity (stavudine [d4T], didanosine [ddI], treatment-dose ritonavir [RTV]) should also be stopped in women who present during pregnancy while taking these medications. Other medications listed below may be continued in women who present during pregnancy, as long as they are well tolerated and result in sustained virologic suppression.	
ABC/3TC/ZDV	Generally not recommended due to inferior virologic efficacy.
d4T*	Not recommended due to toxicity.
ddI*	Not recommended due to toxicity.
IDV/r	Nephrolithiasis, maternal hyperbilirubinemia.
NFV	Lower rate of viral suppression with NFV compared to LPV/r or EFV in adult trials.
RTV*	RTV as a single PI is not recommended because of inferior efficacy and increased toxicity.
SQV/r	Not recommended based on potential toxicity and dosing disadvantages. Baseline ECG is recommended before initiation of SQV/r because of potential PR and QT prolongation; contraindicated with preexisting cardiac conduction system disease. Limited data in pregnancy. Large pill burden. Twice-daily dosing required.
ETR	Not recommended in ART-naive populations.
NVP	Not recommended because of greater potential for adverse events, complex lead-in dosing, and low barrier to resistance. NVP should be used with caution when initiating ART in women with CD4 cell count >250 cells/mm^3. Use NVP and ABC together with caution; both can cause hypersensitivity reactions within the first few weeks after initiation.
T20	Not recommended in ART-naive populations.
TPV/r	Not recommended in ART-naive populations.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte cell; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDC = fixed-drug combination; FPV = fosamprenavir; FTC = emtricitabine; IDV/r = indinavir/ritonavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• In general, HIV-infected pregnant women receiving antiretroviral therapy (ART) 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)**. • HIV antiretroviral (ARV) drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in pregnant women on therapy with virologic failure and HIV RNA levels >1,000 copies/mL **(AI).** In individuals with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)** (see Lack of Viral Suppression).
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 been receiving antiretroviral therapy (ART) for their HIV infection should continue treatment during pregnancy, assuming it is effective in suppressing viral replication and well-tolerated. 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. Furthermore, changes in the pharmacokinetics (PK) of antiretroviral (ARV) drugs during pregnancy may be associated with lack of virologic suppression at the end of pregnancy and increased risk of perinatal transmission.[1]

As newer, highly effective ARV drugs are approved, HIV-infected women may present for prenatal care on ART regimens that include ARV drugs for which there is a lack of significant experience in pregnancy, with limited data on PK and safety. Maintenance of viral suppression is paramount for both maternal health and prevention of perinatal transmission. Thus, if questions arise about particular drugs in an ART regimen, providers are encouraged to consult with an HIV perinatal specialist before considering altering a regimen that is achieving full viral suppression and is well tolerated. Because little is known about the use of newly approved drugs in pregnancy, providers should make every effort to report all ART exposures in pregnant women to the Antiretroviral Pregnancy Registry.

HIV-infected women receiving ART who present for care during the first trimester should be counseled regarding the benefits and potential risks of administration of ARV drugs during this period. Providers should emphasize that continuation of effective ART is recommended. There have been concerns regarding efavirenz use in the first trimester and potential for neural tube defects, based on non-human primate data and retrospective case reports (for more details see Teratogenicity). However, a recent meta-analysis including data on 2,026 women with first-trimester efavirenz exposure from 21 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 0.78, 95% confidence interval [CI], 0.56–1.08). One neural tube defect was identified, resulting in an incidence of 0.05% (95% CI, <0.01 to 0.28) similar to the incidence of neural tube defects in the general population.[2] Although a 2- to 3-fold increased incidence of a rare outcome (e.g., neural tube defects [0.02% to 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 and that risk is not greater than that seen in the general population. The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission recommends that efavirenz be continued in pregnant women receiving efavirenz-based ART who present for antenatal care in the first trimester, provided that the ARV regimen is resulting in virologic suppression.

Resistance testing should be performed in pregnant women on ART when a change in active drugs is being

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considered because of virologic failure with HIV RNA levels >1,000 copies/mL. In individuals with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but it still should be considered. The results can be used to select a new regimen with a greater likelihood of suppressing viral replication to undetectable levels.

Pregnant women for whom nevirapine-containing regimens result in 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/mm^3, an increased risk of hepatic toxicity has not been seen in women continuing nevirapine-based therapy that has resulted in CD4 counts >250 cell/mm^3.

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HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• Obtain an accurate history of all prior antiretroviral (ARV) regimens used for treatment of HIV disease or prevention of transmission, including virologic efficacy, tolerance to the medications, results of prior resistance testing, and problems with adherence **(AIII)**.
• Choose and initiate a combination antiretroviral therapy (ART) regimen based on results of prior resistance testing, if available, prior history of ART, and current ART in pregnancy guidelines, avoiding drugs with potential known adverse effects for the mother or fetus/infant **(AII)**.
• If HIV RNA is above the threshold for resistance testing (i.e., >500–1,000 copies/mL), ARV drug-resistance studies should be performed prior to starting an ARV drug regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AI)**.
• In general, ART should be initiated prior to receiving results of current ARV drug-resistance studies **(BIII)**. ART should be modified based on the results of the resistance assay, if necessary **(AIII)**.
• If the ART regimen results in insufficient viral suppression, repeat resistance testing and assess other considerations including adherence and drug interactions **(BIII)**.
• Consider consulting with an HIV treatment specialist about the choice of ART regimen to initiate in women who previously received ARV drugs or to modify ART in those who are not fully suppressed **(BIII)**.
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 HIV-infected women who are currently not receiving antiretroviral therapy (ART) may have received ART in the past for their own health and/or prevention of perinatal transmission in a prior pregnancy. A small number of clinical trials and observational studies have generated information about effectiveness of combination ART in individuals who previously received ART for prevention of perinatal transmission of HIV.[1-4]

There has been concern that prior time-limited use of ART during pregnancy for prevention of perinatal transmission may lead to genotypic resistance and, thus, reduced efficacy if these ARV drugs are used as a part of subsequent ART regimens. Rates of resistance appear to be low, based on standard genotyping, after time-limited use of ART consisting of zidovudine, lamivudine, and nevirapine during pregnancy.[5,6] However, minority populations of virus with resistance to nevirapine or lamivudine have been detected using sensitive allele-specific polymerase chain reaction techniques, particularly in women whose virus was inadequately suppressed.[6-9] 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 ART, but these results reflect assessments in a limited number of women.[8,10]

Increased risk of treatment failure has not been demonstrated with reinitiation of ART following time-limited use for prevention of perinatal transmission. However, only a limited number of sufficiently large, prospective, observational studies and/or clinical trials have been done to assess the effect of pregnancy-limited ART on the outcome of subsequent treatment. In ACTG 5227, 52 women who had previously received pregnancy-limited ART and who had no evidence of resistance were started on a fixed-dose combination of efavirenz/tenofovir disoproxil fumarate/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 prior ART drug class or whether women had received similar ART in one or more previous pregnancies.[1] Data from the French Perinatal Cohort assessed virologic suppression with PI-based ART administered to women who had received ART during a previous pregnancy for prevention of perinatal transmission. No differences in rates of undetectable viral load at delivery were noted among ARV-naive

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women when compared with those who received ART during previous pregnancies or according to type of ART previously received.[11] In addition, the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland found no increased risk of perinatal transmission in sequential pregnancies compared with a single pregnancy when most women received ART for prevention of perinatal HIV transmission.[12] However, in a comparison between 5,372 ARV-naive pregnant women and 605 women who had previously received ART but were not being treated immediately prior to the current pregnancy, ARV-experienced women had a small but significant increase in the risk of detectable viral load at delivery (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-based as opposed to PI-based therapy.[13]

Women may choose to discontinue ART for a variety of reasons, and the length of time off treatment prior to pregnancy may vary. Choice of ART in pregnant women who have been previously treated should be made based on treatment history and all prior drug resistance testing results, even if results of drug resistance testing obtained during the current pregnancy are not yet available. Interpretation of resistance testing can be complex because it is most accurate if performed while an individual is still taking ART 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 ART is restarted. Therefore, when selecting a new ART regimen, all information including regimens received, viral response, laboratory testing (including HLA-B*5701 results), any tolerance or adherence problems, concomitant medications, and the results of resistance testing should be taken into consideration. In general, ART should be initiated prior to receiving results of current antiretroviral (ARV) drug-resistance studies, especially because duration of ART ≥24 weeks has been associated with reduced transmission rates compared to shorter treatment periods.[14,15] ART should be modified, if necessary, based on subsequent resistance assay results. Careful monitoring of virologic response is essential.

It is reasonable to restart the same ART regimen in a woman with a history of prior ART associated with successful suppression of viral load assuming that it was well tolerated, is currently recommended as first-line or an alternate ART regimen in pregnancy (see Table 6: What to Start), and has no evidence of resistance. However, even experienced healthcare providers may have difficulty with the selection of appropriate ART for women with advanced HIV disease, a history of extensive prior ART, or previous significant toxicity or nonadherence to ARV drugs. In addition to obtaining genotypic resistance testing, it is strongly recommended that specialists in the treatment of HIV infection be consulted early in the pregnancy about the choice of a suitable ART regimen for such women.

If ART produces an insufficient viral response (e.g., <1 log drop over 4–8 weeks), repeat resistance testing and assess medication adherence and potential drug interactions (including, if available, relevant pharmacokinetic studies) to inform potential regimen changes. Consultation with an HIV treatment specialist is recommended.

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Monitoring of the Woman and Fetus During Pregnancy (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations

- 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) and to inform decisions about optimal treatment of the newborn (see Infant ARV Prophylaxis) **(AIII)**.
- CD4 T lymphocyte (CD4) cell count should be monitored at the initial antenatal visit **(AI)** and every 3 to 6 months during pregnancy **(BIII)**. Monitoring of CD4 cell count can be performed every 6 months in patients on combination antiretroviral therapy (ART) with consistently suppressed viral load who have CD4 counts well above the threshold for opportunistic infection risk **(CIII)**.
- HIV drug-resistance studies should be performed before starting ARV regimens in all ARV-naive pregnant women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) unless they have already been tested for ARV resistance **(AIII)**. 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., >500 to 1,000 copies/mL) while receiving ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy **(AII)**. If ART is initiated before the results of the drug-resistance assays are available, the ARV regimen should be modified, if necessary, based on the resistance assay results **(BIII)**.
- 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)**.
- HIV-infected women taking ART 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 (PI)-based regimens initiated before pregnancy, similar to recommendations for women with risk factors for glucose intolerance **(BIII)**. For further information on PIs see Combination Antiretroviral Drug Regimens and Pregnancy Outcome.
- Ultrasound in the first trimester, or as soon as possible thereafter, 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)**.
- In women on effective antiretroviral therapy (ART), no perinatal transmissions have been reported after amniocentesis, but a small risk of transmission cannot be ruled out. Amniocentesis should be performed on HIV-infected women only after initiation of an effective ART regimen and, ideally, 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 **(BIII)**.

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*

More frequent viral load monitoring is recommended in pregnant than non-pregnant individuals because of the importance of rapid and sustained viral suppression in preventing perinatal HIV transmission. In individuals who are adherent to their antiretroviral (ARV) regimen and 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 and may be dependent on starting viral load. Most patients with adequate viral response at 24 weeks of treatment have had at least a 1 log viral load decrease within 1 to 4 weeks after starting therapy.[1,2] Viral load should be monitored in HIV-infected pregnant women at the initial visit, 2 to 4 weeks after initiating or changing 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.[3]

Viral load also should be assessed at approximately 34 to 36 weeks' gestation to inform decisions about mode of delivery and about optimal treatment of newborns (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 CD4 counts well above the threshold for opportunistic infection risk.[1,4,5]

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Whenever feasible, ARV drug-resistance testing should be performed before initiation of ARV drugs if HIV RNA levels are above the threshold for resistance testing, but therapy should not be delayed once the blood is drawn and results are pending. If the results demonstrate resistance, then the regimen can subsequently be adjusted. Testing also should be performed on women taking an ARV regimen who have suboptimal viral suppression or who have persistent 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 is most useful if performed while patients are receiving ARV drugs or within 4 weeks after discontinuation of drugs. Even if more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing can still provide useful information to guide therapy, though it may not detect previously selected resistance mutations. 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. Pregnant women in general are more likely to have elevated liver enzymes than their non-pregnant counterparts.[6,7]

Pregnancy increases the risk of hyperglycemia. PI drugs have been associated with increased risk of hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis.[8-11] However, the majority of studies in HIV-infected pregnant women 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.[12] In both groups, the rate of impaired glucose tolerance was high (38%), but that may be related to high body mass index and race/ethnicity among trial subjects. HIV-infected women receiving antiretroviral therapy (ART) during pregnancy should receive the standard glucose screening at 24 to 28 weeks' gestation that is recommended for all pregnant women. Some experts would perform earlier glucose screening in women receiving ongoing PI-based ART initiated before pregnancy, similar to recommendations for women with risk factors for glucose intolerance.

Accurate estimation of date of delivery is critical to planning elective cesarean deliveries at 38 weeks' gestation to prevent perinatal transmission in HIV-infected women with elevated HIV RNA viral loads. Therefore, first-trimester ultrasound is recommended to confirm gestational age and to provide the most accurate estimation of gestational age at delivery (see Transmission and Mode of Delivery).[13-15] In patients who are not seen until later in gestation, second-trimester ultrasound can be used for both anatomical survey and determination of gestational age.

Although data are still somewhat limited, the risk of HIV transmission does not appear to be increased with amniocentesis or other invasive diagnostic procedures in women receiving effective ART resulting in viral suppression. This is in contrast to the era before effective ART, 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.[16-19] Although no transmissions have occurred among 159 cases reported to date of amniocentesis or other invasive diagnostic procedures among women on effective ART, a small increase in risk of transmission cannot be ruled out.[20-23] 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. At a minimum, HIV-infected pregnant

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women should receive effective ART before undergoing any invasive prenatal testing and, ideally, have an undetectable HIV RNA level at the time of the procedure, and every effort should be made to avoid inserting the needle through, or very close to, the placenta. Consideration can also be given to the use of noninvasive methods of prenatal risk assessment, using tests with high sensitivity and low false-positive rates, such as serum screening alone or combined with nuchal translucency, anatomic ultrasound, and noninvasive molecular prenatal testing.[24,25] In women with detectable HIV RNA levels for whom amniocentesis is deemed necessary, consultation with an expert should be considered.

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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• 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., >500 to 1,000 copies/mL) unless they have already been tested for ARV resistance **(AIII)**. • Antiretroviral therapy (ART) should be initiated in pregnant women prior to receiving results of ARV-resistance studies. ART should be modified, if necessary, based on the results of the resistance assay **(BIII)**. • HIV drug-resistance studies should be performed before modifying ART regimens for those 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 ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy **(AII)**. • Documented zidovudine resistance does not affect the indications for use of intrapartum zidovudine **(BIII)**. • 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) **(AIII)**. • HIV-infected pregnant women should be given ART to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission **(AII)**. • 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)**.
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 for the selection of more effective and durable antiretroviral (ARV) regimens, genotypic resistance testing (in addition to a comprehensive history of ARV drug use) is recommended:

- Before initiating antiretroviral therapy (ART) 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 ART in HIV-infected pregnant women who have received ARV drugs for prevention of perinatal transmission in prior pregnancies if HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL), *and*
- 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 ART or who have suboptimal virologic response to ARV drugs started during pregnancy

In most settings, the results of resistance testing guide selection of the initial ART regimen. However, given the association of earlier viral suppression with lower risk of perinatal transmission, in ARV-naive pregnant women, ART should be initiated without waiting for the results of resistance testing, with modification of the regimen, if required, when test results return (see HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) section).

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. In addition, pre-existing resistance to a drug in an ART regimen may diminish the

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regimen's efficacy in preventing perinatal transmission. 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. Issues relating to discontinuation of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART 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.

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 the presence of resistance mutations increases the 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;[1] however, women in this cohort had characteristics that would indicate a need for ART 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 virus and virus with low-level zidovudine resistance, only wild-type virus was detected in their infants,[2] and other studies have suggested that drug-resistance mutations may diminish viral fitness,[3] 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 of 91 infants (12.1%) born between 1989 and 1999 and 8 of 42 (19%) infants born between 2001 and 2002 had mutations associated with decreased drug susceptibility. However, perinatal exposure to ARV drugs was not found to be a significant risk factor for the presence of resistance during either time period.[4,5] 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.[6]

Maternal Response to Subsequent Treatment Regimens

The French Perinatal Cohort evaluated the association between exposure to ARV drugs to prevent 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.[7] In 1,166 women not receiving ARV drugs at the time of conception, 869 were ARV-naive and 247 had received ARV drugs to prevent 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 dual ARV drugs in 19%, and zidovudine as a single ARV drug in 29%. A PI-based ART 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 (ACTG A5227) evaluated viral suppression in 52 women with prior combination ARV exposure to prevent perinatal transmission who had stopped ARV drugs at least 24 weeks before study entry and were now initiating ART (efavirenz, tenofovir disoproxil fumarate, and emtricitabine) for treatment.[8] 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 drug exposures to prevent perinatal transmission or the drug class of prior exposure. Recent clinical series have confirmed this observation.[9,10]

Management of Antiretroviral Drug Resistance during Pregnancy

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, intravenous (IV) zidovudine still should be given during labor when indicated (i.e., HIV RNA

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>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.[2] Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[3] 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.[11-13] Zidovudine crosses the placenta readily and has a high cord-to-maternal blood ratio. In addition, zidovudine is metabolized to the active triphosphate within the placenta,[14,15] 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 other nucleoside analogues except stavudine, which has similar CNS penetration; this may help eliminate a potential reservoir for transmitted HIV in the infant.[16,17] 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). There is no evidence that neonatal prophylaxis regimens customized based on the presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

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 ARV regimen to achieve maximal viral suppression.

Several studies have demonstrated that women's adherence to ART may worsen in the postpartum period.[18-23] Clinicians caring for postpartum women receiving ART should specifically address adherence, including evaluating specific factors that facilitate or impede adherence. A systematic review has identified viral load monitoring as a means of enhancing adherence.[24]

Previous versions of the Perinatal Guidelines have provided guidance about the situation in which women stop their ART regimen post-partum. However, we strongly recommend that ART regimens, once initiated, not be discontinued. If a woman desires to discontinue ART after delivery, a consultation with an HIV specialist is strongly recommended (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult Guidelines).

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Lack of Viral Suppression (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations

• 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 **(AII)**.
• If an ultrasensitive HIV RNA assay indicates failure of viral suppression (after an adequate period of treatment):
  • Assess adherence and resistance (if HIV RNA level is high enough for resistance testing) **(AII)**.
  • Consult an HIV treatment expert and consider possible antiretroviral regimen modification **(AIII)**.
• Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery **(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*

Virologic suppression is defined as a confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay, and virologic failure is the inability to achieve or maintain an HIV RNA level <200 copies/mL.

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.[1,2] HIV RNA levels should be assessed 2 to 4 weeks after an antiretroviral (ARV) drug regimen is initiated or changed to provide an initial assessment of effectiveness.[3] Most patients with an adequate viral response at 24 weeks of treatment have had at least a 1 log copies/mL HIV RNA decrease within 1 to 4 weeks after starting therapy.[3] Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible, because maternal antenatal HIV RNA level correlates with risk of perinatal transmission of HIV. The lack of virologic suppression by late pregnancy may indicate virologic failure but may also represent inadequate time on antiretroviral therapy (ART). 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 the ability to achieve maximal suppression at delivery.[1] Among 1,070 HIV-infected treatment-naive pregnant women participating in IMPAACT P1025, a prospective cohort study, initiation of ART at >32 weeks' gestation was also associated with a significantly higher risk of having viral load >400 copies/mL at delivery.[4] A recent report from the French Perinatal Cohort found no perinatal transmission among 2,651 infants born to women who were receiving ART before conception, continued ART throughout pregnancy and delivered with a plasma HIV-RNA <50 copies/mL (upper limits of confidence interval [CI] 0.1%). In the entire cohort of 8,075 mother/infant pairs followed from 2000 through 2011, HIV-RNA level and timing of ART initiation were independently associated with perinatal transmission in a logistic regression analysis.[5]

The response to ART may also be affected by the presence of acute HIV-1 infection. In a prospective study of serial measures of plasma HIV-RNA and CD4 T lymphocyte (CD4) counts after ART initiation (non-nucleoside reverse transcriptase inhibitor-based) in 25 women with acute HIV and 30 women with chronic HIV in Kenya, mean baseline HIV viral load was similar but the rate of viral decline following ART initiation was significantly slower among women with acute HIV than those with chronic infection (after adjustment for baseline CD4 count). Strategies to accelerate viral decline may be considered in this situation, in consultation with HIV treatment experts.[6]

A three-pronged approach is indicated for management of women on ART regimens who have suboptimal suppression of HIV RNA, taking into account time on treatment. The 3 steps should be:

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- ARV drug resistance studies (if plasma HIV RNA is above the threshold for resistance testing, generally >500 or >1,000 copies/mL);
- Assessment of adherence, tolerability, incorrect dosing, or potential problems with absorption (e.g., nausea/vomiting, lack of attention to food requirements); and
- Consideration of ART regimen modification.

The role of therapeutic drug monitoring in reducing the risk of virologic failure is still undefined.[7-9]

Experts in the care of ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary due to resistance or adverse effects. In certain situations, regimen simplification may be considered to promote better adherence, as well. Hospitalization can be considered for directly observed drug administration, adherence education, and treatment of comorbidities such as nausea and vomiting.[10]

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% CI, 1.07–2.57; $P = 0.024$), highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize the need to modify treatment.[11]

A recent systematic review and meta-analysis of adherence to ART 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 63.5% of pregnant women on ART had adequate (>80%) adherence to it.[12] Evaluation of and support for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

Because of the ability of raltegravir to rapidly suppress viral load (approximately 2 log copies/mL decrease by week 2 of therapy), 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.[13-16] However, the efficacy and safety of this approach have not been evaluated in clinical trials, and only anecdotal reports and case series are available.[17,18] 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. There have been two recent reports of marked elevations in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with return to normal levels after raltegravir discontinuation.[17,19] 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 near the time of delivery.[20,21]

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Stopping Antiretroviral Drugs during Pregnancy (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• If an antiretroviral (ARV) drug regimen must be stopped during pregnancy (e.g., for severe toxicity), all ARV drugs should be stopped simultaneously and antiretroviral therapy should be reinitiated as soon as possible **(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*

Discontinuation of antiretroviral (ARV) drug regimens during pregnancy may be indicated in some situations, including serious drug-related toxicity, pregnancy-induced hyperemesis unresponsive to anti-emetics, or acute illnesses or planned surgeries that preclude oral intake. Other reasons for discontinuation of ARV drug regimens during pregnancy include lack of available medication or patient request. If an ARV drug regimen must be stopped for any reason, all ARV drugs should be stopped simultaneously and ARV therapy should then be reinitiated simultaneously as soon as possible, whether restarting the same regimen or a new regimen.

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 *in utero* transmission of HIV. An analysis from a prospective cohort of 937 HIV-infected mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated with perinatal transmission. In the first trimester, the median time at interruption was 6 weeks' gestation and length of time without therapy was 8 weeks (interquartile range [IQR], 7–11 weeks); in the third trimester, the median time at interruption was 32 weeks and length of time without therapy was 6 weeks (IQR, 2–9 weeks). Although the perinatal transmission rate for the entire cohort was only 1.3%, transmission occurred in 4.9% (95% CI, 1.9% to 13.2%; adjusted odds ratio [AOR] 10.33; $P = .005$) with first-trimester interruption and 18.2% (95% CI, 4.5% to 72.7%; AOR 46.96; $P = .002$) with third-trimester interruption.[1]

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, all ARV drugs generally should be stopped simultaneously and reintroduced simultaneously as soon as possible. This can be problematic with drugs (e.g., efavirenz) that have long half-lives and low thresholds for developing HIV viral resistance. 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. Efavirenz can be detected in blood for longer than 3 weeks after discontinuation;[2,3] if an efavirenz-containing regimen must be stopped for more than a few days due to toxicity, consideration should be given to assessing for rebound viremia and potential drug resistance.[4]

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 antiretroviral therapy administered during the antepartum or intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert.

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HIV/Hepatitis B Virus Coinfection (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• All HIV-infected pregnant women should be screened during the current pregnancy for hepatitis B virus (HBV) and hepatitis C virus, unless they are known to be coinfected (see HIV/Hepatitis C Virus Coinfection) **(AIII)**.
• All HIV-infected pregnant women who screen negative for HBV (i.e., HBV surface antigen-negative, HBV core antibody-negative, and HBV surface antibody-negative) should receive the HBV vaccine series **(AII)**.
• Women with chronic HBV infection who have not already received the hepatitis A virus (HAV) vaccine series should be screened for immunity to HAV because they are at increased risk of complications from coinfection with other viral hepatitis infections **(AIII)**. Women with chronic HBV infection who are hepatitis A immunoglobulin G antibody-negative should receive the HAV vaccine series if they have never received it **(AII)**.
• All pregnant and postpartum women with HIV/HBV coinfection should receive antiretroviral therapy (ART). Antepartum ART in HIV/HBV-coinfected pregnant women should include tenofovir disoproxil fumarate plus lamivudine or emtricitabine **(AI)**.
• 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)**.
• Women with chronic HBV should be counseled on the importance of continuing anti-HBV medications indefinitely, both during and after pregnancy. If ARV drugs that include anti-HBV activity are discontinued in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt re-initiation of treatment for both HIV and HBV if a flare is suspected **(BIII)**.
• Decisions concerning mode of delivery in HIV/HBV-coinfected pregnant women should be based on standard obstetric and HIV-related indications alone; HBV coinfection does not necessitate cesarean delivery, if not otherwise indicated (see Intrapartum Care) **(AIII)**.
• 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 **(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, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

For additional information on hepatitis B virus (HBV) and HIV, see HIV/Hepatitis B (HBV) Coinfection in the Adult and Adolescent Guidelines[1] and Hepatitis B Virus Infection in the Adult and Adolescent OI Guidelines.[2] The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended.

Screening and Vaccination

All HIV-infected women should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All HIV-infected pregnant women should be screened for HBV and HCV during each pregnancy, unless they are known to be coinfected. Screening for HBV should include hepatitis B surface antigen [HBsAg], hepatitis B core antibody [anti-HBc], and hepatitis B surface antibody [anti-HBs]. Women who test positive for HBsAg should have follow-up testing that includes liver function tests, prothrombin time, HB e antigen, HB e antibody, and HBV DNA.[1] To prevent horizontal transmission of HIV as well as HBV from HIV/HBV-infected women to their male partners, their sexual contacts should be counseled and tested for HIV, HBV and hepatitis A (HAV). All HAV/HBV susceptible contacts should receive both HAV and HBV vaccines and all HIV-uninfected partners of HIV/HBV-coinfected women should be counseled about the potential benefits and risks of starting pre-exposure prophylaxis (PrEP).[2,3]

HIV-infected pregnant women who screen negative for HBV (i.e., HBsAg-negative, anti-HBc-negative, and anti-HBs-negative) should receive the HBV vaccine series. HIV-infected women with remote HBV infection and current isolated anti-HBc antibody (negative HBV DNA, HBsAg, and anti-HBs) may have lost immunity to HBV and should be vaccinated.[2] HIV-infected women whose anti-HBs titers are below 10 IU/mL despite

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having received the HBV vaccine series should receive a second vaccine series; some experts advise using a double dose of HBV vaccine (e.g. 40 mg dose) and delaying revaccination until after a sustained increase in CD4 T lymphocyte (CD4) cell count is achieved on antiretroviral therapy (ART).[2] Data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg.[4] Anti-HBs titers should be obtained 1 month after completion of the vaccine series in HIV-infected patients; if anti-HBs titers are below 10 IU/mL, a second vaccine series is recommended (some specialists delay revaccination until after a sustained increase in CD4 cell count is achieved on ART). There is no consensus for management of patients whose anti-HBs titers remain below 10 IU/mL following a second vaccine series.[2]

A positive test for anti-HBc alone can be false-positive; alternatively, it may signify remote exposure with subsequent loss of anti-HBs antibody or longstanding chronic HBV infection with loss of surface antigen ("occult" HBV infection, which can be confirmed by detection of HBV DNA).[5,6] Incidence of HBV viremia in HIV-infected patients with the isolated anti-HBc pattern ranges from 1% to 36%. The clinical significance of isolated anti-HBc is unknown.[7,8] Some experts recommend that HIV-infected individuals with anti-HBc alone be tested for HBV DNA to inform decisions about vaccination for HBV and treatment with antiretroviral (ARV) drugs. It may also be important to check HBV DNA levels in women with isolated anti-HBc before ARV drugs are initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS). HIV-infected pregnant women with isolated anti-HBc and occult HBV infection typically have very low levels of HBV DNA and are thought to be at extremely low risk of transmitting HBV to their infants.[2,9]

Women who are found to have HBV infection should also be screened for HAV using antibody testing for immunoglobulin G (IgG) because of the added risk of hepatic decompensation from acute infection with HAV in individuals with chronic HBV or HCV. If HAV IgG is negative, and if the HAV vaccine was not given previously, HIV/HBV-coinfected women should receive the HAV vaccine series. Responses to the HAV vaccine were reduced in HIV-infected patients with CD4 counts <200 cells/mm^3. Antibody response should be assessed 1 month after vaccination is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm^3.[2] Women who have already received the HAV vaccine series when their CD4 cell count was ≥200 cells/mm^3 do not need to repeat it because they are likely protected (even if they have undetectable HAV IgG levels using commercially available assays). 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]

Therapy for HIV and Hepatitis B Virus in Pregnancy

An ART 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 all pregnant women. Initiation of ART may be associated with reactivation of HBV and development of IRIS, particularly in patients with high HBV DNA levels and more severe liver disease.[2,10] Risk of preterm labor and delivery may be increased with acute HBV infection (see Hepatitis B Infection in the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents).

In addition, use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia, potentially further reducing the risk of HBV transmission beyond the reduction seen with neonatal prophylaxis with hepatitis B immune globulin (HBIG) and hepatitis B vaccine.[11] High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.[12-14] Several small studies and a recent meta-analysis suggest that lamivudine or telbivudine 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.[15-23] Although a high HBV viral load clearly is important, it is not the only factor predisposing to failure of HBV prophylaxis.[9,24] In a study of 2,048 HIV-infected pregnant women in Malawi, 5% (103 women) were HBsAg-positive, 70 of whom were also HBV DNA-positive. Nearly 10%

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of infants born to HBV/HIV co-infected mothers had HBV DNA detected by age 48 weeks despite being immunized at ages 6, 10, and 14 weeks per standard-of-care health practices in this population.[25]

Lamivudine, tenofovir disoproxil fumarate (TDF), and emtricitabine have activity against both HIV and HBV. TDF with emtricitabine or lamivudine is the preferred dual nucleoside reverse transcriptase inhibitor backbone in women who are HIV/HBV-coinfected (see Table 6). These agents are recommended for use in pregnancy (see Table 6). Please see individual drug sections for TDF, emtricitabine, and lamivudine for detailed review of safety, pharmacologic, and other clinical data for use in pregnancy.

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 68 cases of exposure to each of these drugs during the first trimester have been reported to the Antiretroviral Pregnancy Registry prospectively, with no increased risk of birth defects being reported.[26] Telbivudine was given to 135 HBV-positive, HIV-seronegative women during the third trimester; it was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers than in the controls not on telbivudine (0% vs. 8%; $P = 0.002$).[18,27] In two separate meta-analyses 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.[19,28] In a recent systematic review and meta-analysis of single-drug anti-hepatitis B antiviral therapy during pregnancy in chronic HBV mono-infection, Brown et al. found that antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. Compared to the use of HBIG and vaccination alone, TDF, lamivudine, or telbivudine all improved maternal HBV viral suppression at delivery with no significant difference in postpartum hemorrhage, cesarean section or creatinine kinases levels.[29] For HIV/HBV coinfected pregnant women, both entecavir and telbivudine should be administered only in addition to a fully suppressive ART 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 ART regimen as well as confer the potential for developing cross-resistance to other ARV drugs (e.g., entecavir can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine). Although adefovir does not have significant anti-HIV activity, it is not recommended for treatment of HBV because it is less potent and has a higher risk of selecting for resistance mutations than the preferred HBV nucleos(t)ides.[2] 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). If a pregnant woman coinfected with HIV/HBV treated with ART with 2 anti-HBV nucleos(t)ides continues to have detectable HBV DNA viremia, consultation with an expert in HIV and HBV is strongly recommended.

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 their direct antigrowth and antiproliferative effects.[30]

Monitoring of HIV/Hepatitis B Virus-Infected Women during Pregnancy

Prior to initiation of ARV drugs active against HBV, a baseline HBV DNA level should be measured. After initiation of therapy, HBV DNA should be monitored every 12 weeks to ensure adequate response to therapy (see Adult OI Guidelines).

Following initiation of ARV drugs, an elevation in hepatic enzymes can occur in HIV/HBV-coinfected women—particularly those with low CD4 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

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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 TDF has potential to cause renal toxicity, kidney function also should be monitored regularly in pregnant women as in non-pregnant adults.

Once HBV therapy with anti-HBV nucleos(t)ide analogs is initiated, treatment is recommended to be continued indefinitely.[1,2] Discontinuation of anti-HIV agents that also have anti-HBV activity may be associated with hepatocellular damage resulting from reactivation of HBV. If ART with anti-HBV-active drugs must be discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected.[2]

Mode of Delivery

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). There are no data on the role of cesarean delivery in reducing perinatal transmission of HBV in HIV/HBV-coinfected women or when HBV-infected women receive antiviral therapy active against HBV. Current guidelines for HBV-monoinfected women advise that cesarean delivery is not indicated to prevent perinatal transmission of HBV.[31-33]

Treatment of HIV/HBV-coinfected pregnant women with ART that includes TDF and emtricitabine and/or lamivudine will result in low or suppressed HBV viral loads near delivery, which should further reduce risk of HBV perinatal transmission

Evaluation and Management of Hepatitis B Virus-Exposed Infants

Within 12 hours of birth, all infants born to mothers with chronic HBV infection should receive HBIG and the first dose of the HBV vaccination series. For infants weighing ≥2,000 g at birth, the second and final doses of the vaccine series should be administered at ages 1 and 6 months, respectively. For infants with birth weights <2,000 g at birth, do not count the birth dose as part of the vaccine series and administer three additional doses at ages 1, 2–3, and 6 months.[34,35] This regimen is >95% effective in preventing HBV infection in these infants.

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 three-dose series and retested 1 to 2 months after the final dose of vaccine.

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HIV/Hepatitis C Virus Coinfection (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• All HIV-infected pregnant women should be screened during the current pregnancy for hepatitis B virus (HBV) and hepatitis C virus (HCV), unless they are known to be coinfected (see HIV/Hepatitis B Virus Coinfection section) **(AIII)**. • All HIV-infected pregnant women who screen negative for HBV (i.e., HBV surface antigen-negative, HBV core antibody-negative, and HBV surface antibody-negative) should receive the HBV vaccine series **(AII)**. • Women with chronic HBV or HCV 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 **(AIII)**. Women with chronic HCV who are negative for hepatitis A immunoglobulin G should receive the HAV vaccine series if they have never received it **(AII)**. • The management of HIV/HCV coinfection in pregnancy is complex because none of the approved HCV oral medications have been evaluated in pregnant women, and the use of ribavirin is contraindicated in pregnancy **(AIII)**. If considering treatment of HCV in an HIV-coinfected pregnant woman, consultation with an expert in HIV and HCV is strongly recommended **(AIII)**. • Recommendations for antiretroviral (ARV) drug use during pregnancy are the same for HIV-infected women whether or not they have chronic HCV **(BIII)**. • Pregnant women with HIV/HCV coinfection receiving 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)**. • Decisions concerning mode of delivery in HIV/HCV-coinfected pregnant women should be based on standard obstetric and HIV-related indications alone; HCV coinfection does not necessitate cesarean delivery, if not otherwise indicated (see Intrapartum Care) **(AIII)**. • Infants born to women with HIV/HCV coinfection should be evaluated for HCV infection with anti-HCV antibody testing after age 18 months **(AII)**. Infants who screen positive should undergo confirmatory HCV RNA testing. If earlier diagnosis is desired, HCV RNA virologic testing can be done after age 2 months **(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*

For additional information on hepatitis C virus (HCV) and HIV, see Hepatitis C Virus in the Pediatric Opportunistic Infections Guidelines, HIV/Hepatitis C Coinfection in the Adult and Adolescent Antiretroviral Guidelines and Hepatitis C Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines. The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and International Antiviral Society-USA recently updated their HCV treatment guidelines to add newly approved interferon-free direct-acting antiviral regimens and to provide more information about treating patients with HIV/HCV coinfection and decompensated liver disease. The guidelines are available online at HCVguidelines.org. The management of HIV/HCV coinfection in pregnancy is complex and consultation with an expert in HIV and HCV infection is strongly recommended, particularly if treatment of HCV infection during pregnancy is being considered.

Screening and Vaccination

All HIV-infected women should be screened for hepatitis B virus (HBV) and HCV at entry into general HIV care unless they are known to be previously infected. HIV-infected women should be rescreened for HBV and HCV during each pregnancy, unless they are known to be infected by one or both of these viruses. HCV coinfection is not uncommon in HIV-infected women, particularly those infected via parenteral use of drugs; among HIV-infected pregnant women in a European cohort, the observed HCV seroprevalence rate was 12%.[1] The male partners of all HIV/HCV-coinfected patients should be referred for both HIV and hepatitis counseling and testing to prevent horizontal transmission of HIV as well as HCV from women to their male partners. All HIV-uninfected partners of HIV/HCV-coinfected women should be counseled about the potential benefits and risks of starting oral pre-exposure prophylaxis to prevent HIV acquisition.

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Current HCV treatment guidelines recommend therapy for all HCV-infected patients with estimated life expectancies >12 months. However, the management of HIV/HCV coinfection in pregnancy is complex because none of the approved HCV oral medications have been evaluated in pregnant women, and the use of ribavirin is contraindicated in pregnancy. If considering treatment of HCV in an HIV-coinfected pregnant woman, consultation with an expert in HIV and HCV is strongly recommended. In addition, the risks of perinatal HCV transmission are much lower than of perinatal HIV transmission, and many infected children will clear HCV infection spontaneously, making the balance of risks and benefits for treating HCV in pregnancy different from treating HIV.

The primary reasons for HCV testing during pregnancy, therefore, are:

- To identify HCV-infected women at a time when they are engaged with the health system, so that HCV treatment can be offered after delivery (ideally before a subsequent pregnancy);
- To be aware of the increased risk of HCV-related hepatotoxicity related to antiretroviral (ARV) use and potential for increased risk of preterm birth with HCV infection[2] in coinfected women;
- To ensure vaccination against other viral hepatitides (hepatitis A virus [HAV] and HBV) if needed; and
- To ensure appropriate follow-up and evaluation of HCV-exposed infants.

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, but it is uncommon with the more sensitive immunoassays. If HCV infection is suspected despite a negative HCV antibody screen, a quantitative HCV RNA assay can be performed. 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 during pregnancy 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 injection drug use.[3]

Because of the added risk of hepatic decompensation from acute infection with any viral hepatitis, women with HCV infection should also be screened for both HAV and HBV. Using HAV antibody testing for immunoglobulin G (IgG), if HAV IgG is negative, HIV/HCV-coinfected women 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] HIV/HCV-coinfected 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. HIV-infected women who are HBsAb negative despite having received the HBV vaccine series may benefit from revaccination.[5] Data indicate no apparent risk to developing fetuses from hepatitis B vaccination, as current vaccines contain noninfectious HBsAg.[4]

Impact of Hepatitis C Virus on HIV Management

Few data exist on the optimal management of HIV-infected pregnant women with HCV coinfection. Recommendations for ARV drug use during pregnancy for treatment of HIV and prevention of perinatal transmission are the same for women who have HIV/HCV coinfection as for those infected only with HIV (see HIV/Hepatitis C Coinfection in the Adult and Adolescent Antiretroviral Guidelines).

Hepatitis C Virus-Specific Therapy in Pregnancy

All currently available oral anti-HCV treatments lack sufficient safety data to be recommended during pregnancy. Until recently, most anti-HCV therapy included both interferon and ribavirin. Interferons are not recommended for use in pregnancy because they are abortifacient at high doses in monkeys and have direct antigrowth and antiproliferative effects.[6] Ribavirin is contraindicated (Food and Drug

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Administration 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.[7] Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or http://www.ribavirinpregnancyregistry.com).

Newer interferon-free and ribavirin-free agents approved for treatment of HCV include the protease inhibitor (PI) simeprevir (Pregnancy Category C), the nucleotide analogue NS5B polymerase inhibitor sofosbuvir (Pregnancy Category B), NS5A inhibitors ledipasvir (Pregnancy Category B) and daclatasvir (no concerning animal data and no human data to inform risk in pregnancy), and three fixed-dose combinations: ledipasvir/sofosbuvir, paritaprevir (NS3/4A PI)/ritonavir/ombitasvir (HS5A inhibitor) plus twice-daily dasabuvir (NS5B polymerase inhibitor), given with ribavirin except for genotype 1b, and elbasivir (NS5A inhibitor) and grazoprevir (NS3/4 PI).[8] However, these medications are not yet recommended for use in pregnancy because of the lack of pharmacokinetic and safety data. In addition, potential drug interactions between these newer anti-HCV drugs and ARV drugs, particularly certain HIV PI regimens and non-nucleoside reverse transcriptase inhibitors, may reduce the effectiveness of HCV medications if used together or increase exposure to tenofovir disoproxil fumarate if it is included in the regimen. For more detailed information on drug interactions and newly approved medications, see Adult and Adolescent Antiretroviral Guidelines, Adult Opportunistic Infections Guidelines and the HCV treatment guidelines (http://www.hcvguidelines.org).

Although the HCV viral load appears to peak in the third trimester, pregnancy does not appear to influence the course of HCV infection. Women with chronic HCV generally do quite well during pregnancy, provided that they have not progressed to decompensated cirrhosis.[9,10]

In a majority of studies of women with untreated HIV/HCV coinfection, the incidence of perinatal HCV transmission approximately doubles if the mother is coinfected with HIV, with transmission rates between 10% and 20% reported primarily among women not treated with antiretroviral therapy (ART).[11-14] These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impact on HCV disease activity.[15] However, early and sustained control of HIV viremia with ART may reduce HCV transmission to infants.[10,16,17] A European study of perinatal transmission of HCV found that use of effective ART for HIV was associated with a strong trend toward reduction in HCV transmission (odds ratio 0.26, 95% confidence interval, 0.07–1.01).[16]

Maternal HIV/HCV coinfection also may increase the risk of perinatal transmission of HIV.[18] Perinatal HIV transmission may be reduced in HIV/HCV–coinfected pregnant women by following standard recommendations for ART for all women with HIV infection, regardless of CD4 T-lymphocyte (CD4) cell count or HIV viral load.

Monitoring of HIV/ HCV-Coinfected Women during Pregnancy

An elevation in hepatic enzymes following initiation of ART 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 ART. 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 of 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.

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Mode of Delivery

The majority of studies of elective cesarean delivery in HCV-infected women with or without HIV coinfection have found that the procedure does not reduce the risk of perinatal transmission of HCV.[16,19-21] Thus, the general recommendations for mode of delivery are the same in women with HIV/HCV coinfection as in those with HIV infection alone (see Intrapartum Care).

Evaluation of HCV-Exposed Infants

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.[22,23] Because HCV viremia can be intermittent, two negative HCV RNA tests at or after age 2 months, including one at or after age 12 months, are needed to definitively exclude HCV infection. Children are considered to be HCV-infected if they have two or more positive HCV RNA polymerase chain reaction results at any age, or are HCV antibody-positive beyond age 18 months.

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HIV-2 Infection and Pregnancy (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• HIV-2 infection should be considered in pregnant women who are from—or have partners from—countries in which the disease is endemic and who have positive results on an HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay. They should be tested with a supplemental HIV-1/HIV-2 antibody differentiation assay. If they are indeed HIV-2 infected it would show negative HIV-1 antibodies and positive HIV-2 antibodies **(AII)**.
• Pregnant women with HIV-1 and HIV-2 coinfection should be treated as per guidelines for HIV-1 monoinfection, but using antiretroviral drugs to which HIV-2 is sensitive (see below).
• No randomized clinical trials have been performed to address when to start treatment or what the optimal treatment is for HIV-2 monoinfection.
• Optimal prophylactic regimens have not been defined for HIV-2-monoinfected pregnant women. A regimen with two nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor or integrase strand transfer inhibitor is recommended for all HIV-2-infected pregnant women **(AIII)**.
• Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used **(AIII)**.
• All infants born to HIV-2-infected mothers should receive the standard 6-week zidovudine prophylactic regimen **(BIII)**.
• In the United States, where safe infant formula is readily available, breastfeeding is not recommended for infants of HIV-2-infected mothers **(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*

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.[1-4] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.[5] HIV-2 remains rare in the United States. Between 1998 and 2010, 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.[6] Of the 50 women aged 15 to 44 years at diagnosis, 24 (48%) were pregnant at or after HIV-2 diagnosis.[6] 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 have positive results on an HIV-1/HIV-2 antibody or HIV-1/HIV-2 antigen/antibody immunoassay. They should be tested with a supplemental HIV-1/HIV-2 antibody differentiation immunoassay. If they are indeed HIV-2 infected it would show negative HIV-1 antibodies and positive HIV-2 antibodies. In rare instances, a woman may have dual infection with HIV-1 and HIV-2 and both tests will be positive.

In 2014, the CDC released a new HIV Testing Algorithm, which may enhance the diagnosis of HIV-2. The first step in that algorithm is performance on serum or plasma of an HIV-1/HIV-2 antigen/antibody combination assay (e.g., Abbott Architect HIV Ag/Ab combo assay, BioRad GS Combo Ag/Ab EIA, Alere Determine).[7] This test does not distinguish between antibodies to HIV-1 and HIV-2. Specimens which are reactive on this test must be tested with a Food and Drug Administration (FDA)-approved second-generation antibody assay to distinguish HIV-1 from HIV-2 antibodies. There are two HIV-2 antibody supplemental tests now approved by FDA that can be used as part of the CDC recommended HIV laboratory testing algorithm: Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) and GeeniuS (Bio-Rad Laboratories). Viral load assays for HIV-2 are not commercially available, but may be available under research protocols. The University of Washington (http://depts.washington.edu/labweb/AboutLM/Contact.htm)[8] and the New York State Department of Health (http://www.hivguidelines.org/wp-content/uploads/2014/04/human-immunodeficiency-virus-type-2-hiv-2.pdf)[9] offer HIV-2 viral load assays. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional

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confirmatory testing for HIV-2 by the CDC.[10] No validated HIV-2 genotype or phenotype resistance assays are available in the United States. 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).[11]

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.[3,12,13] Several studies confirm that rates of perinatal transmission of HIV-2 are low with and without interventions (0% to 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.[14-17] 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 monoinfection, can occur.[18]

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 antiretroviral therapy (ART) regimen chosen is also appropriate for treatment of HIV-2 (see below). Once treatment is started, the ART regimen should be continued postpartum, as is recommended for all HIV-1-infected patients. In a systematic review of non-pregnant, HIV-2-infected patients from 1996–2012, Ekouevi et al noted a heterogeneity of treatment outcomes among HIV-2-infected patients initiating ART, especially in resource-limited settings.[19] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.[20,21] HIV-2 has variable sensitivity to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity.[22] The integrase strand transfer inhibitors (raltegravir, elvitegravir, and dolutegravir) also appear to be effective against HIV-2.[3,23-28] 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.[29,30] HIV-2 drug resistance has been documented with various antiretroviral (ARV) drugs.[31,32]

The care of HIV-2-monoinfected pregnant women has been based on expert opinion. A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted PI or an integrase strand transfer inhibitor currently is recommended for all HIV-2-infected pregnant women. Based on efficacy and available data on safety in HIV-1-infected pregnant women, darunavir/ritonavir, lopinavir/ritonavir, or raltegravir plus abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine is preferred; zidovudine/lamivudine can be an alternative dual NRTI.[33,34] NNRTIs should not be used because they are not active against HIV-2. Single-drug prophylaxis with zidovudine alone has also been considered by some experts for prevention of perinatal transmission in women with HIV-2 monoinfection because HIV-2 has a significantly lower risk of perinatal transmission than HIV-1.15 However, this may not be an optimal choice as there seems to be a low genetic barrier to resistance in HIV-2, with as few as two mutations conferring full zidovudine resistance.[33,35]

There are no data to address whether treatment should be continued after pregnancy in HIV-2 monoinfected women. To date, no randomized trials have addressed the question of optimal treatment strategy for HIV-2 infection, although clinical trials are underway. The Adult and Adolescent Guidelines note that although the optimal CD4 T lymphocyte (CD4) cell count threshold to initiate ART in HIV-2 monoinfection is unknown, therapy should be started before there is clinical progression.[36] For HIV-2 monoinfected pregnant women with CD4 cell counts >500 cells/mm^3 and no significant clinical disease, who currently do not require treatment for their own health, some experts would stop ART postpartum; however, in analogy to HIV-1 infection, many experts would recommend continuation of treatment after pregnancy in women with HIV-2 monoinfection, as is recommended for HIV-1 monoinfection or HIV-1/HIV-2 coinfection.

All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen.[34] The possible risks and benefits of ARV prophylaxis should be discussed with the mothers.

Other than the standard obstetric 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.[15]

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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.[37] Quantitative HIV-2 plasma RNA viral load testing for clinical care is available from the University of Washington[8] and the New York State Department of Health.[9] 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.[34]

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The Management of Prenatal Care and General Principles of Antiretroviral Therapy and HIV Management in Women Who Were Infected Perinatally (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations

- The management of prenatal care and general principles of antiretroviral therapy (ART) and HIV management do not differ between pregnant women who were infected perinatally and those who acquired HIV infection postnatally. With appropriate ART and prenatal management (and when optimal viral suppression is attained) the risk of perinatal transmission does not appear to be increased in women who acquired HIV perinatally **(AII)**.
- Using the same guiding principles that are used for heavily ART-experienced adults, optimal ART regimens should be selected on the basis of resistance testing, prior ART history, and pill burden **(AII)**.
- The presence of extensive drug resistance may warrant the use of ARV drugs for which there is limited experience in pregnancy. Consultation with experts in HIV and pregnancy is recommended **(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*

With the availability of potent antiretroviral therapy (ART), morbidity and mortality have significantly declined in HIV-infected individuals, including those with perinatally acquired HIV. An increasing number of those who were perinatally infected with HIV are now reaching childbearing age and becoming pregnant. A significant number of these pregnancies are unintended.[1-3] The components of prenatal care and general principles of ART and HIV management do not differ between pregnant women who were perinatally infected and those who acquired HIV infection in other ways. However, there are unique challenges in this population related to reproductive health care needs and the prevention of perinatal transmission. Adherence to ART is commonly a major challenge for perinatally infected women. In addition, because most perinatally infected pregnant women are adolescents and young adults, they may be at higher risk of certain pregnancy complications such as preterm delivery, low birthweight, and preeclampsia.[4-8]

Antiretroviral resistance rates have been reported to be as high as 30% to 50% in perinatally infected pregnant women.[8,9] This is due to extensive ART exposure prior to pregnancy, including exposure to suboptimal monotherapy or dual-therapy regimens as children.[8] Optimal ART regimens should be selected on the basis of resistance testing, prior ART history, and the same guiding principles used for heavily ART-experienced adults. Consideration should be given to regimens that optimize dosing intervals and minimize pill burden. Consultation with experts in HIV and pregnancy is recommended.

Studies comparing perinatally and horizontally infected (e.g., through sexual contact or injection drug use) pregnant women have reported that perinatally infected women are more likely to have lower median CD4 T lymphocyte counts, detectable viral loads, and genotypic drug resistance (40% vs 12%).[8,10] In a retrospective analysis of 37 pregnancies among perinatally infected women and 40 pregnancies among age-matched horizontally infected women delivering during the same time period, the viral load decline achieved during pregnancy in the perinatally infected women was not sustained during postpartum follow up in contrast to the horizontally infected women. During 4 years of follow up, there were 4 deaths due to AIDS-related complications in the perinatally infected women and none in the horizontally infected women.[10] Although genotypic mutations were more common in perinatally infected women, loss of viral suppression resulting in progression of disease postpartum was more likely related to adherence, highlighting the need for special focus on adherence interventions after delivery.

Study results have been conflicting as to whether perinatally infected women have elevated rates of preterm and small-for-gestational-age (SGA) infants when compared with horizontally infected women. Williams et al reported a 31% incidence of preterm delivery and/or premature rupture of membranes in a cohort of

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10 perinatally infected pregnant women.[9] In a cohort of 79 pregnant women (17 with perinatal and 62 with horizontal infection) with 87 live births, Jao et al reported a four-fold increased risk for SGA births among the women infected perinatally.[11] Munjal et al reported perinatally infected women were more likely to deliver at an earlier gestational age and their infants had lower average birthweights than horizontally infected women.[10] In contrast, Agwu found no differences in adverse pregnancy outcomes in 96 pregnancies between perinatally and horizontally infected women; however, there were high rates of preterm births in both groups (29.4% among women with perinatal infection and 36.3% among those with horizontal infection).[12] Badell et al did not find differences in birth outcomes between 20 women with perinatal infection and 80 with horizontal infection.[8] Jao et al compared the growth patterns in the first year of life between 152 children born to perinatally HIV-infected as compared to horizontally infected women in the United States. The infants born to the perinatally infected women had lower mean length for age throughout the first year of life.[7] Several studies have suggested that perinatally infected pregnant women are more likely to have a cesarean delivery most commonly related to prevention of HIV infection due to lack of optimal viral load suppression.[9,10] Cesarean section in these young women raises concerns for increased risk of adverse obstetric outcomes if repeated cesarean sections are required for future pregnancies. Reassuringly, despite prolonged HIV infection, receipt of multiple ART regimens, and increased likelihood of having drug-resistant virus in perinatally infected women, with appropriate ART, prenatal management and when optimal viral suppression is attained, the risk of perinatal transmission does not appear to be increased in this population.[8-10,13-15]

Among perinatally infected adolescents, pregnancy may create additional burdens in the transition from pediatric/adolescent HIV care to adult care. Psychosocial challenges may be magnified due to the presence of a lifelong chronic illness, high rates of depression,[16] and frequently the loss of one or both parents. Attention to developmentally appropriate adherence counseling is critical. A systematic review and meta-analysis of 50 eligible studies on ART adherence in HIV-infected individuals aged 12 years to 24 years, in which adequate adherence was defined as greater than 85% by self-report or undetectable viral load, reported 62.3% adherence overall among HIV-infected youth. Youth from U.S. studies had the lowest average rate of adherence, at 53%.[17] Sheth et al found that a history of depression was associated with nonadherence to ART among pregnant women who were perinatally infected.[18] Focused attention on diagnosis and treatment of depression in the preconception period may lead to more optimal medication adherence. Kim et al found that self-motivation and social support were key to medication adherence in an HIV-infected adolescent population in the UK.[19]

Coordination of care across multiple disciplines including HIV primary care, ob/gyn, and perinatal case management is advised. Integration of reproductive health counseling and pregnancy prevention including consistent condom use and developmentally appropriate skill building to support disclosure are all recommended.

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Acute HIV Infection (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• When acute retroviral syndrome is suspected in pregnancy or during breastfeeding, a plasma HIV RNA test should be obtained in conjunction with a routine HIV antibody screening test or an antigen/antibody immunoassay test (see Acute and Recent (Early) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines and http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf) **(AII)**.
• Repeat HIV testing in the third trimester is recommended for pregnant women with initial negative HIV antibody tests who are known to be at risk of acquiring HIV, who are receiving care in facilities that have an HIV incidence in pregnant women of at least 1 per 1,000 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 and http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf) **(AII)**.
• All pregnant women with acute or recent HIV infection should start an antiretroviral therapy as soon as possible to prevent perinatal transmission, with the goal of suppressing plasma HIV RNA to below detectable levels **(AI)**.
• In women with acute HIV infection, baseline genotypic resistance testing should be performed simultaneously with initiation of antiretroviral therapy, and the regimen should be adjusted, if necessary, to optimize virologic response **(AIII)**. A ritonavir-boosted-protease-inhibitor-based regimen with tenofovir disoproxil fumarate/emtricitabine should be initiated **(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*

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.[1]

In North Carolina, from 2002 to 2005, of 15 women found to have acute HIV infection on nucleic acid amplification testing of pooled HIV antibody-negative specimens, 5 were pregnant at the time of testing.[2] All five women received antiretroviral (ARV) drugs and delivered HIV-uninfected infants. From 2002 to 2006, of 3,396 HIV-exposed neonates 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 (OR 15.19; 95% CI, 3.98–56.30).[3] 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, 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%) ($P < 0.0001$).[4] 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[5] 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.[6,7] 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. Antiretroviral therapy (ART) is currently recommended for all adults and adolescents with HIV infection, including those with acute or recent infection.[8] Whether treatment of acute or recent HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown.

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When acute retroviral syndrome is suspected in pregnancy or during breastfeeding, a plasma HIV RNA test should be obtained in conjunction with a routine HIV antibody screening test or an antigen/antibody immunoassay test. Updated guidance for HIV testing recommends initial testing for HIV with a Food and Drug Administration-approved antigen/antibody combination (fourth generation) immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen. These tests are used to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. These fourth-generation tests have the advantage of a shorter window to detect infection (2 weeks compared with 4 weeks by Western Blot testing).[9] The fourth-generation tests are becoming increasingly available and will likely result in improved detection of acute and early HIV infection (see Acute and Recent (Early) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines and http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf). Positive fourth-generation tests are followed by a type-specific antibody differentiation assay. Negative antibody differentiation assays are followed by HIV nucleic acid testing, which (if positive) confirms acute HIV infection. Serologic testing should be performed within 3 months on patients whose acute HIV infection is diagnosed with virologic testing but who are antibody-negative.

Recent HIV infection also can be detected by repeat HIV testing later in pregnancy in women whose initial HIV test earlier in pregnancy was negative.[10] 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.[10,11] 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 and http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf).[12]

Acute or recent HIV infection during pregnancy and breastfeeding is associated with a high risk of perinatal transmission of HIV. Therefore, all HIV-infected pregnant women with acute or recent infection should start ART as soon as possible, with the goal of preventing perinatal transmission by optimal suppression of plasma HIV RNA below detectable levels.[13] 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.[14,15] 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 ART should not be delayed. A protease inhibitor (PI)-based ARV drug regimen generally should be initiated because clinically significant resistance to PIs is uncommon. Choice of regimen should be based on recommendations for use of ARV drugs in pregnancy (see Table 6 and Table 8).[16] Dolutegravir plus tenofovir disoproxil fumarate (TDF)/emtricitabine is considered a reasonable treatment option for treatment of acute infection in non-pregnant adults but data are limited regarding efficacy of this regimen in treatment of early infection and until safety and dosing are determined, it is not recommended during pregnancy (see Acute or Recent (Early) HIV Infection in the Adult Guidelines). Due to the lower resistance barrier raltegravir should not be used in this situation as viral loads are expected to be high.[17] Some clinicians would consider combining raltegravir with a boosted PI for treatment of acute infection during pregnancy. Abacavir is not recommended for empiric treatment of acute infection unless the patient is known to be HLA-B*5701 negative so TDF/emtricitabine is the preferred nucleoside reverse transcriptase inhibitor backbone for treatment of acute infection.

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 confirmed (see Breastfeeding in Infants of Mothers Diagnosed with HIV Infection in Infant Antiretroviral Prophylaxis). Women can continue to express and store breast milk while awaiting confirmation of infection status. In such a situation, given the high risk of transmission to the infant with acute maternal infection, consultation with a pediatric HIV specialist regarding appropriate infant management is strongly recommended.

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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[18-23] even when controlling for sexual risk behaviors.[18] It is hypothesized that the heightened risk may be attributable to hormonal changes that affect the genital tract mucosa or immune responses.[18] Although only limited data exist on HIV serodiscordance rates in the United States, data on women from sub-Saharan Africa show that women in serodiscordant relationships may be particularly vulnerable to acquisition of HIV.[24-26] All women should be asked if they know the HIV status of their partner. HIV testing of the sexual partners of pregnant women should be encouraged; initiation of ART is recommended for partners who are identified to be HIV-infected to reduce the risk of HIV acquisition by the woman.[27] Furthermore, 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 ARV prophylaxis also should be emphasized (see Reproductive Options for HIV-Concordant and Serodiscordant Couples).

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Intrapartum Care (Last updated October 26, 2016; last reviewed October 26, 2016)

Intrapartum Antiretroviral Therapy/Prophylaxis

Panel's Recommendations

- Women should continue their antepartum combination antiretroviral therapy (ART) 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 ART regimens who have HIV RNA ≤1,000 copies/mL during late pregnancy and near delivery and no concerns regarding adherence to the ART regimen **(BII)**. Scheduled cesarean delivery at 38 weeks' gestation (compared to 39 weeks for most indications) is recommended for women who have HIV RNA >1,000 copies/mL near delivery (see Transmission and Mode of Delivery) **(AI)**.
- Women who present in labor with unknown HIV status should undergo expedited antigen/antibody HIV testing **(AII)**. If the results are positive, an HIV-1/HIV-2 antibody differentiation test should be done as soon as possible and maternal (IV zidovudine)/infant (combination antiretroviral [ARV] prophylaxis) ARV drugs should be initiated pending results of the differentiation test **(AII)**. If the maternal HIV differentiation test is positive, infant ARV drugs should be managed as discussed in the Infant Antiretroviral Prophylaxis section **(AI)**. If the maternal HIV differentiation test is negative and acute HIV infection has been excluded with a negative HIV RNA test, the maternal and infant ARV drugs should be stopped **(AIII)**. Women with positive initial testing should not initiate breastfeeding until HIV infection is definitively ruled out (see Postpartum Care) **(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*

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. Antiretroviral therapy (ART) regimens are now recommended for all pregnant women regardless of CD4 T lymphocyte (CD4) cell count and HIV viral load for treatment of HIV 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 more than 11,000 HIV-infected pregnant women receiving antiretroviral (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.[1] 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 no different (4.8% vs. 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 receiving an ART 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.[2] 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; $P = 0.23$).[3] In a cohort of Irish women receiving ART 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.[4]

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Based on these studies, IV zidovudine is not required for HIV-infected women receiving ART with HIV RNA ≤1,000 copies/mL in late pregnancy and/or near delivery and for whom there are no concerns about adherence to or tolerance of their ART 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,[1,2,4] a threshold of ≤1,000 copies/mL is now recommended for consideration to not administer 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 ART with plasma HIV RNA levels ≤1,000 copies/mL and no concerns about adherence. 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 undergoing 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.[5] Systemic and intracellular zidovudine levels increased from baseline but appeared to stabilize after 3 hours of infusion; cord blood zidovudine levels were assocated with maternal levels and maternal infusion duration. If cesarean delivery 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 zidovudine was not used in the antenatal ART regimen because of known or suspected zidovudine resistance, intrapartum use of the drug is still 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. In studies of oral dosing in labor, levels were lower than with IV dosing, and PK parameters suggested erratic absorption during labor.[6,7] 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 of zidovudine using a 600-mg loading dose and 400 mg every 3 hours[7] can be considered.

Continuation of Antenatal Antiretroviral Drugs during Labor

Women who are receiving an antepartum ART 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 drug 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 ART regimens may not achieve complete viral suppression by the time of delivery because of factors such as difficulty with adherence, viral resistance, or late entry into care.

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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 the risk of transmission (see Transmission and Mode of Delivery).

Women with HIV RNA levels above 1,000 copies/mL at the time of delivery should receive IV zidovudine along with their other ARVs orally, as described above. While additional maternal ART such as single-dose nevirapine is not recommended, 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 (see Infant Antiretroviral Prophylaxis and Table 7).

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 for HIV with expedited testing unless they decline (opt-out screening). Expedited repeat 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.[8] Factors that may increase risk of infection include diagnosis of a sexually transmitted disease, illicit drug use, exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of or with known HIV infection, signs/symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age.[8] Initial testing for HIV should be done with a Food and Drug Administration (FDA)-approved antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies for established infection with HIV-1 or HIV-2 and HIV-1 p24 antigen to screen for acute HIV-1 infection. No further testing is required for specimens that are nonreactive on the initial immunoassay. Women with positive initial antigen/antibody combination immunoassay result should be tested with an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies. Reactive results on the initial antigen/antibody combination immunoassay and the HIV-1/HIV-2 antibody differentiation immunoassay should be interpreted as positive for HIV-1 antibodies; HIV-2 antibodies; or HIV antibodies, undifferentiated (see Revised Recommendations for HIV Testing in Adults, Adolescents, and Pregnant Women in Health-Case Settings).

Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit (NICU). Statutes and regulations regarding expedited testing vary from state to state (see http://nccc.ucsf.edu/clinical-resources/hiv-aids-resources/state-hiv-testing-laws for a review of state HIV testing laws). Current information about testing also should be available at all facilities with a maternity service and/or NICU.

Women who test positive on the initial test should be presumed to be infected until follow up testing clarifies their infection status. IV zidovudine should be started immediately in all women with positive initial HIV tests in labor to prevent perinatal transmission of HIV, as discussed below. Women with positive initial testing should not initiate breastfeeding until HIV infection is definitively ruled out.

In the postpartum period, along with follow-up HIV testing, these women should receive appropriate assessments as soon as possible to determine their health status, including CD4 cell count, HIV-1 RNA viral load, and HIV genotype for resistance. Arrangements also should be made for establishing HIV care and providing ongoing psychosocial support after discharge. If the follow-up antibody testing is negative, an HIV RNA test should be done to rule out acute infection as a cause of the initial positive test before ART is stopped (see Acute Infection in Pregnancy).

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

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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 inhibitors, non-nucleoside reverse transcriptase inhibitors, and the integrase inhibitor raltegravir cross the placenta well, whereas protease inhibitors do not (see Table 8). Data on placental transfer of other integrase inhibitors are lacking at present. The efficacy of newer drugs such as integrase inhibitors in this situation has not been evaluated.

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.[9] Therefore, based on the efficacy of the neonatal regimen and no benefit seen with the addition of maternal single-dose nevirapine to a regimen of maternal short-course zidovudine and infant single-dose nevirapine in the Mashi trial by Shapiro et al in Botswana, intrapartum maternal single-dose nevirapine is not recommended for a woman in this situation.[10] The efficacy of newer drugs such as integrase inhibitors in this situation has not been evaluated. In the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, women diagnosed with HIV infection during labor or the early postpartum period should be counseled against breastfeeding.

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Transmission and Mode of Delivery (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• Scheduled cesarean delivery at 38 weeks' gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1,000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral therapy (ART) **(AII)**. Scheduled cesarean delivery performed solely for prevention of perinatal transmission in women receiving ART with HIV RNA ≤1,000 copies/mL is not routinely recommended due to the low rate of perinatal transmission in this group **(AII)**. In women with HIV RNA levels ≤1000 copies/mL, if scheduled cesarean delivery or induction is indicated, it should be performed at the standard time for obstetrical indications.
• In women with an HIV RNA >1,000 copies/mL or unknown HIV RNA level who present in spontaneous labor or with ruptured membranes, there is insufficient evidence to determine whether cesarean reduces the risk of perinatal HIV transmission. Management of women originally scheduled for cesarean delivery because of HIV infection who present in labor must be individualized at the time of presentation **(BII)**. In these circumstances, consultation with an expert in perinatal HIV (e.g., telephone consultation with the National Perinatal HIV/AIDS Clinical Consultation Center at (888) 448-8765) may be helpful in rapidly developing an individualized delivery plan.
• In women on ART with HIV RNA ≤1,000 copies/ml, duration of ruptured membranes is not associated with an increased risk of perinatal transmission, and vaginal delivery is recommended **(BII)**.
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*

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 >1,000 copies/mL near delivery and for women with unknown HIV RNA levels.

This recommendation is based on findings from a multicenter, randomized clinical trial[1] and from a large individual patient data meta-analysis.[2] These two studies were conducted at a time when the majority of HIV-infected women received no antiretroviral (ARV) drugs 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 antiretroviral therapy (ART) during pregnancy is 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% CI, 0–1.7). The protective effect 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.[1] 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.[2]

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 >1,000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery.[3] Initially, the threshold of 1,000 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 <1,000 copies/mL.[4] Studies reported since then have demonstrated that HIV transmission can occur in infants born to women with low viral loads.

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In an analysis of 957 women with plasma viral loads ≤1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications (AOR 0.30; $P = 0.022$); however, zidovudine alone was the regimen primarily used as prophylaxis.[5] Among infants born to 834 women with HIV RNA ≤1,000 copies/mL receiving ARV medications, 8 (1%) were HIV-infected. In a 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, some of which appear to represent *in utero* transmission.[6]

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. Furthermore, there is evidence that complication rates for cesarean deliveries are higher in HIV-infected women compared with HIV-uninfected women.[7] Therefore, decisions about mode of delivery for women receiving ART with HIV RNA levels ≤1,000 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 ART with HIV RNA ≤1,000 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 ART (i.e., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery.[6] Given the low transmission rates achievable with use of maternal ART, the benefit of scheduled cesarean delivery is difficult to evaluate. Both the randomized clinical trial[1] and meta-analysis[2] 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 on births to HIV-infected women from the United Kingdom and Ireland between 2000 and 2011, perinatal transmission rates in women on ART with HIV RNA<1,000 copies/mL with planned cesarean delivery (13/3,814; 0.3%) were not significantly different than those in similar women with planned vaginal delivery (6/2,238; 0.3%).[8] Similarly, data from the French Perinatal Cohort showed no difference in transmission rates between vaginal delivery and planned cesarean delivery among women on ART with suppressed viral loads, 0.3% in both. For preterm deliveries with HIV RNA <1,000 copies/mL, transmission rates were slightly higher among planned vaginal deliveries but the numbers were small and the differences were not statistically significant (1/9 [11.1%] vs. 1/17 [5.9%] for HIV RNA 400–1000 copies/mL; 1/39 [2.6%] vs. 1/56 [1.8%] for HIV RNA 50–400 copies/mL; 1/189 [0.5%] vs. 0/143 [0%] for HIV RNA <50 copies/mL, for planned vaginal deliveries and elective cesarean deliveries, respectively).[9] Therefore, no evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving ART 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, a 1-hour loading dose followed by a continuous intravenous (IV) zidovudine infusion for 2 hours (3 hours total) before scheduled cesarean delivery should be administered. 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).[10] 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 >1,000 copies/mL, consideration can be given to shortening the interval between initiation of IV zidovudine administration and delivery. For

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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 ≤1,000 copies/mL at baseline. Even if ART 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.[11-13] 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.[14,15] 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.[15] 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.[16] 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 scheduled cesarean delivery is performed in HIV-infected women with an HIV RNA ≤1,000 copies/mL for an indication other than decreasing HIV transmission, cesarean delivery should be scheduled based on ACOG guidelines for HIV-uninfected women.

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 ART.[17-22] 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.[23] Complication rates in most studies[1,24-28] 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. A recent U.S. study of nationally representative data from a large administrative database demonstrated that (even in the era of ART) infectious complications, surgical trauma, prolonged hospitalization, and in-hospital deaths remain higher among HIV-infected women compared to HIV-uninfected women.[7] The rate of any complication associated with cesarean delivery was 117 per 1,000 deliveries among HIV-infected women compared with 67 per 1,000 deliveries among HIV-uninfected women. Therefore, HIV-infected women should be counseled regarding the specific risks associated with undergoing cesarean delivery in the setting of HIV infection.

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Management of Women Who Present in Early Labor or with Ruptured Membranes

New 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 as 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.[29] However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.[30] A prospective study of 707 women in Ireland showed that among the 493 women on ART with HIV RNA levels <1,000, no cases of perinatal transmission occurred with membranes ruptured for up to 25 hours. Only a viral load of >10,000 copies/mL was an independent risk factor for perinatal transmission.[31] A prospective review of 2,398 HIV-infected women in the UK and Ireland most of whom were virally suppressed showed no association between duration of ruptured membranes and perinatal transmission in 2,116 term deliveries, regardless of viral load. Eighty-nine percent had HIV RNA levels <50 copies/mL; among the remaining 11%, 9% had HIV RNA levels 50–399 copies/mL, 1% 400–999 copies/mL, 0.4% 1000–9999 copies/mL, and 0.6% >10,000 copies/mL. Among mother-baby pairs with perinatal transmission and no evidence of in utero transmission, 2 had undetectable HIV RNA levels (<50 copies/ml), one had an HIV RNA level of 50–399 copies/ml, and 2 had levels >10,000 copies/ml. Among term deliveries, median duration of rupture of membranes was 3 hours 30 minutes; 71 (3.4%) had rupture of membranes >24 hours and 24 (1.1%) had rupture of membranes >48 hours. The authors concluded that obstetric care of women on ART at term with ruptured membranes should be "normalized."[32,33] Because it is not clear whether cesarean delivery after onset of labor reduces the risk of perinatal HIV transmission, management of women originally scheduled for cesarean delivery who present in labor must be individualized at the time of presentation. In these circumstances, consultation with an expert in perinatal HIV may be helpful. Because the delivery plan in the setting of labor must be made quickly, telephone consultation with a 24-hour, 7-day-a-week hotline (e.g., the National Perinatal HIV/AIDS Clinical Consultation Center (888) 448-8765) may be helpful in rapidly developing an individualized plan.

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.

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Other Intrapartum Management Considerations (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• Artificial rupture of membranes (ROM) performed in the setting of antiretroviral therapy and virologic suppression is not associated with increased risk of perinatal transmission and can be performed for standard obstetric indications **(BII)**

• The following should generally be avoided because of a potential increased risk of transmission, unless there are clear obstetric indications:
  • Artificial ROM in the setting of viremia **(BIII)**
  • Routine use of fetal scalp electrodes for fetal monitoring **(BIII)**
  • Operative delivery with forceps or a vacuum extractor **(BIII)**
  • Episiotomy **(BIII)**

• The ART 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) 450 3A4 enzyme inhibitor (e.g., 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 **(BIII)**.

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*

Data on the association of duration of rupture of membranes (ROM) and perinatal transmission in the era of effective antiretroviral therapy (ART) are reassuring. A prospective cohort study of 707 HIV-infected pregnant women on ART included 493 women with delivery HIV-RNA <1,000 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.[1] A large prospective population-based surveillance study in the UK and Ireland included 2,116 pregnancies delivered at term vaginally or by emergency Cesarean delivery in women on ART during the period 2007-2012 with information on duration of ROM. The median duration of ROM was 3 hours 30 minutes (interquartile range, IQR 1-8 hours) and the overall perinatal transmission rate was not significantly different with longer duration of ROM (0.64% with duration of ROM ≥4 hours compared with 0.34% for ROM <4 hours, [OR 1.90, 95% CI 0.45-7.97]). In those women with a viral load <50 copies/mL, there was no difference in perinatal transmission rates with duration of ROM ≥4 hours, compared with <4 hours (0.14% for ≥4 hours versus 0.12% for <4 hour; OR 1.14, 95% CI 0.07–18.27). Among infants born preterm, there were no transmissions in 163 deliveries where the maternal viral load was <50 copies/mL.[2] If spontaneous ROM occurs before or early during the course of labor, interventions to decrease the interval to delivery (e.g., administration of oxytocin) can be considered based on obstetric considerations in HIV-infected women with viral suppression. Artificial ROM should be avoided unless there is a clear obstetric indication in women with detectable viral loads.

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.[3-6] Data are limited on use of fetal scalp electrodes in labor in women receiving suppressive ART s who have undetectable viral loads; routine use of fetal scalp electrodes for fetal monitoring should generally be avoided in the setting of maternal HIV infection.

Similarly, data are limited to those obtained in the pre-ART 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.[4,6] These procedures should be performed only if there are clear obstetric indications. Delayed cord clamping has been associated with improved iron status in preterm infants and benefits such

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as decreased risk of intraventricular hemorrhage in preterm births to HIV-uninfected mothers.[7,8] Even though HIV-specific data on the practice are lacking, there is no reason to modify it in HIV-infected mothers.

Intrapartum Epidural Use and Pharmacologic Interactions with Antiretroviral Drugs

Ritonavir inhibition of cytochrome P450 (CYP) 3A4 decreases the elimination of fentanyl by 67%, raising concerns about possible increased risk of respiratory depression, particularly with patient-controlled analgesia during labor, in women receiving ritonavir-containing regimens. However, a recent pharmacokinetic simulation study suggests that even with maximal clinical dosing regimens of epidural fentanyl over 24 hours, ritonavir-induced CYP3A4 inhibition is unlikely to produce plasma fentanyl concentrations associated with a decrease in minute ventilation.[9] This suggests that epidural anesthesia can be used safely regardless of ART regimen.

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 CYP3A4 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 antiretroviral drugs that are CYP3A4 inducers (e.g., nevirapine, efavirenz, etravirine) are used because of the potential for decreased methergine levels and inadequate treatment effect.

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Postpartum Care (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• Antiretroviral therapy (ART) is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission **(AI)**. Decisions regarding continuing or modifying ART after delivery should be made in consultation with the woman and her HIV care provider, ideally before delivery, taking into consideration the preferred regimens for non-pregnant adults versus those for pregnant adults **(AIII)**.
• Because the immediate postpartum period poses unique challenges to antiretroviral adherence, arrangements for new or continued supportive services should be made before hospital discharge **(AII)**.
• Contraceptive counseling is a critical aspect of postpartum care **(AIII)**.
• Women with a positive expedited HIV antibody test during labor should receive intravenous (IV) zidovudine immediately (see Intrapartum Care: Women Who Present in Labor without Documentation of HIV Status) and should not breastfeed unless a confirmatory HIV test is negative.
• 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, continued ART, and assessment of the need for opportunistic infection prophylaxis **(AII)**.
• Breastfeeding is not recommended for HIV-infected women in the United States **(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;
- Coordination of care through case management for a woman, her child(ren), and other family members; *and*
- Prevention of secondary transmission for serodiscordant partners, including counseling on the use of condoms, antiretroviral therapy (ART) to maintain virologic suppression in the infected partner (i.e., Treatment as Prevention [TasP]), and potential use of pre-exposure prophylaxis by the uninfected partner.

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.

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Immediate linkage to care, comprehensive medical assessment, counseling, and follow-up are required for women who test positive on expedited HIV antibody assay during labor or at delivery. If test results are available during labor and delivery, the woman should receive IV zidovudine immediately. Women who test positive on a rapid HIV antibody assay should not breastfeed unless a confirmatory HIV test is negative. To minimize the delay in definitive diagnosis, the fourth-generation combined antibody-antigen test should be employed if available; specimens with a reactive antigen/antibody combination immunoassay result should be tested with a Food and Drug Administration-approved immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies per the updated Centers for Disease Control and Prevention guidance for HIV testing. Women with a new HIV diagnosis should receive the same thorough evaluation as other newly identified infected patients, including recommendation for lifelong ART, and prophylaxis for opportunistic infections as indicated. Other children and partner(s) should be referred for HIV testing. Counseling on prevention of secondary transmission to the uninfected partner should include condoms, ART for the infected partner to maintain viral suppression, and potential use of pre-exposure prophylaxis by the uninfected partner.

During the postpartum period, maternal medical services must be coordinated between obstetric care providers and HIV specialists. Decisions about changes to an ART regimen after delivery should be made in consultation with a woman and her HIV care provider, ideally prior to delivery. It is especially critical to ensure continuity of ART between the antepartum and postpartum periods. The mother should receive the medication prior to discharge because outpatient pharmacies may not stock zidovudine for neonatal administration. Special hospital programs may need to be established to support this.

ART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission.[1] The START and TEMPRANO trials were randomized clinical trials that demonstrated that early ART can reduce the risk of disease progression even in individuals with CD4 T lymphocyte cell count >500 cells/mm^3, and the HPTN 052 randomized clinical trial demonstrated that early ART can reduce risk of sexual transmission to a discordant partner by 96%.[2-4] It is important to counsel a woman that no single method (including treatment) is 100% protective against HIV transmission, so safer sexual practices should be continued.

Understanding the need for lifelong ART is a priority for postpartum care, but does represent a number of specific challenges. Studies have demonstrated significant decreases in ART adherence postpartum.[5-9] During the postpartum period, women may have difficulty with medical appointment follow-up, which can affect ART adherence. Systematic monitoring of retention in HIV care is recommended for all HIV-infected individuals, but special attention is warranted during the postpartum period. A number of studies have suggested that postpartum depression may be common among HIV-infected women.[10-15] All women, particularly HIV-infected women, should be screened for postpartum depression using a validated tool, given the deleterious effects of depression on ART adherence. 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.[16-19]

Health care providers should be vigilant in screening for signs of depression, intimate partner violence, and illicit drug or alcohol use that may require intervention to avoid problems with ART adherence. Interventions to improve adherence to medical care and ART can include medication management services, referral to psychological services, community outreach, one-on-one adherence support, group education and support, peer support, reminder devices, and home visits by HIV case managers.[20] Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of ART.[21-23] In women who achieve viral suppression by the time of delivery, postpartum simplification to once-daily coformulated regimens (which are often preferred initial regimens for non-pregnant adults but for pregnant women) could promote adherence during this challenging time. Efforts to maintain adequate adherence during the postpartum period may ensure effectiveness of therapy (see the section on Adherence in the Adult and Adolescent Antiretroviral Guidelines). For women continuing ART who had received increased protease inhibitor doses during pregnancy, available data suggest that standard doses can be used

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again, beginning immediately after delivery.

It is important that comprehensive family planning and preconception care be integrated into routine prenatal and health visits. 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.[24] Interpregnancy intervals of less than 18 months have been associated with increased risk of poor perinatal and maternal outcomes in HIV-uninfected women.[25] 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 contraception and, thus, unintended pregnancy.[26] 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 to a partner, and acquisition or transmission of sexually transmitted disease.[27] Long-acting reversible contraceptives (LARC), such as injectables, implants, and intrauterine devices (IUDs), should be included as options.

The postpartum period is a critical time for addressing safer sex practices in order to reduce sexual transmission of HIV to HIV-uninfected partners and contraception to avoid unwanted pregnancies. Ideally these issues will be addressed during the prenatal period. Treating the infected partner with virologically suppressive ART and providing pre-exposure prophylaxis to the uninfected partner are effective methods to reduce sexual transmission of HIV.

The potential for drug-drug interactions between a number of antiretroviral (ARV) drugs and hormonal contraceptives is 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 and recommends the use of all contraceptive methods in women with HIV.[28,29] Findings from a systematic review of hormonal contraceptive methods and risk of HIV transmission to uninfected partners concluded that oral contraceptives and medroxyprogesterone do not increase risk of HIV transmission in women who are on ART although data are limited and have methological issues.[30] Permanent sterilization is appropriate only for women who are certain they do not desire future childbearing.

Avoidance of breastfeeding has been and continues to be a standard, strong recommendation for HIV-infected women in the United States, because maternal ART dramatically reduces but does not eliminate breastmilk transmission. Further, safe infant feeding alternatives are readily available in the United States. In addition there are concerns about other potential risks, including toxicity for the neonate or increased risk of development of ARV drug resistance, should transmission occur, due to variable passage of drugs into breastmilk. However, clinicians should be aware that women may face social, familial, and personal pressures to consider breastfeeding despite this recommendation.[31] It is important to address possible barriers to formula feeding beginning during the antenatal period. Similarly, there are risks of HIV transmission via premastication (prechewing) of infant food.[32]

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Infant Antiretroviral Prophylaxis (Last Updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendations
• All HIV-exposed infants should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
• Infant ARV prophylaxis—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 **(AII)**.
• A 4-week neonatal zidovudine prophylaxis regimen can be used for full-term infants when the mother has received a standard antiretroviral therapy regimen (ART) during pregnancy with sustained viral suppression and there are no concerns related to maternal adherence **(BII)**. Otherwise, a 6-week course as part of a combination infant prophylaxis regimen is recommended **(AI)**.

• A combination infant prophylaxis regimen is recommended in infants at higher risk of HIV acquisition, including those born to HIV-infected women who:
  • Have not received antepartum or intrapartum ARV drugs **(AI)**, *or*
  • Have received only intrapartum ARV drugs **(AI)**, *or*
  • Have received antepartum ARV drugs but do not have viral suppression near delivery **(BIII)**.

• For infants born to mothers with unknown HIV status, expedited HIV testing of mothers and/or infants is recommended as soon as possible, either during labor or after birth, with immediate initiation of infant ARV prophylaxis if the initial expedited test is positive **(AII)**. 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 most important contributors to the risk of HIV transmission to an HIV-exposed infant are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load; the risk of transmission is increased if maternal antepartum/intrapartum treatment was incomplete or not received and if maternal viral load is detectable, particularly if it is very high. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery and maternal health status.

In all situations, infant prophylaxis should be initiated as soon as possible after delivery.

The interval during which infant prophylaxis can be initiated and still be of benefit is undefined; however, most studies support providing prophylaxis as early as possible after delivery.[1-6]

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
- Are at higher risk of transmitting HIV infection to their infant including those who
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs
  - Received antepartum and intrapartum ARV drugs but who have detectable viral load at delivery, particularly if delivery was vaginal

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- Have unknown HIV status
- Have known ARV drug-resistant virus.

Infant Zidovudine Prophylaxis

Zidovudine was shown in the PACTG 076 study to effectively reduce perinatal HIV transmission and is recommended for all neonates born to mothers with HIV infection. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week infant zidovudine regimen was studied in PACTG studies 076 and 316 (both performed during an era when a greater proportion of women did not receive antenatal ART). However, in the United Kingdom and many other European countries, a 4-week neonatal zidovudine prophylaxis regimen is now recommended for infants born to mothers who have received ART regimens during pregnancy and have viral suppression, with no apparent increase in the overall HIV perinatal transmission rate.[7,8] In addition, 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.[9]

Therefore, Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel) recommends a 4-week neonatal zidovudine prophylaxis regimen for full-term infants if the mother has received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and there are no concerns related to maternal adherence. In all other cases, the infant should receive a 6-week course of zidovudine as part of a combination infant prophylaxis regimen. Dosing recommendations for zidovudine are available for premature infants and an intravenous preparation is available. Table 7 shows recommended zidovudine dosing based on gestational age, birthweight, and the status of maternal antepartum ARV regimens.

Infant Combination Antiretroviral Prophylaxis

A combination infant prophylaxis regimen is recommended for infants at higher risk of HIV acquisition including those born to HIV-infected women who have not received antepartum or intrapartum ARV drugs or have received only intrapartum ARV drugs **or** have received antepartum ARV drugs but do not have viral suppression near delivery.

There is a paucity of data from randomized clinical trials to guide the optimal selection of an infant combination prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 study is the only randomized clinical trial of combination prophylaxis in infants at high risk of HIV acquisition. 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 1 of 3 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. Forty-one percent of mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-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 2 combination regimens were similar, neutropenia was significantly more common with the 3-drug regimen than with the 2-drug or zidovudine-alone regimen (27.5% vs. 15%, $P < .0001$). Based on this study, the 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine has previously been recommended by the Panel for infants at higher risk of HIV acquisition.

Data from Europe and the United States indicate increasing use of combination infant prophylaxis in HIV-exposed infants. In the United Kingdom and Ireland, use increased from 9% of HIV-exposed infants in 2001 to 2004 to 13% between 2005 to 2008 and in a poll of 134 U.S.-based providers, 62% reported using combination prophylaxis in high-risk infants.[10-12] However, interpretation of these observational studies are complicated by the definition of combination prophylaxis, dosages of drugs in the regimen, and combining heterogeneous combination prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many include single-dose nevirapine in combination with another ARV, usually zidovudine, as

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combination therapy. Most do not report whether nevirapine was administered at the prophylaxis dose or at a higher dose needed for treatment of HIV infection.

More recently, many experts are recommending a three-drug infant prophylaxis regimen using treatment doses of ARV drugs in infants at high risk of HIV acquisition. Enthusiasm for this approach followed a case of a "functional cure" of HIV in an infant reported in 2013.[13] 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 expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs 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*. At age 18 months, the mother discontinued combination therapy; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for over 2 years on no therapy. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest, another case of virologic rebound following 4 years of suppression in an infant treated since birth has subsequently been reported.[14]

Further support of a 3-drug infant prophylaxis regimen comes from Canadian investigators who have reported outcomes in 136 infants considered at high risk of HIV acquisition (born to HIV-infected women who had detectable viral load and/or poor adherence to therapy prior to delivery) who received treatment doses of triple ARV prophylaxis within 72 hours of birth. Of the infants born into scenarios associated with higher risk of HIV transmission, 12 were found to be HIV-infected and no major toxicities were identified.[15] There was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug prophylaxis regimens. Another Canadian study compared the safety of combination prophylaxis using treatment doses of ARV drugs in 148 infants with high-risk exposure (incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) and 145 control low-risk infants who received only zidovudine. Thirteen infants in the combination ARV group were HIV-infected, 5 with a positive HIV NAT within the first 48 hours of life, suggesting *in utero* infection. No infant in the low-risk zidovudine-only group was HIV-infected. The infants receiving a combination ARV regimen demonstrated more non-specific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects compared to none of the infants receiving zidovudine only (10.2% vs. 0%, $P < .001$). ARV drug treatment was also more likely to be discontinued prematurely in the infants receiving combination ARV drugs (9.5% vs. 2.1%, $P = .01$).[16]

Use of ARV regimens of three drugs at treatment doses in infants is consistent with Center for Disease Control and Prevention recommendations for occupational and non-occupational post-exposure prophylaxis in adults, where risk of infection is often lower than in infants at high risk of HIV acquisition.[17,18] However, there are two key safety issues related to the choice and dose of ARV drugs in these infants. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight 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. There are very limited data in infants under age 2 weeks 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. Recent data from a nevirapine pharmacokinetic (PK) model and 2 observational studies suggest that nevirapine, 6 mg/kg twice daily, meets these target treatment parameters.[19-21] Second, lopinavir/ritonavir 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) and efficacy require further study before a general recommendation can be made.

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There are three ongoing clinical trials investigating a three-drug infant ARV prophylaxis regimen containing zidovudine, lamivudine, and nevirapine at treatment doses shortly after birth in infants at high-risk of HIV infection (international multisite IMPAACT P1115, ClinicalTrials.gov identifier NCT02140255), or those known to be infected (BHP-074 in Botswana, NCT02369406, and the Leopard Study in South Africa, NCT02431975). Additional safety and PK data from these studies will guide future recommendations.

At this time, the Panel recommends a combination ARV prophylaxis regimen in infants at high risk of HIV acquisition. However, the Panel was unable to reach clear consensus on the specific ARV prophylaxis regimen in these infants. The NICHD-HPTN 040/PACTG 1043 study supports the recommendation of 6 weeks of zidovudine plus three doses of nevirapine at prophylactic doses 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). Many Panel members recommend a three-drug infant ARV prophylaxis regimen using treatment doses of zidovudine, lamivudine, and nevirapine, administering nevirapine at 6 mg/kg twice daily under investigation in IMPAACT P1115 as the initial regimen. This nevirapine dosage is currently under investigation in IMPAACT P1115. All infants should receive 6 weeks of zidovudine. The optimal duration of lamivudine and nevirapine is unknown. Many experts recommend continuation of nevirapine for a 6-week course while others recommend discontinuation after 2 weeks of life if HIV a nucleic acid amplification test (NAAT) is negative at birth. Table 7 provides dosing information based on gestational age, birthweight, and the status of maternal antepartum ARV regimens.

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 treatment regimens during pregnancy and labor and had undetectable viral loads at delivery. A 4-week infant zidovudine regimen is recommended in full-term infants when a mother has received standard ART during pregnancy with sustained viral suppression. 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.

Infants Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Intrapartum Antiretroviral Drugs Only, or Who Have Received Combination Antiretroviral Drugs and Do Not Have Sustained Viral Suppression

All infants born to mothers with detectable viral load at the time of delivery, who received intrapartum ARVs only or who have received no ARVs during pregnancy or delivery are at higher risk of HIV acquisition and should receive combination ARV prophylaxis (see Infant Combination Antiretroviral Prophylaxis).[5,22-26]

For those women who received ARV drugs during pregnancy but have a detectable viral load at delivery, the level of viremia in the mother that would trigger the use of combination infant prophylaxis is not definitively known. In 2 large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had viral load measurements <50 copies/mL at delivery. Rates of transmission increased to 1.1% and 1.5% when viral load measurements were 50–399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.[27,28] However, there has been no study to demonstrate relative efficacy of combination infant prophylaxis compared to standard infant prophylaxis at these different thresholds of maternal viremia. While some experts would recommend infant combination

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prophylaxis with any level of detectable viremia, others reserve infant combination therapy until higher levels of maternal viral load are documented. The decision to administer infant combination prophylaxis should be made following discussion with the parents weighing the risks and benefits of combination therapy.

In addition to a combination infant ARV prophylaxis regimen, scheduled cesarean delivery is recommended for prevention of perinatal transmission in women who have received antepartum ARV drugs but who have detectable viremia (HIV RNA >1000 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.[29] 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 or unscheduled cesarean.

Infants Born to Mothers with Unknown HIV Infection Status

Expedited 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.[30] If expedited testing is positive, infant combination ARV prophylaxis should be initiated immediately, without waiting for the results of supplemental tests as described above. 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 NAT (includes DNA and RNA PCR and related assays). Initial positive HIV antibody tests in the mother can be confirmed using a recommended HIV-1/2 diagnostic testing algorithm.[31] Supplemental tests should be performed on mothers (or their infants) as soon as possible after the initial positive test. If the test results on a mother (or infant) are negative, ARV prophylaxis can be discontinued. If the supplemental test results in the mother are positive or if the mother is unavailable or declines testing, 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 ART according to the Pediatric Antiretroviral Guidelines. Clinicians should be aware of their state laws, as there is variability in the testing allowed without parental consent.

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 or antibody/antigen 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.[32]

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 or through consultation with the National Perinatal HIV Hotline (888-448-8765).

Data from the WITS study suggest that in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted.[33,34] Thus, the 6-week infant zidovudine prophylaxis (along with maternal IV intrapartum zidovudine) continues to be recommended, even when maternal zidovudine-resistant virus with thymidine-associated mutations is identified.

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Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.[34] However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.[35-39]

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. However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis

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.

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[25,40,41] 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.[42] 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.[43]

Tenofovir disoproxil fumarate (TDF) with and without emtricitabine has been investigated in several small studies to define the safety and PKs of the agents in newborns.[44,45,46] However, at this time, TDF 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.[47,48] Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.[42,49-52]

Nevirapine is the only non-nucleoside reverse transcriptase inhibitor drug with a pediatric drug formulation and neonatal prophylactic (but only preliminary evidence of therapeutic) dosing information (see the Adult and Adolescent Antiretroviral Guidelines).[53] In rare cases, chronic multiple-dose nevirapine prophylaxis 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 two-drug zidovudine regimen plus three 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.[5,54-57] Resistance to nevirapine can occur, however, with exposure to nevirapine in infants who become infected despite prophylaxis.[58,59]

Of the protease inhibitors, pediatric drug formulations are available for lopinavir/ritonavir, 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. In addition, lopinavir/ritonavir oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm infants. 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 lopinavir/ritonavir. Although the lopinavir area under the curve (AUC) was significantly lower with dosing 300 mg

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lopinavir/75 mg ritonavir/m^2 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.[60] Studies are ongoing but data are not yet available for infants aged <2 weeks. However, in four premature infants (2 sets of twins) started on lopinavir/ritonavir from birth, heart block developed that resolved after drug discontinuation.[61,62] In studies of adults, both ritonavir and lopinavir/ritonavir 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 lopinavir/ritonavir compared with zidovudine in the neonatal period. Levels of 17-hydroxyprogesterone were greater in infants who were also exposed to lopinavir/ritonavir in utero compared with those exposed only in the neonatal 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.[63] 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,[64] predominantly in preterm neonates, the US Food and Drug Administration (FDA) now recommends that lopinavir/ritonavir oral solution **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. However, a recent study (ANRS 12174) randomized 1,273 infants, 615 assigned to lopinavir/ritonavir and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 T lymphocyte (CD4) cell counts above the local threshold for treatment at the time. Infant study prophylaxis was initiated at 7 days of life and only infants greater than 2 kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that lopinavir/ritonavir is safe in term infants, 7 days of age and older.[65] At this time, the Panel does not recommend the early use of lopinavir/ritonavir.

Raltegravir is the only integrase inhibitor with an available pediatric drug formulation. However, it is not FDA-approved for use in infants aged <4 weeks or weight <3 kg. Raltegravir readily crosses the placenta; its elimination was highly variable and extremely prolonged in some infants following maternal dosing. Raltegravir competes with bilirubin for albumin binding sites, which could increase unbound (free) unconjugated bilirubin levels in the neonate.66 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.[67] Raltegravir is currently being studied in IMPAACT P1110, a phase I multicenter trial enrolling full-term HIV-1-exposed neonates at high risk of acquiring HIV-1-infection, with or without in utero raltegravir exposure. Study design includes 2 Cohorts: Cohort 1 infants receive 2 single raltegravir doses 1 week apart; Cohort 2 infants receive daily raltegravir dosing for first 6 weeks of life. PK results from Cohort 1 were combined with that from older infants and children receiving daily dosing in a population PK model and simulations performed to develop a daily raltegravir dosing regimen under evaluation in Cohort 2.[68] The raltegravir dosing regimen chosen and currently under investigation in Cohort 2 for infants unexposed to raltegravir in utero is: 1.5 mg/kg daily starting within 48 hours of life through day 7; 3 mg/kg twice daily aged 8 days through 28 days; 6 mg/kg twice daily after 4 weeks of age. Preliminary findings have been reported on the first 12 infants enrolled and the PK targets and safety guidelines have been met for those patients.[69] Use of raltegravir in neonates is not recommended until adequate PK and safety data are available.

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Neonatal Antiretroviral Drug Dosing

Table 7. Neonatal Dosing for Prevention of Perinatal Transmission of HIV

All HIV-Exposed Infants Initiated as soon after delivery as possible		
Regimen	**Dosing**	**Duration**
ZDV **Note:** Twice-daily dosing prophylaxis should be started as soon after birth as possible, preferably within 6–12 hours of delivery For infants unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.	≥35 Weeks' Gestation at Birth: *Birth to Age 6 Weeks:* • 4 mg/kg orally twice daily **Simplified Weight-Band Dosing for Infants ≥35 Weeks:** **Weight Band (kg)** / *** Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily** **2 to <3 kg** / **1 mL** **3 to <4 kg** / **1.5 mL** **4 to <5 kg** / **2 mL**	Birth through 4–6 weeks[a]
	≥30 to <35 Weeks' Gestation at Birth: *Birth to Age 2 Weeks:* • 2 mg/kg orally twice daily *Age 2 Weeks to 4–6 Weeks:* • 3 mg/kg orally twice daily	Birth through 6 weeks
	<30 weeks' Gestation at Birth: *Birth to Age 4 Weeks:* • 2 mg/kg orally twice daily *Age 4 Weeks to 6 Weeks:* • 3 mg/kg orally twice daily	Birth through 6 weeks
Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants Who are at High Risk of HIV Acquisition Initiated as soon after delivery as possible		
NICHD-HPTN 040/PACTG 1043 Study Regimen		
NVP In addition to ZDV as shown above	Birth Weight 1.5–2 kg: • 8 mg/dose PO Birth Weight >2 kg: • 12 mg/dose PO	Three Doses in the First Week of Life: 1. Within 48 hours of birth 2. 48 hours after first dose 3. 96 hours after second dose
Three-Drug Infant Combination Antiretroviral Prophylaxis Regimen This regimen is under investigation, but is already used in clinical practice by some experts		
3TC In addition to ZDV as shown above	≥32 Weeks' Gestation at Birth: *Birth to Age 4 Weeks:* • 2 mg/kg PO twice daily *Aged 4 Weeks to 6 Weeks:* • 4 mg/kg PO twice daily	Birth through 2–6 weeks
NVP In addition to ZDV as shown above	≥34 Weeks' Gestation at Birth: *Birth to Age 4 Weeks:* • 6 mg/kg PO twice daily *Aged 4 Weeks to 6 Weeks:* • 200 mg/m^2 of BSA/dose twice daily	Birth through 2–6 weeks[b]

[a] A 4-week neonatal ZDV prophylaxis regimen may be used when the mother has received standard ART during pregnancy with sustained viral suppression and there are no concerns related to maternal adherence. All other infants should receive a 6-week course of ZDV.

[b] The optimal duration of NVP is unknown. Some experts recommend continuation of NVP for a 6-week course while others recommend discontinuation after 2 weeks of life if HIV nucleic acid amplification test is negative.

Key to Abbreviations: 3TC=lamivudine; BSA = body surface area; IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine

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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 7).[25,54,70-77] Some PK studies suggest that the standard neonatal zidovudine dosing regimen might be excessive and associated with bone marrow and metabolic toxicity, but no alternative dosing regimens have been studied.[78,79] If an infant is unable to tolerate oral medications, the zidovudine prophylaxis regimen can be administered IV. The zidovudine dosing requirements differ for premature infants and term infants (see Table 7 and Antiretroviral Drug Dosing for Premature Infants).

PKs and safety of the single-dose nevirapine regimen to mother and infant[80] and chronic prophylactic nevirapine administration to infants to prevent HIV transmission during breastfeeding have been studied.[81] The three-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 drugs during the antepartum period has also been studied.[53] Nevirapine concentrations were measured in 14 newborns participating in a PK sub-study 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 treatment) and nevirapine (prophylaxis only) (see Table 7). 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.[82,83] The recommended zidovudine dosage for preterm infants is shown in Table 7.

Nevirapine PKs have been described in low-birthweight neonates receiving a single postnatal prophylactic dose of the drug. In a study of 81 infants <37 weeks' gestation, of whom 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.[84]

Use of ARV drugs other than zidovudine, lamivudine 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

Women with suspected HIV infection (e.g., a positive initial screening test) should stop breastfeeding until HIV infection is ruled out. 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 ART (see Infant Feeding Practices and Risk of HIV Transmission).[85]

The risk of acquisition of HIV associated with breastfeeding depends on multiple infant and maternal factors, including maternal viral load and CD4 cell count.[86] Infants of women who develop acute HIV infection while breastfeeding are at greater risk of becoming infected than are those whose mothers have chronic HIV infection[87] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.[88]

Other than discontinuing breastfeeding, optimal strategies for managing infants born to HIV-infected mothers

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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.[89]

Several studies of infants breastfed by women with chronic HIV infection have shown that daily infant nevirapine, lamivudine, or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.[54-56,90] 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.[5] 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 an ART 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 ART 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.[89] As in other situations, decisions regarding administration of a prophylactic or pre-emptive 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 ARV drugs, 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 do many HIV RNA assays. Therefore, if non-subtype B or group O HIV infection is considered possible in an infant, 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 ART according to the Pediatric Antiretroviral Guidelines. Resistance testing should be performed and the ART regimen modified if needed (see the Pediatric Antiretroviral Guidelines).

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Initial Postnatal Management of the HIV-Exposed Neonate (Last updated October 26, 2016; last reviewed October 26, 2016)

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)**.
- Hemoglobin and neutrophil counts should be remeasured 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 at 14 to 21 days of life and at ages 1 to 2 months and 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 breastfeeding and premastication; instruct HIV-infected caregivers to avoid these practices, 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*

Hematologic Toxicity

A complete blood count 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.[1] 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 remeasure 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 remeasure 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 more anemia and/or neutropenia compared with that seen in infants exposed to zidovudine alone.[2-5] 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. Some experts recommend more intensive monitoring of

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hematologic and serum chemistry and liver function assays at birth and when diagnostic HIV PCR tests are obtained in infants exposed to combination ARV drug regimens *in utero* or during the neonatal period.

In addition, data are limited on infants receiving zidovudine in combination with other ARV drugs for prophylaxis. However, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine and other combination prophylactic regimens compared with those receiving zidovudine alone or zidovudine plus nevirapine.[6-8] Hemoglobin levels and neutrophil counts, therefore, should be remeasured 4 weeks after initiation of prophylaxis and/or at the time that diagnostic HIV PCR testing is done in infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens.[9]

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, and risk of HIV infection (as assessed by the mother's history of ARV prophylaxis, viral load near delivery, and mode of delivery). 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 women received zidovudine antenatal monotherapy). In the United Kingdom and other European countries, a 4-week neonatal chemoprophylaxis regimen is now recommended for infants born to mothers who have received antiretroviral therapy (ART) regimens and have viral suppression, with no apparent increase in the overall HIV perinatal transmission rate.[10,11] Additionally, a 4-week zidovudine regimen has been reported to result in earlier recovery from anemia in otherwise healthy infants compared with the 6-week zidovudine regimen.[12] Therefore, a 4-week zidovudine neonatal chemoprophylaxis regimen can be considered when a mother has received standard ART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence.

Hyperlactatemia

Hyperlactatemia has been reported in infants with *in utero* exposure to ARV drugs, but it appears to be transient and, in most cases, asymptomatic.[13,14] 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.[13,14] 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.

Prophylaxis Against Pneumocystis jirovecii Pneumonia

To prevent *Pneumocystis jirovecii* pneumonia, all infants born to HIV-infected women should begin trimethoprim-sulfamethoxazole prophylaxis at age 4 to 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 OI Guidelines).[15]

HIV Testing of the Infant

HIV infection in infants should be diagnosed using HIV nucleic acid amplification virologic assays, which include DNA and RNA PCR and related assays. Maternal HIV antibody crosses the placenta and will be detectable in all HIV-exposed newborns; therefore, standard antibody tests should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed at 14 to 21 days of life and at ages 1 to 2 months and 4 to 6 months.[16] 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 cannot 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. There is no evidence of a delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the zidovudine regimen.[1,17] However, the effect of maternal or infant exposure to combination ARV drug

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regimens on the sensitivity of infant virologic diagnostic testing—particularly using HIV RNA assays—is unknown. Therefore, some experts prefer to use HIV DNA PCR assays for diagnosing infection in neonates who receive combination ARV drug regimens. Any newly diagnosed infant should undergo viral resistance testing by genotype and/or phenotype to assess for susceptibility to ART.

HIV can be **presumptively** excluded with 2 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 or more 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.[18] Alternative algorithms exist for presumptive and definitive HIV exclusion.16 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. For a detailed discussion of pediatric HIV diagnosis, see the Pediatric Guidelines.

Postnatal Management

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, Zika virus, 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 OI Guidelines).

No evidence is available to enable the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 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.[19] Maternal receipt of ART is likely to reduce free virus in breast milk, but the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and, therefore, may continue to pose a transmission risk.[20] However, clinicians should be aware that women may face social, familial, and personal pressures to consider breastfeeding despite this recommendation. It is important to address possible barriers to formula feeding beginning during the antenatal period (see Postpartum Follow Up).

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.[21,22]

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Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendation
• Children with *in utero*/neonatal exposure to antiretroviral drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction **(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*

Data remain insufficient to address definitely the effect that exposure to antiretroviral (ARV) agents *in utero* might have on long-term risk of neoplasia or organ system toxicities in children; however, the balance of evidence over 2 decades, particularly with zidovudine, is reassuring. Potential toxicities require further, long-term investigation, especially as individual antenatal ARV and ARV combinations continue to evolve. Initial 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] However, concerns remain that exposure to ARVs may have long-term effects on mitochondrial and immunologic function. Ongoing studies within the Pediatric HIV/AIDS Cohort Study (PHACS) and other HIV-exposed uninfected cohorts may help to identify the long-term risks of ARV drugs in exposed infants.

Potential Mitochondrial Toxicity

Nucleoside reverse transcriptase inhibitor (NRTI) drugs induce some degree of mitochondrial dysfunction reflecting varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mt DNA) depletion and dysfunction.[3-5] Aberrant histological morphology of mitochondria, mt DNA mutations, alterations in mt DNA levels in cord blood mononuclear cells, and even aneuploidy in cord blood cells have all been described in both non-human primates and neonates exposed *in utero* to NRTI drugs.[6-9] Reported increased and decreased alterations in mt DNA levels add further complexity to interpretation of their clinical significance; in addition, the data may be confounded by stage of maternal HIV infection and differences in laboratory assays and cell lines used.[8,10-12] One study has reported that respiratory chain mitochondrial function is subtly and transiently perturbed, with an increased incidence of abnormal newborn metabolic screen results for products of intermediary metabolism (elevated amino acids and acylcarnitines) in HIV-exposed (but uninfected) infants compared with HIV-unexposed infants.[13] The degrees to which these theoretical concerns and documented mitochondrial abnormalities are clinically relevant are unknown but are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[8,14]

Evidence of clinically apparent effects of mitochondrial toxicity is also conflicting. A low rate of hyperlactatemia (3.4%) is documented among HIV-exposed, uninfected infants born to U.S. women receiving antiretroviral therapy (ART).[15] However, earlier studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects possibly reflecting mitochondrial dysfunction including seizures, cognitive and motor delays, abnormal neuroimaging, hyperlactatemia, cardiac dysfunction, and two deaths, with abnormal mitochondrial histology noted among some HIV-uninfected infants born to HIV-infected women (who received or did not receive ARV drugs during pregnancy: 12/2,644 vs. 0/1,748, respectively, $P = 0.002$).[16,17] Further clinical studies from the United States and Europe have not duplicated these French reports.[18-24] 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 among a cohort of 1,037 HIV-exposed uninfected infants.[23] Definitive diagnosis was not possible

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because none of the children had biopsies for mitochondrial function; however, 3 of the 20 children had no exposure to ARV drugs. In the 17 remaining children, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester, but overall exposure to NRTI drugs was not associated with symptoms. Some small alterations in mt DNA and oxidative phosphorylation enzyme activities were documented in stored specimens from these children, but the clinical significance of these observations remains unknown.[25,26]

Given the above data, 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. It is important that the long-term medical record of an uninfected child includes information about ARV exposure, should unusual symptoms develop later in life, or if adverse late effects of HIV or ARV exposure in uninfected children are identified in the future.[8,27,28]

Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs

Although older studies have not found an association between *in utero* ARV exposure and malignances, follow-up was limited to early childhood.[1,2,24] Animal studies have reported potential trans-placental genotoxicity of nucleoside analogue therapy in monkeys and micronucleated erythrocytes have been identified among infants with *in utero* nucleoside analogue exposure.[29,30] In an initial report from the French Perinatal Cohort in 2008, which included cross-check with the French National Cancer Registry, the incidence of cancer among 9,127 HIV-exposed uninfected children (median age 5.4 years) was not significantly different from that expected for the general population; however, the relative risk of cancer for children exposed to a didanosine/lamivudine combination was higher than that for zidovudine monotherapy.[31] An updated report from the French Perinatal Cohort described 21 cancers in 15,163 HIV-uninfected children (median age 9.9 years) exposed *in utero* to HIV and at least one NRTI drug.[32] While the total number of cases was not significantly different than expected for the general population, didanosine exposure was noted in a third of children who developed cancer, with a 5.5 hazard (95% CI, 2.1–14.4) of cancer with first trimester didanosine exposure. Continued follow-up of HIV- and ARV-exposed uninfected children is needed to evaluate the potential risk of cancer as these children age into adulthood.

Potential Immunologic Dysfunction

The potential impact of HIV exposure on the immune system of an uninfected infant is unclear. One study reported lower CD4 T lymphocyte (CD4) cell counts in HIV-exposed uninfected infants born to mothers whose viral load at the time of delivery was >1,000 copies/mL compared to HIV-exposed uninfected infants whose mothers had a viral load <50 copies/mL at the time of delivery.[33] The French Perinatal Cohort Group has reported an increased risk of serious bacterial infections with encapsulated organisms in HIV-exposed infants born to mothers with low CD4 number near the time of delivery.[34] Other data suggest that exposure to HIV *in utero* may be associated with alterations in CD4 and CD8 cell-mediated immune responses in infants to vaccines and non-specific antigens in infants.[35]

Recent data from Botswana also show higher rates of morbidity and mortality in HIV-exposed uninfected infants and children than in HIV-unexposed infants.[36-38] Further study is needed regarding the reproducibility of these data, and whether they are primarily associated with advanced maternal HIV disease.

Conclusion

Ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and infant feeding approaches include 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 much of the available follow-up data to date relate to in utero exposure to antenatal zidovudine or other NRTIs alone, and most HIV-infected pregnant women currently receive ART regimens, it is critical that studies to evaluate potential adverse effects of *in utero* drug

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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.

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Appendix A: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission (Last updated October 26, 2016; last reviewed October 26, 2016)

One of the major achievements in HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial that administration of zidovudine to pregnant women and their infants could reduce the risk of perinatal transmission by nearly 70%.[1] Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. In addition, a number of studies have examined optimal regimens to reduce postnatal transmission during breastfeeding. This Appendix provides a table summarizing results of major studies of antiretroviral (ARV) interventions to prevent perinatal transmission (see Supplemental Table 1) and a brief discussion of lessons learned. In many cases, the 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 the 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.[2,3] 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.[4-13] 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 during only the antepartum and intrapartum periods or the intrapartum and postpartum periods.[5,14,15]

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, even when lacking an infant prophylaxis component.[10-12] However, longer-duration antenatal zidovudine prophylaxis, beginning at 28 weeks' gestation, is more effective than shorter-duration zidovudine prophylaxis, beginning at 35 weeks' gestation.[13] The PHPT-5 trial demonstrated a significantly increased risk of transmission associated with less than 8 weeks of prophylaxis during pregnancy.[16] The European National Study of HIV in Pregnancy and Childhood demonstrated that each additional week of an antenatal, triple-drug regimen corresponded to a 10% reduction in risk of transmission.[17] More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.[13]

The PROMISE study is the first randomized clinical trial to demonstrate the superiority of antiretroviral therapy (ART) over zidovudine-based prophylaxis for prevention of *in utero* transmission in women with CD4 T lymphocyte (CD4) cell counts >350 cells/mm^3.[18] Pregnant women were randomized to one of three study arms:

- Zidovudine plus single-dose nevirapine at delivery plus postpartum tenofovir disoproxil fumarate (TDF)/emtricitabine tail
- Zidovudine plus lamivudine plus lopinavir/ritonavir
- TDF plus emtricitabine plus lopinavir/ritonavir

The rate of perinatal transmission through 14 days of life was significantly lower among women receiving triple ARV prophylaxis (0.6%, 9 infections among 1,710 infants) compared with those in the zidovudine arm (1.8%, 25 infections among 1,326 infants).

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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 epidemiological data in resource-rich countries.[19] 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
- 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)
- 6 weeks of zidovudine plus lamivudine and nelfinavir given from birth through age 2 weeks.[20]

The study demonstrated that both the dual- and triple-combination regimens reduced the 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 born to women at increased risk for transmission including those with limited or no prenatal ART, inadequate adherence, or detectable viremia, with the dual regimen of zidovudine plus 3 doses of nevirapine in the first week of life being preferred because of 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.

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.[21] 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.[22] Clinical trials have demonstrated that both infant prophylaxis (daily infant nevirapine, lamivudine, and ritonavir-boosted lopinavir) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease postnatal infection (see Supplemental Table 1).[2,23-31] Hypothetically, 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

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several weeks to months before full viral suppression in breast milk is achieved.[27,32] 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).[22] Finally, both infant nevirapine prophylaxis and maternal triple-drug prophylaxis during breastfeeding may be associated with the 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.[33-37]

Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 1 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
Pediatric AIDS Clinical Trials Group (PACTG) 076; United States, France;[1] Formula feeding	ZDV vs. placebo	Long (from 14 weeks) IV IP	Long (6 weeks); infant only	Perinatal transmission at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).
CDC Short-Course ZDV Trial; Thailand;[12] Formula feeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	Perinatal transmission at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).
DITRAME (ANRS 049a) Trial; Ivory Coast, Burkina Faso;[11,38] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother only	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%, respectively, 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).
CDC Short-Course ZDV Trial; Ivory Coast;[10,11] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	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).
PETRA Trial; South Africa, Tanzania, Uganda;[5] Breastfeeding and formula feeding	AP/IP/PP ZDV plus 3TC vs. IP/PP ZDV plus 3TC vs. IP-only ZDV plus 3TC vs. Placebo	Short (from 36 weeks) Oral IP	Short (1 week); mother and infant	Perinatal transmission was 5.7% at 6 weeks for AP/IP/PP ZDV plus 3TC, 8.9% for IP/PP ZDV plus 3TC, 14.2% for IP-only ZDV plus 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 plus 3TC, 18.1% for IP/PP ZDV plus 3TC, 20.0% for IP-only ZDV plus 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).

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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 2 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
HIVNET 012 Trial; Uganda;[4] Breastfeeding	SD NVP vs. ZDV	No AP ARV Oral IP: • SD NVP vs. oral ZDV	SD NVP within 72 hours of birth, infant only vs. ZDV (1 week); infant only	Perinatal transmission was 11.8% in NVP arm vs. 20.0% in ZDV arm at 6–8 weeks (42% efficacy) and 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).
SAINT Trial; South Africa;[6] Breastfeeding and formula feeding	SD NVP vs. ZDV plus 3TC	No AP ARV Oral IP: • SD NVP vs. ZDV plus 3TC	SD NVP within 48 hours of birth, mother and infant vs. ZDV plus 3TC (1 week); mother and infant	Perinatal transmission was 12.3% in SD NVP arm vs. 9.3% in ZDV plus 3TC arm at 8 weeks (difference not statistically significant, $P = 0.11$).
Perinatal HIV Prevention Trial (PHPT-1); Thailand;[13] Formula feeding	Four ZDV regimens with different durations of AP and infant PP administration; no placebo	Long (from 28 weeks), short (from 36 weeks) Oral IP	Long (6 weeks), short (3 days); infant only	Short-short arm was stopped at interim analysis (10.5%). Perinatal transmission was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm at 6 months (no statistical difference). *In utero* transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).
PACTG 316 Trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States;[21] Formula feeding	SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV plus other ARV drugs (77% combination therapy)	Non-study ARV regimen Oral IP: • Placebo vs. SD NVP plus IV ZDV	Placebo vs. SD NVP within 72 hours of birth plus non-study ARV drugs (ZDV); infant only	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 *in utero*).
Perinatal HIV Prevention Trial (PHPT-2); Thailand;[39] Formula feeding	ZDV alone vs. ZDV plus maternal and infant SD NVP vs. ZDV plus maternal SD NVP	ZDV from 28 weeks Oral IP: • ZDV alone, or • ZDV plus SD NVP	ZDV for 1 week with or without SD NVP; infant only	ZDV-alone arm was stopped because of higher perinatal transmission than the NVP-NVP arm (6.3% vs. 1.1%, respectively). In arms in which the mother received SD NVP, the perinatal transmission rate did not differ significantly between the infant receiving or not receiving SD NVP (2.0% vs. 2.8%, respectively).
DITRAME Plus (ANRS 1201.0) Trial; Ivory Coast;[15] Breastfeeding and formula feeding	Open label, ZDV plus SD NVP	ZDV from 36 weeks Oral IP: • ZDV plus SD NVP	SD NVP plus ZDV for 1 week; infant only	Perinatal transmission was 6.5% (95% CI, 3.9% to 9.1%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) Trial; Ivory Coast;[15] Breastfeeding and formula feeding	Open label, ZDV plus 3TC plus SD NVP	ZDV plus 3TC from 32 weeks (stopped at 3 days PP) Oral IP: • ZDV plus 3TC plus SD NVP	SD NVP plus ZDV for 1 week; infant only	Perinatal transmission was 4.7% (95% CI, 2.4% to 7.0%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.

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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 3 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
NVAZ Trial; Malawi;[7] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP or IP ARV (latecomers)	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission was 15.3% in SD NVP plus ZDV arm and 20.9% in SD NVP-only arm at 6–8 weeks. Perinatal transmission rates at 6–8 weeks among infants who were HIV uninfected at birth were 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP plus ZDV Trial; Malawi;[8] Breastfeeding	Neonatal SD NVP vs. SD NVP plus ZDV	No AP ARV Oral IP: • SD NVP	SD NVP with or without ZDV for 1 week; infant only	Perinatal transmission was 16.3% in NVP plus ZDV arm and 14.1% in SD NVP-only arm at 6–8 weeks (difference not statistically significant). Perinatal transmission rates at 6–8 weeks among infants who were HIV uninfected at birth were 6.5% and 16.9%, respectively.
Post-Exposure Infant Prophylaxis; South Africa;[9] Breastfeeding and formula feeding	Neonatal SD NVP vs. ZDV for 6 weeks	No AP or IP ARV	SD NVP vs. ZDV for 6 weeks	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 ($P = 0.03$).
Mashi; Botswana;[40,41] Breastfeeding and formula feeding	Initial: • Short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding Revised: • Short-course ZDV plus infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 counts <200 cells/mm^3 receive combination therapy.	First Randomization: • ZDV from 34 weeks Oral IP: • ZDV plus either SD NVP or placebo	Second Randomization: • Breastfeeding plus ZDV (infant) 6 months plus SD NVP; infant only, vs. • Formula feeding plus ZDV (infant) 4 weeks plus SD NVP; infant only	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 plus 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 plus infant SD NVP arm and 3.7% in maternal placebo plus infant SD NVP arm (no significant difference; no interaction with mode of infant feeding). Perinatal transmission at 7 months was 9.1% in breastfeeding plus ZDV arm and 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding plus ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% in the breastfeeding plus ZDV arm vs. 14.2% in the formula-feeding arm.

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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 4 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
SWEN; Uganda, Ethiopia, India;[24] 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.
PEPI-Malawi Trial; Malawi;[23] Breastfeeding	SD NVP plus 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 plus ZDV for 1 week (control) vs. Control plus NVP for 14 weeks vs. Control plus 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;[26] 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;[29] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 count >250 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 count >250 cells/mm^3) 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;[25] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 count >200 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 count >200 cells/mm^3) for 6 months, infant ZDV/3TC for 1 week	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.

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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 5 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
Kesho Bora; Multi-African;[28] Breastfeeding primarily	Antepartum ZDV/SD NVP with no postnatal prophylaxis vs. Maternal triple-drug prophylaxis in women with CD4 counts 200–500 cells/mm^3	Arm 1: • ZDV/3TC/LPV/r Arm 2: • ZDV plus SD NVP From 28 weeks through labor	Arm 1: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 1 week Arm 2: • Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis), infant SD NVP plus 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 counts 350–500 cells/mm^3, 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).
Mma Bana; Botswana;[2] Breastfeeding	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 counts >200 cells/mm^3	Arm 1: • ZDV/3TC/ABC Arm 2: • ZDV/3TC/LPV/r From 26 weeks through labor	Arm 1: • Maternal ZDV/3TC/ABC for 6 months, infant SD NVP plus ZDV for 4 weeks Arm 2: • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 4 weeks	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).
BAN; Malawi;[27,42] Breastfeeding	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 counts ≥250 cells/mm^3	No AP drugs IP Regimens *Arm 1 (Control):* • ZDV/3TC plus SD NVP *Arm 2:* • ZDV/3TC plus SD NVP *Arm 3:* • ZDV/3TC plus SD NVP	Arm 1 (Control): • Maternal ZDV/3TC for 1 week, infant SD NVP plus ZDV/3TC for 1 week Arm 2: • Control as above, then maternal ZDV/3TC/LPV/r for 6 months Arm 3: • Control as above, then infant NVP for 6 months	Postnatal Infection in Infants Uninfected at Age 2 Weeks: • 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), and 1.7% in infant NVP Arm 3 (P <0.001 vs. control). • Perinatal transmission at age 48 weeks was 7.0% in control Arm 1, 4.0% in maternal triple-drug prophylaxis Arm 2 (P = 0.0273 vs. control), and 4% in infant NVP Arm 3 (P = 0.0027 vs. control). 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).

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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 6 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;[37,43] Breastfeeding	Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks. Arm 1: • Daily infant NVP from age 6 weeks through age 6 months Arm 2: • Daily infant placebo from age 6 weeks through age 6 months	In infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3% to 1.8%) in the extended NVP Arm 1 and 2.4% (1.3% to 3.6%) in the placebo Arm 2 (P = 0.048). 18-month postnatal infection rates were 2.2% (1.1% to 3.3%) in the extended NVP Arm 1 and 3.1% (1.9% to 4.4%) in the placebo Arm 2 (P = 0.28). HIV infection and mortality rates did not differ between arms at any age through 18 months. At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-drug ARV regimen for the treatment of HIV. 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 the extended NVP Arm 1 (0.5%) and placebo Arm 2 (0%). For mothers with CD4 counts >350 cells/mm^3 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% to 1.5%) in the extended NVP Arm 1 and 2.8% (1.3% to 4.4%) in the placebo Arm 2 (P = 0.014).
NICHD-HPTN 040/ PACTG 1043 Trial; Brazil, Argentina, South Africa, United States;[44] Formula feeding	Infant prophylaxis with 6 weeks ZDV vs. 6 weeks infant ZDV plus 3 doses of NVP in first week of life vs. 6 weeks infant ZDV plus 2 weeks 3TC/NFV	No AP drugs If mother presented early enough, IV ZDV during labor through delivery	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 age 2 weeks	IP HIV transmission among infants with negative HIV test at birth: 4.8% (3.2% to 7.1%) with ZDV (Arm 1) vs. 2.2% (1.2% to 3.9%) with ZDV plus NVP (Arm 2) (P = 0.046 compared with Arm 1) vs. 2.4% (1.4% to 4.3%) with 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% to 14.0%) with ZDV (Arm 1) vs. 7.1% (5.2% to 9.6%) with ZDV plus NVP (Arm 2) (P = 0.035 compared with Arm 1) vs. 7.4% (5.4% to 9.9%) with 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 <0.001).

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Supplemental Table 1. Results of Major Studies on Antiretroviral Interventions to Prevent Perinatal HIV Transmission (page 7 of 7)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
ANRS 12174 Trial; Burkina Faso, South Africa, Uganda, Zambia;[30,31] Breastfeeding	Compared 2 infant ARV prophylaxis regimens during breastfeeding; infants testing PCR-negative at birth, born to mothers with CD4 counts >350 cells/mm^3	As per standard of care	Arm 1: • Daily infant LPV/r from 1 week through 50 weeks of age Arm 2: • Daily infant 3TC from 1 week through 50 weeks of age	Postnatal Infection in Infants Uninfected at Birth: • Postnatal transmission at age 50 weeks was 1.4% (0.70–2.76) in Arm 1 and 1.5% (0.80–2.91) in Arm 2 (*P* = 0.83). • HIV-free survival was 96.5% (84.6–97.7) in Arm 1 and 96.3% (94.4–975) in Arm 2 (*P* = 0.85).
PROMOTE; Uganda;[45] Breastfeeding	Compared 2 triple-ARV regimens; no CD4 restriction	Arm 1: • AZT/3TC/LPV/r Arm 2: • AZT/3TC/EFV • ARVs started at 12–28 weeks' gestation and continued through labor	Randomized regimen continued postpartum through 1 year of breastfeeding	HIV-free survival was 92.9% in the LPV/r arm vs. 97.2% in the EFV arm (*P* = 0.10). Only 2 of 374 liveborn infants acquired infection, both in the LPV/r arm.
PROMISE; India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe;[18] Breastfeeding and formula feeding (antepartum component)	Compared 2 ARV regimens during pregnancy among women >14 weeks gestation and CD4 counts ≥350 cells/mm^3	Arm 1: • ZDV during pregnancy plus SD NVP plus TDF plus FTC at delivery Arm 2: • ZDV plus 3TC plus LPV/r Arm 3: • TDF plus FTC plus LPV/r	Arm 1: • TDF/FTC tail continued for 6–14 days postpartum Arms 2 and 3: • Triple-drug regimen continued for 6–14 days postpartum Infants received once-daily NVP for 6 weeks.	Infant HIV Infection Rates by Age 14 Days *Arm 1:* • 1.8% (25/1,386) *Arm 2:* • 0.5% (7/1,385) *Arm 3:* • 0.6% (2/325) Combined triple-ARV arms vs. Arm 1 difference in perinatal transmission risk: -1.28% (95% CI, -2.11% to -0.44%)

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CI = confidence interval; EFV = efavirenz; FTC = emtricitabine; IP = intrapartum; IV = intravenous; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; PCR = polymerase chain reaction; PP = postpartum; SD = single-dose; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • 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.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Data are available from clinical trials in human pregnancy for the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleotide NRTI tenofovir disoproxil fumarate (TDF). The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. TDF, 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 the Recommendations for Use of Antiretroviral Drugs During Pregnancy and Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants section.

Abacavir (Ziagen, ABC)

(Last updated April 29, 2016; last reviewed April 29, 2016)

The available human and animal data suggest that abacavir does not increase the risk of major birth defects overall compared with the background rate.[1]

Animal Studies

Carcinogenicity
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.[1]

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).[1]

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 (i.e., increased resorptions and 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).[1]

Placental and Breast Milk Passage
Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.[1,2]

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Human Studies in Pregnancy

Pharmacokinetics

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.[3] A population pharmacokinetics (PK) study (266 samples from 150 pregnant women) found no effect of any co-variate (including age, body weight, pregnancy or gestational age) on abacavir PK.[4] Thus, no dose adjustment for abacavir is needed during pregnancy.

Placental and Breast Milk Passage

Placental transfer of abacavir is high, with cord blood to maternal plasma concentration ratios at delivery of approximately 1.0.[3,5] In the Mma Bana study,[2] 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 of 9 breastfeeding infants whose mothers were receiving abacavir.

Teratogenicity

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 2.9% (29 of 993 births; 95% CI, 2.0% to 4.2%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[6] There was no association of birth defects with first-trimester exposure to abacavir in the SMARTT study (aOR 0.94 [0.53–1.65]),[7] in the French Perinatal Study (aOR 1.01, [0.73–1.41]),[8] or in a series of 897 births to HIV-infected women in Spain between 2000 to 2009 (aOR 0.99, [0.34–2.87]).[9]

Safety

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. Patients who test positive for HLA-B*5701 are at highest risk; HLA screening should be done before initiation of abacavir. Two meta-analyses have confirmed the association of this genotype and the hypersensitivity reaction.[10,11]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/3TC/ZDV) *Trizivir* (ABC/DTG/3TC) *Triumeq*	ABC (Ziagen): *Tablet:* • 300 mg *Solution:* • 20 mg/mL Epzicom: • ABC 600 mg plus 3TC 300-mg tablet Trizivir: • ABC 300 mg plus 3TC 150 mg plus ZDV 300-mg tablet Triumeq: • ABC 600 mg plus DTG 50 mg plus 3TC 300-mg tablet	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 *Triumeq:* • 1 tablet daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] 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.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 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:** <0.3

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; PK = pharmacokinetic; ZDV = zidovudine

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Didanosine (Videx, ddI)

(Last updated April 29, 2016; last reviewed April 29, 2016)

Didanosine is classified as Food and Drug Administration (FDA) Pregnancy Category B.[1]

Animal Studies

Carcinogenicity Studies
Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies of 0.7 to 1.7 times human exposure in mice and 3 times human exposure in rats have been negative.[1]

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.

Placental and Breast Milk Passage
A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta.

Human Studies in Pregnancy

Pharmacokinetics
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.[2] The drug was well tolerated during pregnancy by the women and the fetuses. Pharmacokinetic (PK) parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

Placental and Breast Milk Passage
Placental transfer of didanosine was low-moderate in a Phase I/II safety and PK study.[2] This was confirmed in a study of 100 HIV-infected pregnant women who were receiving nucleoside reverse transcriptase inhibitors (NRTIs) (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.[3]

It is not known if didanosine is excreted in human breast milk.

Teratogenicity
The French Perinatal Cohort reported an association of head and neck birth defects with first-trimester exposure to didanosine (0.5%, AOR = 3.4 (95% Confidence Interval [CI] 1.1–10.4), $P = 0.04$).[4] The PHACS/SMARTT cohort found no association between any NRTIs and birth defects.[5] Among 897 births to HIV-infected women in a Spanish cohort, there was no significant difference in the rate of birth defects between first-trimester compared to the second- and third-trimester exposure (OR 0.61, 95% CI, 0.16, 2.27).[6] Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.7% (20 of 423 births; 95% CI, 2.9% to 7.2%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[7] 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.

Safety
Lactic acidosis, fatal in some cases, has been described in pregnant women receiving the combination of

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didanosine and stavudine along with other ARV agents;[8-10] 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.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name.*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Didanosine (ddI) *Videx* *Videx EC*	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	Standard Adult Doses *Body Weight ≥60 kg:* • 400 mg once daily *With TDF:* • 250 mg once daily; take 1/2 hour before or 2 hours after a meal. *Body Weight <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.	Low-moderate placental transfer to fetus.[b] In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddI compared to general population was noted after both first-trimester (20/423, 4.7%; 95% CI, 2.9% to 7.2%) and later exposure (20/461, 4.3%; 95% CI 2.7% to 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

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 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:** <0.3

Key to Acronyms: APR = Antiretroviral Pregnancy Registry; CI = confidence interval; d4T = stavudine; ddI = didanosine; EC = enteric coated; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Emtricitabine (Emtriva, FTC)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Emtricitabine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Emtricitabine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term carcinogenicity studies of oral 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.[1]

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 and male mice and 140-fold higher in male rats than human exposure at the recommended therapeutic dose.[1]

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.[1]

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.[2]

Human Studies in Pregnancy

Pharmacokinetics

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.[3] Emtricitabine exposure was modestly lower during the third trimester (8.6 mcg*h/mL [5.2–15.9]) compared with the postpartum period (9.8 mcg*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 52 ng/mL [14–180]) compared with the postpartum period (86 ng/mL [<10 to 306]). In the IMPAACT P1026s study, similar alterations were seen, but the 24-hour, post-dose levels were well above the inhibitory concentration 50% (IC_{50}) in all patients.[4] Similar differences in PK parameters of emtricitabine among women during pregnancy or after delivery were found in the PACTG 394 study[5] and in a European study.[6,7] The increase in emtricitabine clearance in pregnancy correlated with the normal pregnancy-related increase in glomerular filtration rate.[7] These changes are not believed to be large enough to warrant dosage adjustment during pregnancy.

Placental and Breast Milk Passage

Emtricitabine has been shown to have high 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).[3] In a study of 15 women who received emtricitabine during pregnancy, the mean cord-to-maternal-blood ratio was 1.2 (90% confidence interval [CI], 1.0–1.5).[4] In 8 women who were given a single dose of 600 mg emtricitabine with 900 mg tenofovir disoproxil fumarate (TDF), 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).[5]

Emtricitabine is excreted into human milk. In a study in the Ivory Coast, 5 HIV-infected women who exclusively breastfed their newborn infants were given 400 mg emtricitabine, 600 mg TDF, and 200 mg

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nevirapine at onset of labor, followed by 200 mg emtricitabine and 300 mg TDF 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 IC_{50} for HIV-1.[8]

Teratogenicity/Developmental Toxicity

In a study of pregnancies occurring during an HIV pre-exposure prophylaxis (PrEP) trial in which HIV-uninfected participants were randomized to placebo, TDF, or TDF plus emtricitabine, there was no increase in congenital anomalies in the TDF-plus-emtricitabine arm.[9] There was no overall difference in the rate of pregnancy loss in the TDF-plus-emtricitabine or TDF-alone arms of this PrEP study. In a large French cohort, emtricitabine exposure in the first trimester was associated with lower risk of birth defects.[10] In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increase in cardiovascular and genitourinary defects (the most common classes). No such increase in birth defects has been observed with emtricitabine. Among cases of first-trimester emtricitabine exposure reported to the APR, the prevalence of birth defects was 2.4% (47 of 1,984 births; 95% CI, 1.7% to 3.1%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[11]

Excerpt from Table 8[a] (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Emtricitabine (FTC) *Emtriva* (FTC/TDF) *Truvada* (FTC/TDF/EFV) *Atripla* (FTC/TDF/RPV) *Complera* (FTC/TDF/EVG/COBI) *Stribild* (FTC/TAF/RPV *Odefsey* (FTC/TAF/EVG/COBI) *Genvoya*	Emtriva (FTC) *Capsules:* • 200 mg *Oral Solution:* • 10 mg/mL Truvada: • FTC 200 mg plus TDF 300 mg tablet Atripla: • FTC 200 mg plus TDF 300 mg plus EFV[c] 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 Odefsey: • FTC 200 mg plus TAF 25 mg plus RPV 25 mg tablet Genvoya: • FTC 200 mg plus TAF 10 mg plus EVG 150 mg plus COBI 150 mg tablet	Standard Adult Dose(s) *Emtriva (FTC)* *Capsule:* • 200 mg once daily without regard to food *Oral Solution:* • 240 mg (24 mL) once daily without regard to food Truvada: • 1 tablet once daily without regard to food Atripla: • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. Complera: • 1 tablet once daily with food Stribild: • 1 tablet once daily with food Odefsey: • 1 tablet once daily with food Genvoya: • 1 tablet once daily with food PK in Pregnancy: • PK of FTC not significantly altered in pregnancy. Dosing in Pregnancy: • No change in FTC dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). If HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.

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Excerpt from Table 8[a] (page 2 of 2)

[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:** <0.3

[c] See Teratogenicity for discussion of EFV and risks in pregnancy.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Lamivudine (Epivir, 3TC)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Available evidence does not suggest that lamivudine use by pregnant women is associated with an increased risk of adverse fetal or pregnancy outcomes.

Animal Studies

Carcinogenicity

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.[1]

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.[1]

Teratogenicity/Developmental Toxicity

There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits.

Early embryo lethality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.[1]

Human Studies in Pregnancy

Pharmacokinetics

Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in two separate studies.[2,3] 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.[4] 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 adults.[4] Thus, no dose adjustment in pregnancy is necessary.

Placental and Breast Milk Passage

Lamivudine readily crosses the placenta in humans, achieving cord blood levels comparable to maternal concentrations.[3] 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.[4] Other studies have also noted accumulation of lamivudine in amniotic fluid due to urinary excretion of lamivudine by the fetus into amniotic fluid.[2]

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.[5] In infants who were exposed to lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (IC_{50} of lamivudine against wild-type HIV = 0.6–21 ng/mL).

Teratogenicity/Developmental Toxicity

In a large French cohort, lamivudine exposure in the first trimester was associated with an increased risk of overall birth defects (adjusted odds ratio = 1.37; 95% confidence interval [CI], 1.06–1.73) but there was no organ system or specific birth defect that predominated.[6] However, in the Antiretroviral Pregnancy Registry (APR), 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 cardiovascular and

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genitourinary defects (the most common classes). No such increase in birth defects has been observed with lamivudine. Among cases of first-trimester lamivudine exposure reported to the APR, the prevalence of birth defects was 3.1% (143 of 4,566 births; 95% CI, 2.6% to 3.7%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[7]

Other Pregnancy Outcomes

An analysis of APR data demonstrated lower risk of spontaneous abortions, induced abortions, and preterm births for lamivudine-containing regimens compared with non-lamivudine antiretroviral regimens.[8]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Lamivudine (3TC) *Epivir* (3TC/ZDV) *Combivir* (3TC/ABC) *Epzicom* (3TC/ZDV/ABC) *Trizivir* (3TC/ABC/DTG) *Triumeq*	3TC (Epivir) *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 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 Triumeq: • 3TC 300 mg plus ABC 600 mg plus DTG 50-mg tablet	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 *Triumeq:* • 1 tablet once daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If HBV-coinfected, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.

[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:** <0.3

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; HBV = hepatitis B virus; PK = pharmacokinetic; ZDV = zidovudine

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Stavudine (Zerit, d4T)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Stavudine is classified as Food and Drug Administration (FDA) Pregnancy Category C.

Animal Studies

Carcinogenicity

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.[1]

Reproduction/Fertility

Stavudine has not been shown to have an effect on reproduction or fertility in rodents. No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.[1] A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100 µM and of post-blastocyst development at 10 µM.[2]

Teratogenicity/Developmental Toxicity

No evidence of teratogenicity was noted in rats or rabbits with exposures (based on C_{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.[1]

Placental and Breast Milk Passage

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.[1]

In primates (pig-tailed macaques), fetal/maternal plasma concentrations were approximately 0.80.[3] Stavudine is excreted into the breast milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

In a Phase I/II safety and pharmacokinetic (PK) study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332), both drugs were well tolerated, with stavudine PK parameters similar to those in non-pregnant adults.[4]

Placental and Breast Milk Passage

Stavudine crosses the human placenta, resulting in a cord/maternal blood concentration of 1.0–1.3.[5] Stavudine also crosses into human breast milk, resulting in breast milk/maternal plasma concentrations of 1.0 to 1.76. Concentrations in nursing infants were negligible.[6,7]

Teratogenicity/Developmental Toxicity

No association was found between first-trimester exposure to stavudine and birth defects in a large French

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cohort study that had 70% power to detect an increased adjusted odds ratio of 1.5.[8] In the Antiretroviral Pregnancy Registry (APR), 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 APR, the prevalence of birth defects was 2.6% (21 of 810 births; 95% CI, 1.6% to 3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.[9]

Other Safety Data

Lactic acidosis, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents.[10-12] 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 Recommendations for Use of Antiretroviral Drugs During Pregnancy and Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants). These drugs should not be prescribed together for pregnant women.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Stavudine (d4T) *Zerit*	d4T (Zerit) *Capsules:* • 15 mg • 20 mg • 30 mg • 40 mg *Oral Solution:* • 1 mg/mL following reconstitution	Standard Adult Dose(s)[d] *Body Weight ≥60 kg:* • 40 mg twice daily without regard to meals *Body Weight <60 kg:* • 30 mg twice daily without regard to meals PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). d4T should not be used with ddI or ZDV. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.

[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:** <0.3

[c] See Teratogenicity for discussion of EFV and risks in pregnancy.

[d] WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: d4T = stavudine; ddI = didanosine; PK = pharmacokinetic; WHO = World Health Organization; ZDV = zidovudine

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Tenofovir Alafenamide (Genvoya, Odefsey, Descovy, TAF)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Tenofovir alafenamide (TAF), an orally bioavailable form of tenofovir, has insufficient data on human use in pregnancy to inform a drug-associated risk determination for birth defects or miscarriage.

Animal Studies

Carcinogenicity

Because TAF is rapidly converted to tenofovir, and tenofovir exposure in rats and mice is lower after TAF administration compared to tenofovir disoproxil fumarate (TDF) administration, carcinogenicity studies were performed with TDF. Long-term oral carcinogenicity studies of tenofovir in mice and rats were carried out at 167 times (mice) and 55 times (rats) tenofovir exposure compared to that seen after TAF administration at recommended doses in humans. In female mice, liver adenomas were increased. In rats, no carcinogenic findings were observed.[1,2]

Reproduction/Fertility

Reproduction studies have been performed in rats and rabbits at exposures similar to and 53 times higher than human exposure, respectively, and revealed no evidence of impaired fertility or mating performance associated with tenofovir.[1,2]

Teratogenicity/Developmental Toxicity

No effects on early embryonic development were seen when TAF was administered to male or female rats at 62 times the human therapeutic exposure.[1-3]

Placental and Breast Milk Passage

Rat studies demonstrated secretion of tenofovir in breast milk after administration of TDF; whether TAF is present in animal milk is unknown.[1,3]

Human Studies in Pregnancy

Pharmacokinetics

No pharmacokinetic studies of TAF have been reported in pregnant women.

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of TAF in humans.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, no exposures to TAF have been reported yet.[4]

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tenofovir Alafenamide (TAF) (TAF/FTC/EVG/COBI) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/FTC) *Descovy*	Genvoya: • TAF 10 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet Odefsey: • TAF 25 mg plus FTC 200 mg plus RPV 25 mg tablet Descovy: • TAF 25 mg plus FTC 200 mg tablet	Standard Adult Dose *Genvoya, Odefsey:* • 1 tablet once daily with food *Descovy:* • 1 tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without pharmacoenhancers PK in Pregnancy: • No PK studies in human pregnancy Dosing in Pregnancy: • Insufficient data to make dosing recommendation	No data on placental transfer of TAF are available. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats. Renal function should be monitored because of potential for renal toxicity.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Antiretroviral 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:** <0.3

[c] See Teratogenicity for discussion of EFV and risks in pregnancy.

Key to Acronyms: COBI = cobicistat; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Tenofovir Disoproxil Fumarate (Viread, TDF)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Tenofovir disoproxil fumarate (TDF), an orally bioavailable form of tenofovir, is classified as Food and Drug Administration Pregnancy Category B.[1]

Animal Studies

Carcinogenicity

Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir 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.[1]

Reproduction/Fertility

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose, respectively, 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.[1]

Teratogenicity/Developmental Toxicity

Chronic exposure of fetal monkeys to tenofovir at high doses (exposure equivalent to 25 times the area under the curve (AUC) achieved with therapeutic dosing in humans) resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment.[1]

Placental and Breast Milk Passage

Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir crosses the placenta.[2]

Human Studies in Pregnancy

Pharmacokinetics

In a retrospective population pharmacokinetic study of 46 pregnant women and 156 non-pregnant women receiving combination regimens including tenofovir, pregnant women had a 39% higher apparent clearance of tenofovir compared with non-pregnant women, which decreased slightly but significantly with increasing age.[3] In a P1026s study of 37 pregnant women receiving TDF-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum, the percentage of women with tenofovir AUC exceeding the target of 1.99 µg*hour/mL (the 10th percentile in non-pregnant adults) was lower in the third trimester (73%, 27 of 37 women) than postpartum (84%, 27 of 32 women); trough levels and AUCs were 17% to 20% lower during the third trimester compared to postpartum. The median weight of the women below the target exposure (97.9 kg) was significantly higher than the median weight of the women who met the target exposure (74.2 kg).[4] In another study of 34 women receiving TDF plus emtricitabine in the third trimester and postpartum, tenofovir AUC, peak, and trough were all about 25% lower in pregnant women compared to postpartum women, but these decreased exposures were not associated with virologic failure.[5] Standard dosing during pregnancy continues to be recommended.

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Placental and Breast Milk Passage

In studies of pregnant women on chronic TDF, the cord-to-maternal-blood ratio of tenofovir ranged from 0.60 to 1.03, indicating high placental transfer.[4-7] In studies of pregnant women receiving single-dose TDF (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.[8,9] Intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of 600 mg TDF with 400 mg emtricitabine, but intracellular tenofovir-diphosphate was detectable in only 2 (5.5%) of 36 infants.[10]

Sixteen breast milk samples were obtained from 5 women who received 600 mg TDF 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, resulting in nursing infants ingesting an estimated daily amount of tenofovir that corresponds to 0.03% of the proposed oral dose of TDF for neonates.[11] Because the form of tenofovir in breastmilk is expected to have lower bioavailability than TDF, these exposures are likely overestimates. No studies have measured tenofovir blood levels in infants breastfed by women taking TDF.

Reproduction/Fertility

A retrospective analysis of 7,275 women (1,199 receiving TDF-based 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.[12]

Teratogenicity/Developmental Toxicity

In a study of 431 pregnancies occurring during an HIV pre-exposure prophylaxis trial in which HIV-uninfected women were randomized to placebo, TDF, or TDF plus emtricitabine, there was no difference in risk of congenital anomalies between the TDF-containing and placebo arms.[13] No association was seen between maternal TDF and offspring birth defects in three large U.S. cohorts: PACT 219/219C (n = 2,202 with 214 first-trimester TDF exposures), P1025 (n = 1,112 with 138 first-trimester TDF exposures),[14,15] and Pediatric HIV AIDS Cohort Study (n = 2,580 with 431 first-trimester TDF exposures).[16] In the French Perinatal Cohort, no association was found between birth defects and TDF with a power of 70% for an odds ratio of 1.5 (n = 13,124 with 823 first-trimester TDF exposures).[17] Finally, in the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to TDF in humans have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. No increase in birth defects has been observed with TDF. Among cases of first-trimester TDF exposure reported to the APR, the prevalence of birth defects was 2.3% (60 of 2,608 births; 95% confidence interval [CI], 1.8% to 3.0%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[18]

Other Safety Data

In a United Kingdom cohort of 71 pregnant women receiving TDF, retrospective analysis of serum creatinine and estimated glomerular filtration rate (eGFR) measured throughout pregnancy and 6 weeks after delivery revealed no decline in renal function during pregnancy and normal renal function (>90 mL/min) 6 weeks postpartum (one woman's postpartum eGFR was 60 mL/min).[19]

Among 382 pregnancies occurring in 302 women in Uganda and Zimbabwe participating in the DART trial—approximately two-thirds of whom received TDF through more than 90% of their pregnancies—there were no differences noted in mortality, birth defects, or growth.[20] In the Pediatric HIV/AIDS Cohort Study from the United States, 449 (21%) of the 2,029 HIV-exposed but uninfected infants had *in utero* exposure to TDF, and there was no difference at birth between those exposed to combination drug regimens with or without TDF in low birthweight, small-for-gestational-age, and newborn length-for-age and head circumference-for-age *z*-scores (LAZ and HCAZ, respectively). However, at age 1 year, infants exposed to combination regimens with TDF had a slight but significantly lower adjusted mean LAZ and HCAZ than those without TDF exposure (LAZ: -0.17 vs. -0.03, $P = 0.04$; HCAZ: 0.17 vs. 0.42, $P = 0.02$), but no difference in weight-for-age *z*-score (WAZ). There were no significant differences between those with and

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without TDF 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.[21] In a different U.S. study (P1025), maternal TDF use was similarly not associated with differences in body size parameters at birth; however, among the 1,496 infants followed for 6 months, TDF exposure after the first trimester, relative to no exposure, was associated with being underweight (WAZ <5%) at age 6 months (OR [95% CI]: 2.06 [1.01, 3.95], $P = 0.04$).[22]

In a cross-sectional study of 68 HIV-exposed uninfected children enrolled at ages 1 to 6 years who had *in utero* exposure to combination regimens with (N = 33) or without (N = 35) TDF, evaluation of quantitative bone ultrasound and parameters of bone metabolism gave similar measures between groups.[23] In contrast, a study evaluating whole body dual-energy X-ray absorptiometry scans within 4 weeks of birth among 74 infants exposed to more than 8 weeks of TDF *in utero* and 69 infants with no TDF exposures, the adjusted mean whole body bone mineral content (BMC) was significantly lower in the TDF group by 6.3 g ($P = 0.004$) as was the whole-body-less-head BMC (-2.6 g, $P = 0.056$). The duration and clinical significance of these findings require further longitudinal evaluation.[24]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/FTC) *Truvada* (TDF/FTC/EFV) *Atripla* (TDF/FTC/RPV) *Complera* (TDF/FTC/EVG/COBI) *Stribild*	TDF (Viread) *Tablet:* • 300 mg *Powder:* • 40 mg/1 g oral powder Truvada: • TDF 300 mg plus FTC 200 mg tablet Atripla: • TDF 300 mg plus FTC 200 mg plus EFV[c] 600 mg tablet Complera: • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet Stribild: • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet	Standard Adult Dose *TDF (Viread)* *Tablet:* • 300 mg once daily without regard to food *Powder:* • 8 mg/kg (up to maximum 300 mg), take with food *Truvada:* • 1 tablet once daily without regard to food *Atripla:* • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *Complera:* • 1 tablet once daily with food *Stribild:* • 1 tablet once daily with food PK in Pregnancy: • AUC lower in third trimester than postpartum but trough levels adequate Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). 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 data are conflicting about potential effects on growth outcomes later in infancy. If HBV-coinfected, it is possible that an HBV flare may occur if TDF is stopped; see HIV/Hepatitis B Virus Coinfection. Renal function should be monitored because of potential for renal toxicity.

[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:** <0.3

[c] See Teratogenicity for discussion of EFV and risks in pregnancy.

Key to Acronyms: AUC = area under the curve; COBI = cobicistat; EFV = efavirenz; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Zidovudine (Retrovir, AZT, ZDV)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Zidovudine is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

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.[1] 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 (mice) and 24 times (rats) 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 trans-placental carcinogenicity studies were conducted in mice.[2,3] In one study, zidovudine was administered at doses of 20 mg/kg/day or 40 mg/kg/day from gestational day 10 through parturition and lactation, with postnatal dosing continuing in offspring for 24 months.[3] 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 (~1,000 mg/kg non-pregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 to 18 of gestation.[2] 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 preimplantation mouse embryos can occur, with inhibition of blastocyst and post-blastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses.[4]

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 (100 mg every 4 hours). 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 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 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

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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.

Human Studies in Pregnancy

Pharmacokinetics

Zidovudine pharmacokinetics (PK) are not significantly altered by pregnancy, and standard adult doses are recommended.[5,6] A population PK analysis following oral and intravenous (IV) zidovudine doses during pregnancy and labor found high fetal exposure to zidovudine with current IV intrapartum dosing regimens. Simulations from this modeling suggested that reduced intrapartum zidovudine dosing regimens might provide lower but still adequate fetal zidovudine exposures.[7] However, standard dosing of IV zidovudine during labor continues to be recommended.

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.[8] Zidovudine is excreted into human breast milk with breast milk-to-maternal-plasma zidovudine concentration ratios ranging from 0.44 to 1.35. No zidovudine was detectable in the plasma of the nursing infants, who received zidovudine only via breast milk.[9-11]

Teratogenicity/Developmental Toxicity

In 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.[5,12] Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.[13,14] 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.[15,16] In the PHACS/SMARTT cohort, there was no association between first-trimester exposure and congenital anomalies.[17] 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 3.2% (133 of 4,113 births; 95% CI, 2.7% to 3.8%), compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.[18] Similarly, a series of 897 HIV-exposed infants born in Spain during 2000 through 2009 reported no increase in birth defects among infants with first-trimester zidovudine exposure (aOR 1.21 [0.56–2.63]).[19]

The French Perinatal Cohort reported that first trimester zidovudine exposure was associated with congenital heart defects (1.5% of 3,262 exposures vs. 0.7% of non-exposures; aOR=2.2 [95% CI 1.5–3.2]). In the PRIMEVA trial, female infants of mothers randomized to antepartum treatment with zidovudine/lamivudine/lopinavir/ritonavir had a higher left ventricular shortening fraction at 1 month and increased posterior wall thickness at 1 year, suggestive of myocardial remodeling, when compared to infants whose mothers received lopinavir/ritonavir alone.[20] However, an analysis of cardiac defects among all prenatal zidovudine exposed infants in the Antiretroviral Pregnancy Registry (n = 13,703) reported no difference in the prevalence of ventricular septal defect and congenital heart defects among infants exposed to zidovudine-containing regimens (9/4,000 first trimester, rate 0.23; 22/9,047 later, rate 0.24, $P = 1.00$) and zidovudine-non-containing regimens (2/1,839 first trimester, rate 0.11; 3/538 later, rate 0.56, $P = 0.08$).[21]

Cancer has been observed no more frequently among zidovudine-exposed infants than among other HIV-exposed or HIV-unexposed infants in a long-term follow-up study for the original PACTG 076 study,[22] in prospective cohort studies,[23] and in matches between HIV surveillance and cancer registries.[24,25]

Other Safety Data

In the placebo-controlled perinatal trial PACTG 076, no difference in disease progression was seen between women who received zidovudine and those who received a placebo, based on follow-up through 4 years postpartum.[26]

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No differences in immunologic, neurologic, or growth parameters were seen between PACTG 076 infants with *in utero* zidovudine exposure and those who received a placebo, based on nearly 6 years of follow-up.[12,22]

Mitochondrial dysfunction in mothers and infants exposed to nucleoside reverse transcriptase inhibitors (NRTIs) during pregnancy has been described in some case reports, case series, prospective cohorts, and surveillance systems, but not in others. The result of the dysfunction, although fatal in a few cases, is more often asymptomatic and self-limited (e.g., leukopenia, anemia). At present, while a recognized possibility, the risk of NRTI-associated mitochondrial dysfunction in these mother-infant pairs does not outweigh the clear benefit of these drugs in preventing perinatal HIV transmission.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Zidovudine (ZDV, AZT) *Retrovir* (ZDV/3TC) *Combivir* (ZDV/3TC/ABC) *Trizivir*	ZDV (Retrovir) *Capsule:* • 100 mg *Tablet:* • 300 mg *Oral Solution:* • 10 mg/mL *Intravenous Solution:* • 10 mg/mL Combivir: • ZDV 300 mg plus 3TC 150 mg tablet Trizivir: • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	Standard Adult Dose(s) *ZDV (Retrovir):* • 300 mg BID or 200 mg TID, without regard to food *Active Labor:* • 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery *Combivir:* • One tablet twice daily, without regard to food *Trizivir:* • One tablet twice daily, without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Antiretroviral 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:** <0.3

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; IV = intravenous; PK = pharmacokinetic; TID = three times a day; ZDV = zidovudine

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Non-Nucleoside Reverse Transcriptase Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • 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.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

Five non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) are currently approved: delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Delavirdine is no longer available in the United States.

For information about potential interactions between NNRTIs and methergine, see the Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use section.

Efavirenz (Sustiva, EFV)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Regarding embryo-fetal toxicity, the Food and Drug Administration (FDA) advises women to avoid becoming pregnant while taking efavirenz and health care providers to avoid administration in the first trimester of pregnancy as fetal harm may occur.[1]

Animal Studies

Carcinogenicity

Efavirenz was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A study evaluating genotoxicity of efavirenz in mice noted DNA damage in brain cells after daily dosing for 36 days; no damage was seen in liver, heart, or peripheral blood cells.[2] 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.[1]

Reproduction/Fertility

No effect of efavirenz on reproduction or fertility in rodents has been seen.[1]

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).[1] 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).[3] The malformations

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included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.[1]

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.[1]

Human Studies in Pregnancy

Pharmacokinetics/Pharmacogenomics

In an intensive sampling pharmacokinetic (PK) 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.[4] These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy. A recent review of this study plus four others that measured single efavirenz concentrations in pregnant women found that efavirenz concentrations were not significantly affected by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with efavirenz regimens.[5]

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.[6] 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.[4]

PK interactions between efavirenz and some hormonal contraceptives have been reported, with the potential for failure of the progesterone component, potentially affecting efficacy of emergency contraception, combined oral contraceptive pills, progestin-only pills, and progestin implants.[7-10] A retrospective chart review study suggests that efavirenz may decrease the efficacy of levonorgestrel implants (e.g., Jadelle).[11] Pregnancy occurred among 15 (12.4%) of 115 women on efavirenz using Jadelle, compared to no pregnancies among 208 women on nevirapine-based regimens and no pregnancies among 13 women on lopinavir/ritonavir-based regimens ($P < 0.001$) (see Preconception Counseling and Care). In a prospective clinical trial by Scarsi et al, 3 out of 20 (15%) Ugandan women became pregnant between 36 and 48 weeks with the combination of levonogestrel and efavirenz-based antiretroviral therapy (ART) regimen. In comparison to the ART-naive women, the women on efavirenz-based regimens had lower levonorgestrel PK.[12] Patients should be informed of the potential interactions and possible decreased effectiveness with certain hormonal contraceptives. Barrier contraception should strongly be recommended. A different contraceptive regimen may also be considered. 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.[13] DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval. In addition, intrauterine devices (both copper-containing and levonorgestrel-containing) would be expected to maintain efficacy.

Placental and Breast Milk Passage

In a study of 25 mother-infant pairs, median efavirenz cord blood/maternal blood concentration was 0.49 (range 0.37–0.74).[4] In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery.[14] Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz concentration was significantly higher in maternal plasma than in 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 860 ng/mL and the mean infant plasma efavirenz concentration was 13.1% of maternal plasma concentrations. All infants had detectable plasma concentrations of efavirenz, and 8 of 13 newborns had plasma efavirenz concentrations below the minimum therapeutic concentration of 1000 ng/mL recommended for treatment of HIV-infected adults. In a study of 51 women in

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Nigeria receiving efavirenz 600 mg daily, the median (range) milk/maternal plasma ratio was 0.82 (0.51–1.1) and the median (range) infant efavirenz concentration was 178 (88–340) ng/mL.[15] 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).[16] 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 PK of efavirenz in neonates.

Teratogenicity Data

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2015, birth defects were observed in 21 of 883 live births with first-trimester exposure (2.4%, 95% confidence interval [CI], 1.5% to 3.6%).[17] Although these data provide sufficient numbers of first-trimester exposures to rule out a 2-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 Antiretroviral Pregnancy Registry 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. An undefined abnormality of the cerebral vermis was seen on ultrasound and reported in 2014; however, at birth and with follow-up, the infant is noted to be developing normally as per the parents, who have also declined further testing.[17] 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.[1] 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 23 studies (including the Antiretroviral Pregnancy Registry data) reporting on birth outcomes among women exposed to efavirenz during the first trimester, there were 44 infants with birth defects among 2,026 live births to women receiving first-trimester efavirenz (rate of overall birth defects (1.63%, 95% CI, 0.78% to 2.48%).[18] The rate of overall birth defects was similar among women exposed to efavirenz-containing regimens and non-efavirenz-containing regimens during the first trimester (pooled relative risk [RR] 0.78, 95% CI, 0.56–1.08). Across all births, one neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.05% (95% CI, <0.01 to 0.28), 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 US population is 0.02% to 0.2%).

A recent French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester efavirenz exposure.[19] In the primary analysis using the European Surveillance of Congenital Anomalies (EUROCAT) classification system, no increase in birth defects after first-trimester efavirenz exposure was detected compared to those without efavirenz exposure in pregnancy (adjusted odds ratio 1.16, 95% CI, 0.73–1.85). In a secondary analysis using the modified Metropolitan Atlanta Congenital Defect Program classification used by the Antiretroviral Pregnancy Registry, an association was found between first-trimester efavirenz exposure and neurologic defects. However, none of the four defects (i.e., ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst, and pachygyria) were neural tube defects, and none of the defects had common embryology.[20] First-trimester efavirenz exposure was not associated with an increased risk of defects in a Pediatric HIV/AIDS Cohort Study analysis that included 2,580 live births, 94 after first-trimester efavirenz exposure,[21] or an analysis of a national cohort in Italy that included 1,257 pregnancies, 80 after first-trimester efavirenz exposure.[22]

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

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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 two studies.[23-25] Thus, additional data are needed on first-trimester efavirenz exposures to more conclusively determine if risk of neural tube defects is elevated.

The FDA advises women to avoid becoming pregnant while taking efavirenz and health care providers to avoid administration in the first trimester of pregnancy as fetal harm may occur. 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 more than 2,000 births suggest that there is not a large increase (e.g., a 10-fold increase to a rate of 1%) in the risk of neural tube defects with first-trimester exposure. 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 because of the potential for teratogenicity. 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 to 39 days after the 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,[26] efavirenz can be continued in pregnant women receiving efavirenz-based ART who present for antenatal care in the first trimester. In such situations, additional fetal monitoring (e.g., second-trimester ultrasound) should be considered to evaluate fetal anatomy.

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*)	Formulation	Dosing Recommendations	Use in Pregnancy
Efavirenz (EFV) *Sustiva* (EFV/TDF/FTC) *Atripla*	EFV (Sustiva) *Capsules:* • 50 mg • 200 mg *Tablet:* • 600 mg Atripla: • EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet	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, on 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.	Moderate placental transfer to fetus.[b] Potential fetal safety concern: 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. 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, 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 (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment).

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent 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:** <0.3

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; CNS = central nervous system; EFV = efavirenz; FTC = emtricitabine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Etravirine (Intelence, ETR)

(Last updated April 29, 2016; last reviewed April 29, 2016)

Etravirine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.[1] 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 (AUC) ratios being 0.6-fold (mice) and 0.2- to 0.7-fold (rats).[1]

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).[1]

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).[1]

Human Studies in Pregnancy

Pharmacokinetics

Etravirine pharmacokinetics (PK) in pregnant women have been reported in two studies. Ramgopal et al. found that AUC, C_{min}, and C_{max} were increased approximately 1.4 fold in the second trimester (n = 13) and 1.2 to 1.4 fold in the third trimester (n = 10) compared with the same women postpartum (n = 10).[2] Similarly, Best and colleagues found increases by 1.3 to 1.6 fold in AUC, Cmin, and Cmax during the third trimester (n = 13) compared with the same women postpartum (n = 9).[3] Etravirine was well tolerated in both of these studies. Case report data are available describing etravirine use in a total of seven pregnant women.[4] No adverse effects associated with etravirine use were reported. One report described etravirine PK in four pregnant women whose etravirine PK parameters were similar to those in non-pregnant adults.[5]

Placental and Breast Milk Passage

The median (range) ratio of etravirine concentrations in cord blood to maternal plasma at delivery in 6 mother-infant pairs was 0.76 (0.19–4.25).[3] The median (range) cord blood-to-maternal concentrations in 10 mother-infant pairs in another study was 0.32 (0.19–0.63).[2] 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.[5] In a second mother-infant pair, cord blood and maternal plasma at delivery were 218 ng/

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mL and 421 ng/mL (cord/maternal ratio of 51%).[6] Placental passage of etravirine was described in a report of the use of etravirine, ritonavir-boosted darunavir, and enfuvirtide in a 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).[4]

In 8 women who began etravirine on postpartum day 1, plasma and breast milk concentrations were measured on postpartum days 5 and 14.[7] Plasma PK were not different between days 5 and 14 and were similar to published PK parameters of etravirine in non-pregnant adults. Breast milk $AUC_{0–12}$ was higher in mature milk (Day 14) than in colostrum/transitional milk (Day 5); 12,954 ± 10,200 versus 4,372 ± 3,016 ng-h/mL ($P = 0.046$). Median etravirine concentrations in plasma and breast milk on Day 5 were 300 ng/mL and 241 ng/mL (within subject breast milk/plasma ratio of 109%). Median plasma and breast milk concentrations on day 14 were 197 ng/mL and 798 ng/mL (within-subject breast milk/plasma ratio of 327%). The maximum concentration in breast milk was significantly higher than in plasma (1,245 ± 1,159 vs. 531 ± 336 ng/mL, $P = 0.04$). Two women had detectable HIV RNA in breast milk on Day 14 despite suppressed plasma viral load. Etravirine concentrations in plasma and breast milk were similar in these two women compared to women with undetectable HIV RNA in breast milk. Etravirine penetrates well and may accumulate in breast milk.

Teratogenicity/Developmental Toxicity

In eight reported cases of etravirine use in pregnancy, no maternal, fetal, or neonatal toxicity was noted.[4,6] 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.[4] 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.[8]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Names*	Formulation	Dosing Recommendations	Use in Pregnancy
Etravirine (ETR) *Intelence*	Tablets: • 25 mg • 100 mg • 200 mg For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	Standard Adult Dose(s): • 200 mg twice daily with food PK in Pregnancy: • PK data in pregnancy (n = 26) suggest 1.2–1.6 fold increased etravirine exposure during pregnancy. Dosing in Pregnancy: • No change in dose indicated.	Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 18 mother-infant pairs).[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 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:** <0.3

Key to Acronyms: ETR= etravirine; PK = pharmacokinetic

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Nevirapine (Viramune, NVP)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Nevirapine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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.[1]

Reproduction/Fertility

Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.[1]

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.[1]

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetics (PKs) of nevirapine have been evaluated in pregnant women receiving nevirapine as part of antiretroviral therapy (ART) 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.[2] 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.[3] A Dutch study reported a nonsignificant trend toward lower nevirapine exposure during pregnancy, with steady-state nevirapine concentrations of 5.2 mcg/mL in 45 pregnant women compared to 5.8 mcg/mL in 152 non-pregnant women ($P = 0.08$).[4] No dose adjustment during pregnancy is currently recommended for nevirapine.

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 to1.02).[5,6] 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 (inter-quartile range 0.54–1.06 mcg/mL).[7] In data from 15 breastfeeding women receiving nevirapine-based therapy in Botswana, median maternal plasma concentration at 1 month postpartum was 6.71 mcg/mL and median maternal breast milk concentration was 1.83 mcg/mL, for a median maternal breast-milk-to-plasma ratio of 0.27.[8] Infant exposure was measured at 1 month in 9 infants; all infants had biologically significant detectable nevirapine concentrations in their blood, with a median level of 0.37 mcg/mL (range, 0.24–1.2 mcg/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 mcg/mL, with median concentrations at 2, 6, and 14 weeks postpartum in breastfeeding infants of 0.99 mcg/mL, 1.03 mcg/mL, and 0.73 mcg/mL, respectively.[9]

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Teratogenicity/Developmental Toxicity

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 2.9% (32 of 1,105 births; 95% CI, 2.0% to 4.1%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[10] Similarly, the French Perinatal Cohort recently reported no association between nevirapine and birth defects with 71% power to detect a 1.5-fold increase.[11]

Safety

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 (SJS)—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 ART for post-exposure prophylaxis of nosocomial or sexual exposure to HIV.[12] In general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 0% 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%.[13,14] 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.[15-17] Other studies have found that hepatic adverse events (AEs) with systemic symptoms (often rash) were 3.2-fold more common in women than men.[14] 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.[14] Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash.[16] Rates of hepatotoxicity and rash similar to those in US 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.[18] 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 were associated with nevirapine-related liver toxicity and drug discontinuation.[19] Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants), TRAF proteins, and immune human leukocyte antigen loci may be associated with higher risk of nevirapine-associated AEs and that the relationship between genetic variants and AEs may vary by race.[20-23]

Although deaths as a result of hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of an ART regimen, it is uncertain whether pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs.[24] In a systematic review of 20 studies including 3,582 pregnant women from 14 countries, the pooled proportion of women experiencing a severe hepatotoxic 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 AE (95% CI, 4.0% to 8.4%).[25] 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 AEs 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.[26,27] In contrast, a recent analysis of data collected in the United Kingdom and Ireland from 2000 to 2011 evaluated 3,426 women, one quarter of whom were pregnant, and found that pregnant women taking efavirenz, maraviroc, or nevirapine were at increased risk of liver enzyme elevation.[28]

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In the systematic review, there was a nonsignificant 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 ≥250 cell/mm^3 (OR 1.4, 95% CI, 0.8–2.4).[25] 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/mm^3.[29] A small case-control study (6 cases, 30 controls) in South Africa recently reported that pregnancy increased the chance of developing SJS (OR 14.28, $P = 0.006$, 95% CI, 1.54–131.82).[30] Nevirapine (as a component of a combination regimen) should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. Women with CD4 cell counts <250 cells/mm^3 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 (i.e., pregnancy-related nausea and vomiting), 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; in patients with preexisting liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.[31] 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.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Nevirapine (NVP) *Viramune* *Viramune XR (Extended Release)* **Note:** Generic available for all formulations	NVP (Viramune) *Tablets:* • 200 mg *Oral Suspension:* • 50 mg/5 mL Viramune XR Tablets: • 100 mg • 400 mg	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 >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.	High placental transfer to fetus.[b] 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.

[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:** <0.3

Key to Acronyms: CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic

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Rilpivirine (Edurant, RPV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Rilpivirine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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.[1]

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.[1]

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.[1]

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A case report describing rilpivirine pharmacokinetic (PK) evaluations at 32 weeks' gestation and again postpartum in 2 HIV-infected pregnant women showed that rilpivirine area under the curve [AUC] was decreased by 30% to 43% during pregnancy, while postpartum AUC was similar to that seen in non-pregnant adults.[2] A similar finding was reported in a study presenting PK and safety data from 32 HIV-infected pregnant women receiving rilpivirine. Median rilpivirine AUC and trough concentrations were reduced by about 20% to 30% in the second and third trimesters, compared with postpartum. Median trough rilpivirine concentrations were significantly lower at 14 visits where the women had detectable HIV-1 RNA (30 ng/mL) compared to 62 visits with undetectable HIV-1 RNA (63 ng/mL). Ninety percent of women had trough concentrations above the protein-adjusted EC_{90} for rilpivirine. PK exposure was highly variable in this study.[3]

Placental and Breast Milk Passage

In the case report described above, cord blood and maternal plasma rilpivirine concentrations obtained from one mother-infant pair were 0.016 and 0.021 mg/L, for a cord blood/maternal concentration ratio of 0.74.[2] The PK and safety study described above included rilpivirine delivery concentration data from 9 mother-infant pairs, with median (range) cord blood rilpivirine plasma concentration of 53.8 ng/mL (<10.0 to 219.7 ng/mL), maternal delivery plasma rilpivirine concentration of 103.3 ng/mL (<10.0 to 273.4 ng/mL) and cord blood/maternal plasma ratio of 0.55 (0.38 to 0.83).[4] An *ex vivo* human cotyledon perfusion model also showed that rilpivirine crosses the placenta with fetal transfer rates ranging from 17% to 37%.[5,6] No data exist on whether rilpivirine is excreted in breast milk in humans.

Teratogenicity/Developmental Toxicity

The number of first-trimester exposures to rilpivirine that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.[7]

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Rilpivirine (RPV) *Edurant* (RPV/TDF/FTC) *Complera*	RPV (Edurant) *Tablets:* • 25 mg Complera: • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet	Standard Adult Dose *RPV (Edurant):* • 25 mg once daily with food *Complera:* • 1 tablet once daily with food PK in Pregnancy: • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 30% in pregnancy compared with postpartum, but most pregnant women exceeded target exposure. Dosing in Pregnancy: • Routine dosing adjustment in all women is not recommended for RPV during pregnancy. Individual patients should be closely monitored.	Moderate to high placental transfer to fetus.[b] No evidence of teratogenicity in rats or rabbits. Insufficient data to assess for teratogenicity in humans.

[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:** <0.3

Key to Acronyms: AUC = area under the curve; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Protease Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • 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.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

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.

Atazanavir (Reyataz, ATV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

According to the Food and Drug Administration, atazanavir has been evaluated in a limited number of women during pregnancy, and available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate.[1]

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 was no increase 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 area under the curve (AUC) levels that were 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 produced systemic drug exposure 1.3 times the human exposure resulted in maternal toxicity and 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] A more recent study demonstrated an association of maternal PI use (including atazanavir) with lower progesterone levels which correlated with lower birthweight in mice, but this potential mechanism requires further study.[2,3]

Placental and Breast Milk Passage

Atazanavir is excreted in the milk of lactating rats and was associated with neonatal growth retardation that reversed after weaning.[1]

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Human Studies in Pregnancy

Pharmacokinetics

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of atazanavir/ritonavir in pregnancy.[4] Overall, most pregnant women achieved undetectable HIV RNA at the time of delivery.[1,5-9] In a retrospective study reporting trough atazanavir concentrations at a median of 30 weeks' gestation (14 in the third trimester) in 19 pregnant women receiving atazanavir 300 mg and ritonavir 100 mg once daily, all but two women had a trough atazanavir concentration >100 ng/mL.[10] 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 adults.[5,7,8,11,12] In one of the studies there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than that in non-pregnant HIV-infected historic controls.[7] In the other studies, atazanavir AUC was lower during pregnancy than it was in the same patients postpartum and in non-pregnant control populations.[5,6,8,11,12]

AAtazanavir/ritonavir combined with tenofovir disoproxil fumarate (TDF) and emtricitabine provides a complete once-a-day antiretroviral therapy regimen for pregnant women; however, the atazanavir AUC in pregnant women in the third trimester receiving concomitant TDF compared with women who were not receiving concomitant TDF was 30% lower, an effect similar to that seen in non-pregnant adults.[8,11] The increase in atazanavir AUC postpartum relative to that in the third trimester was similar for women taking concomitant TDF and for those not taking concomitant TDF.[8] On the other hand, a smaller PK study did not demonstrate that concomitant TDF resulted in lower atazanavir AUC or higher risk of trough <0.15 mg/L (target for treatment-naive patients) in pregnant women in their third trimester.[13] In a therapeutic drug monitoring (TDM) study of 103 mostly African women in Paris, there was no difference in risk of atazanavir trough <0.15 mg/L between women who did and those who did not take concomitant TDF.[9]

In studies investigating an increased dose of atazanavir of 400 mg with 100 mg ritonavir once daily during pregnancy,[5,6] pregnant women receiving the increased dose without TDF had an atazanavir AUC equivalent to that seen in historic non-pregnant HIV-infected controls receiving standard-dose atazanavir without TDF. Pregnant women receiving the increased atazanavir dose with TDF had an AUC equivalent to that seen in non-pregnant HIV-infected patients receiving standard-dose atazanavir with TDF.[5,6] 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 antiretroviral-experienced pregnant women in the second and third trimesters also receiving either TDF or an H2-receptor antagonist. TDM of atazanavir in pregnancy may also be useful.[14] For additional details about dosing with interacting concomitant medications, please see Drug Interactions in the Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.

Placental and Breast Milk Passage

In studies of women receiving atazanavir/ritonavir-based combination therapy during pregnancy, cord blood atazanavir concentration averaged 13% to 21% of maternal serum levels at delivery.[1,7,8]

In a study of three women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.[15]

Teratogenicity/Developmental Toxicity

In a multicenter U.S. cohort of HIV-exposed but uninfected children, first-trimester atazanavir exposure was associated with increased odds of congenital anomalies of skin (aOR = 5.24, $P = 0.02$) and musculoskeletal system (aOR = 2.55, $P = 0.007$).[16] On the other hand, there was no association between first-trimester atazanavir exposure and birth defects in a French cohort, though this study had <50% power to detect an adjusted odds ratio of 1.5.[17] The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to atazanavir in humans to be able to detect at least a 1.5-fold increase in risk of overall birth defects and no such increase in birth defects has been observed with atazanavir. The prevalence of birth

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defects with first-trimester atazanavir exposure was 2.2% (24 of 1,093 births; 95% confidence interval [CI], 1.4% to 3.2%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[18]

Maternal PI use (including atazanavir) was associated with lower progesterone levels, but the clinical significance of this finding requires further study.[2]

Other Safety Data

Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir, including during pregnancy.[19] The effects on the fetus of elevated maternal indirect bilirubin throughout pregnancy are unknown. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received atazanavir during pregnancy.[1,5,7,8,10,20-22] 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.[20,21] Elevated neonatal bilirubin in atazanavir-exposed neonates is not associated with UGT-1 genotypes associated with decreased UGT function.[22]

In an evaluation of neurodevelopmental in 374 HIV-exposed but uninfected—infants aged 9 to 15 months, the adjusted mean score on the language domain of the Bayley-III test was significantly lower for infants with perinatal exposure to atazanavir compared to those with exposure to other drugs.[23] In a study of language assessments among 792 HIV-exposed—but uninfected—children (aged 1 and 2 years) atazanavir-exposed children had an 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 children but the association was not significant at 24 months.[24]

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.[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.[25]

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Atazanavir (ATV) *Reyataz* **Note:** Must be combined with low-dose RTV boosting in pregnancy **Atazanavir/ Cobicistat** (ATV/COBI) *Evotaz*	ATZ (Reyataz) *Capsules*: • 150 mg • 200 mg • 300 mg *Oral Powder:* • 50 mg packet Evotaz: • ATV 300 mg plus COBI 150 mg tablet	Standard Adult Dose ATZ (Reyataz) *ARV-Naive Patients* *Without RTV Boosting:* • ATV 400 mg once daily with food; ATV without RTV boosting **is not recommended** when used with TDF, H_2-receptor antagonists, or PPIs, or during pregnancy. *With RTV Boosting:* • ATV 300 mg plus RTV 100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV 400 mg plus RTV 100 mg once daily with food *ARV-Experienced Patients:* • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV. • If combined with an H_2-receptor antagonist: ATV 300 mg plus RTV 100 mg once daily with food • If combined with an H_2-receptor antagonist and TDF: ATV 400 mg plus RTV 100 mg once daily with food Powder Formulation: • Oral powder is taken once daily with food at the same recommended adult dosage as the capsules along with ritonavir. Evotaz: • One tablet once daily with food. PK in Pregnancy *Atazanavir (Reyataz):* • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H_2-receptor antagonist. *Evotaz:* • No PK studies in human pregnancy. Dosing in Pregnancy *Atazanavir [Reyataz]:* • Use of unboosted ATV **is not recommended** during pregnancy. • Use of ATV not recommended for treatment-experienced pregnant women taking TDF **and** an H_2-receptor antagonist. • Use of an increased dose (400 mg ATV plus 100 mg RTV once daily with food) during the second and third trimesters results in plasma concentrations equivalent to those in non-pregnant adults on standard dosing. Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the second and third trimesters also receiving either TDF or an H_2-receptor antagonist. *Evotaz:* • Insufficient data to make dosing recommendation.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Must be given as low-dose RTV-boosted regimen in pregnancy. Effect of *in utero* ATV exposure on infant indirect bilirubin levels is unclear. Non-pathologic elevations of neonatal hyperbilirubinemia have been observed in some but not all clinical trials to date. Oral powder (but **not** capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria.

[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:** <0.3

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; EFV = efavirenz; PK = pharmacokinetic; PPI = proton pump inhibitors; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

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Darunavir (Prezista, DRV)

(Last reviewed October 26, 2016; last updated October 26, 2016)

Darunavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

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).[1]

Reproduction/Fertility

No effects on fertility and early embryonic development were seen with darunavir in rats.[1]

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 age 5–11 days) or multiple doses of darunavir (40 mg/kg–1,000 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.[1]

Placental and Breast Milk Passage

No animal studies of placental passage of darunavir have been reported. Passage of darunavir into breast milk has been noted in rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

Three intensive pharmacokinetic (PK) studies of darunavir/ritonavir administered as 600 mg/100 mg twice a day or 800 mg/100 mg once a day during pregnancy have been completed.[2-4] These studies demonstrate 17% to 33% reductions in darunavir plasma concentrations during the third trimester compared with postpartum.[2-4] Two of these studies measured darunavir protein binding during pregnancy with conflicting results. One study found no change in darunavir protein binding during the third trimester while the other found a decrease.[2,4] Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, especially for antiretroviral-experienced patients. A study of use of an increased twice-daily darunavir dose (800 mg) during pregnancy reported no increase in darunavir exposure in pregnant women receiving the increased dose; use of this increased twice-daily darunavir dose during pregnancy is not recommended.[5] The PK and safety of darunavir/cobicistat during pregnancy have not been studied.

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate was 15%.[6] In 4 studies reporting data from between 8 and 14 subjects each, the median ratio of darunavir concentration in cord blood to

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that in maternal delivery plasma ranged from 13% to 24%.[2-4,7] No data are available describing breast milk passage of darunavir in humans.

Teratogenicity Data

Among cases of first-trimester darunavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.7% (9 of 333 births; 95% CI, 0.9% to 5.0%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[8]

Other Safety Issues

No safety issues have been observed in case reports and small PK studies of darunavir in pregnancy.[2-4,7,9-13]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose ritonavir (RTV) or cobicistat (COBI) boosting **Darunavir/ Cobicistat** (DRV/COBI) *Prezcobix*	DRV (Prezista): • 75 mg • 150 mg • 600 mg • 800 mg Oral Suspension: • 100 mg/mL Prezcobiz (Co-Formulated): • DRV 800 mg plus COBI 150 mg	Standard Adult Dose *ARV-Naive Patients:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food *ARV-Experienced Patients:* *If No DRV Resistance Mutations:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 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 with use of DRV/RTV. Dosing in Pregnancy: • Once-daily dosing with DRV/RTV **is not recommended** during pregnancy. Twice-daily DRV/RTV dosing (DRV 600 mg plus RTV 100 mg with food) recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) during pregnancy does not result in an increase in darunavir exposure and is not recommended. • No pregnancy PK/safety data for DRV/COBI co-formulation, so not recommended for use in pregnancy.	Low placental transfer to fetus.[b] No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be given as low-dose, RTV-boosted regimen.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent 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:** <0.3

Key to Acronyms: ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; PK = pharmacokinetic; RTV = ritonavir

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Fosamprenavir (Lexiva, FPV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Fosamprenavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

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 (mice) and 0.7- to 1.4 (rats) times those in humans given 1400 mg twice daily of fosamprenavir alone and were 0.2- to 0.3 (mice) and 0.3- to 0.7 (rats) times those in humans given 1400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3 (mice) and 0.3- to 0.6 (rats) times those in humans given 700 mg fosamprenavir plus 100 mg ritonavir twice daily.[1]

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 times and in rats at twice 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 twice 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.

Placental and Breast Milk Passage

Amprenavir is excreted in the milk of lactating rats.

Human Studies in Pregnancy

Pharmacokinetics

Data on fosamprenavir in pregnant women are limited. Fosamprenavir pharmacokinetic (PK) 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.[2] For the postpartum period, potential PK interactions with hormonal contraceptives should be taken into account (see Table 3 in Preconception Counseling and Care).

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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) µg/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% confidence interval) of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (0.24, 0.30).[3] Whether amprenavir is excreted in human breast milk is unknown.

Teratogenicity/Developmental Toxicity

Two birth defects out of 108 live births with first-trimester exposure and two birth defects out of 36 live births with second- or third-trimester exposure have been reported to the Antiretroviral Pregnancy Registry. These numbers are insufficient to allow conclusions to be drawn regarding the risk of birth defects.[4]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Fosamprenavir (FPV) *Lexiva (a prodrug of amprenavir)* **Note:** Must be combined with low-dose RTV boosting in pregnancy	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 during the third trimester were adequate for patients without PI resistance mutations. Dosing in Pregnancy: • Use of unboosted FPV or once-daily FPV with RTV boosting **is not recommended** during pregnancy. No change is indicated in standard boosted twice-daily dose (FPV 700 mg plus RTV 100 mg twice daily without food).	Low placental transfer to fetus.[b] 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.

[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:** <0.3

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FPV = fosamprenavir; PI = protease inhibitor; PK = pharmacokinetic; RTV= ritonavir

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Indinavir (Crixivan, IDV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Indinavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

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.[1]

Reproduction/Fertility

No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.[1]

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.[1]

Placental and Breast Milk Passage

Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels.[1]

Human Studies in Pregnancy

Pharmacokinetics

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.[2,3] Use of unboosted indinavir is not recommended in HIV-infected pregnant patients because of the substantially lower antepartum exposures observed in these studies and the limited experience in this patient population.

Several reports have investigated use of indinavir/ritonavir 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 µg/mL; 24% of subjects had trough concentrations below 0.10 µg/mL, the target trough concentration used in therapeutic drug monitoring programs; and 81% had RNA viral loads <50 copies/mL at delivery.[4] 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 µg/mL, 18% of subjects had trough concentrations below 0.12 µg/mL, and 93% had HIV RNA level <200 copies/mL at delivery.[5] In a small study of two patients who received indinavir 800 mg and ritonavir 200 mg twice daily, third-trimester indinavir area under the curve exceeded that for historical non-pregnant controls.[6] The available data are insufficient to allow for definitive

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dosing recommendations for use of indinavir/ritonavir during pregnancy.

Placental and Breast Milk Passage

In studies of pregnant women receiving unboosted indinavir and their infants, transplacental passage of indinavir was minimal.[2,7] In a study of Thai pregnant women receiving indinavir/ritonavir, 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 0.12.[4] In 1 woman taking indinavir 600 mg and ritonavir 200 mg twice daily, indinavir concentrations in breast milk were 90% to 540% of plasma concentrations over the first 5 days after delivery.[8]

Teratogenicity/Developmental Toxicity

Although the French Perinatal Cohort reported an association of head and neck birth defects with first trimester exposure to indinavir (3 defects in 350 first-trimester exposures, 0.9%), the Antiretroviral Pregnancy Registry (APR) has not observed an increase in birth defects with indinavir.[9,10] Among cases of first-trimester indinavir exposure reported to the APR, defects have been seen in 2.4% (7/289; 95% CI, 1.0% to 4.9%) compared to total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention surveillance of 2.7%.[10]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Indinavir (IDV) *Crixivan* **Note:** Must be combined with low-dose RTV boosting in pregnancy	Capsules: • 200 mg • 400 mg	Standard Adult Dose *Without RTV Boosting:* • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal. *With RTV Boosting:* • IDV 800 mg plus RTV 100 mg twice daily without regard to meals PK in Pregnancy: • 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. Dosing in Pregnancy: • Use of unboosted IDV **is not recommended** during pregnancy.	Minimal placental transfer to fetus.[b] No evidence of human teratogenicity in cases reported to the APR (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.

[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:** <0.3

Key to Acronyms: APR = Antiretroviral Pregnancy Registry; IDV = indinavir; PK = pharmacokinetic; RTV = ritonavir

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Lopinavir/Ritonavir (Kaletra, LPV/r)

(Last updated October 26, 2016; last reviewed October 26, 2016)

No difference in the risk of overall major birth defects has been shown for lopinavir/ritonavir (LPV/r) compared to the background rate for major birth defects in the United States. Treatment-related malformations were not observed when LPV/r was administered to pregnant rats or rabbits, but embryonic and developmental toxicities were seen in rats at maternally toxic doses.

Animal Studies

Carcinogenicity

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The 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 area under the curve $[AUC]_{0-24hr}$ 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.[1]

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.[1]

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.[1] In a study of pregnant rats receiving chronic administration of zidovudine, lopinavir, and ritonavir, maternal body weight gain was significantly reduced, but no adverse fetal parameters were observed.[2] In pregnant mice, ritonavir, lopinavir and atazanavir were associated with significantly lower progesterone levels, and the lower progesterone levels directly correlated with lower fetal weight.[3]

Placental and Breast Milk Passage

No information is available on placental transfer of lopinavir in animals.[1]

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a tablet formulation that is heat-stable, has improved bioavailability characteristics, and does not have to be administered with food.[4,5] Pharmacokinetic (PK) 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.[6-8] Further reductions in lopinavir exposure by 33% were demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors attributed this reduction to decreased bioavailability.[9] Increasing the 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.[10,11]

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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-naive subjects, but not the higher trough concentrations recommended for protease inhibitor (PI)-experienced subjects.[4,7] A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences lopinavir clearance and volume, with larger women (>100 kg) or women who missed a dose at higher risk for subtherapeutic trough concentrations when taking the standard dose during pregnancy.[12] Another population PK study in 84 pregnant women and 595 non-pregnant adults found no significant difference in lopinavir concentration in pregnant women taking the more bioavailable tablet formulation compared to non-pregnant adults taking the original capsule formulation.[13] In one study of 29 women, lopinavir plasma protein binding was reduced during pregnancy, but the resulting increase in free (unbound) drug was insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.[14] In a study of 12 women, total lopinavir exposure was significantly decreased throughout pregnancy, but unbound AUC and C_{12} did not differ throughout pregnancy, even with an increased dose of 500/125 mg.[15] A population PK study found a 39% increase in total lopinavir clearance during pregnancy, but measured unbound lopinavir concentrations in pregnancy were within the range of those simulated in nonpregnant adults.[16] Bonafe et al randomized 32 pregnant women to standard dose and 31 pregnant women to the 600/150 mg dose of LPV/r at gestational ages between 14 and 33 weeks. No differences in adverse events (AEs) were seen between groups. In women with baseline viral loads >50 copies/mL, 45% in the standard dose group had plasma viral loads >50 copies/mL during the last 4 weeks of pregnancy, compared to 10.5% in the increased dose group ($P = 0.01$). In women with baseline viral loads <50 copies/mL, no difference was seen between groups in viral load measurements in the last 4 weeks of pregnancy.[17]

These studies have led some experts to support use of an increased dose of LPV/r in HIV-infected pregnant women during the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. If standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations, if available, should be monitored. An alternative strategy to increasing LPV/r dosing during pregnancy by using 3 adult 200/50 mg tablets to provide a dose of 600/150 mg is to add a pediatric LPV/r tablet (100/25 mg) to the standard dose of 2 adult 200/50 mg tablets to provide a dose of 500/125 mg.[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.

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.[18] 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.[18-22]

Teratogenicity/Developmental Toxicity

The French Perinatal Cohort found no association between birth defects and lopinavir or ritonavir with 85% power to detect a 1.5-fold increase.[23] The Pediatric HIV/AIDS Cohort Study found no association between lopinavir and congenital anomalies.[24] Surveillance data from the United Kingdom and Ireland over a 10 year period showed a 2.9% prevalence of congenital abnormalities (134 children of 4,609 lopinavir-exposed pregnancies), comparable to rates in uninfected populations.[25] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to LPV/r have been monitored for detection of at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with LPV/r. Among cases of first-trimester exposure to LPV/r reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was

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2.3% (29 of 1,290; 95% CI, 1.5% to 3.2%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[26]

Safety

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 AEs 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.[27] 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-hydoxyprogesterone 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.[28] 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.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name.*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	Tablets (Co-Formulated): • LPV 200 mg plus RTV 50 mg • LPV 100 mg plus RTV 25 mg Oral Solution: • LPV 400 mg plus RTV 100 mg/5 mL	Standard Adult Dose: • LPV 400 mg plus RTV 100 mg twice daily, *or* • LPV 800 mg plus RTV 200 mg once daily *Tablets:* • Take without regard to food. *Oral Solution:* • Take with food. With EFV or NVP (PI-Naive or PI-Experienced Patients): • 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 and one LPV 100 mg plus RTV 25 mg tablet), *or* • LPV 520 mg plus RTV 130 mg oral solution (6.5 mL) twice daily with food PK in Pregnancy: • With twice-daily dosing, LPV exposure is reduced in pregnant women receiving standard adult doses; increasing the dose by 50% results in exposure equivalent to that seen in non-pregnant adults receiving standard doses. • No PK data are available for once-daily dosing in pregnancy. Dosing in Pregnancy: • Once daily dosing **is not recommended** during pregnancy. • Some experts recommend that an increased dose (i.e., LPV 600 mg plus RTV 150 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI- experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • If standard dosing is used, monitor virologic response and LPV drug levels, if available.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy. Once-daily LPV/r dosing is not recommended during pregnancy

[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:** <0.3

Key to Abbreviations: EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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Nelfinavir (Viracept, NFV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Nelfinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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).[1]

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.[1] 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.[1]

Human Studies in Pregnancy

Pharmacokinetics

A Phase I/II safety and pharmacokinetic (PK) study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants.[2] In the first 9 pregnant HIV-infected women enrolled in the study, nelfinavir administered at a dose of 750 mg 3 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 both those trimesters were somewhat lower than in non-pregnant women.[3,4]

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.[5] Only 16% (4 of 25) of women during the third trimester and 8% (1/12) of 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.

Placental and Breast Milk Passage

In a Phase I study in pregnant women and their infants (PACTG 353), 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.[6] Among 20 mother-infant pairs in the Netherlands, the cord blood-to-maternal-plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.[7]

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Nelfinavir also has low breast milk passage. In a PK study conducted in Kisumu, Kenya, concentrations of nelfinavir and its active metabolite, M8, were measured in maternal plasma and breast milk from 26 mothers receiving nelfinavir as part of antiretroviral therapy and from their 27 infants at birth, 2, 6, 14, and 24 weeks.[8] Peak nelfinavir concentrations were recorded in maternal plasma and breast milk 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%) of 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.

Teratogenicity/Developmental Toxicity

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 1,215 births; 95% CI, 2.8% to 5.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[9]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Nelfinavir (NFV) *Viracept*	Tablets: • 250 mg • 625 mg (tablets can be dissolved in small amount of water) Powder for Oral Suspension: • 50 mg/g	Standard Adult Dose: • 1250 mg twice daily or 750 mg three times daily with food PK in Pregnancy: • 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. Dosing in Pregnancy: • 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.	Minimal to low placental transfer to fetus.[b] 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. Contains aspartame; should not be used in individuals with phenylketonuria.

[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:** <0.3

Key to Abbreviations: NFV = nelfinavir; PK = pharmacokinetic

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Saquinavir (Invirase, SQV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Saquinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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 29% (rat) and 65% (mouse) of those obtained in humans at the recommended clinical dose boosted with ritonavir.[1]

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.[1]

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.[1]

Placental and Breast Milk Passage

Placental transfer of saquinavir in the rat and rabbit was minimal. Saquinavir is excreted in the milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

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.[2-6] 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.[7,8] 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.[7] 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.[9] 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.[8]

One study of 42 pregnant women receiving a combination antiretroviral drug regimen that included ritonavir-boosted saquinavir 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).[10] In a study of 62 pregnant women on a regimen that included ritonavir-boosted saquinavir, one severe adverse event occurred (maternal Grade 3 hepatotoxicity).[8]

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Placental and Breast Milk Passage

In a Phase I study in pregnant women and their infants (PACTG 386), transplacental passage of saquinavir was minimal.[11] In addition, in a study of 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.[12] It is not known if saquinavir is excreted in human milk.

Teratogenicity/Developmental Toxicity

The 184 first-trimester saquinavir exposures monitored by the Antiretroviral Pregnancy Registry are too few to be able to accurately calculate the prevalence of birth defects in exposed cases.[13]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Saquinavir (SQV) *Invirase* **Note:** Must be combined with low-dose RTV for PK boosting	Tablet: • 500 mg Capsule: • 200 mg	Standard Adult Dose: • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal PK in Pregnancy: • Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change. Dosing in Pregnancy: • No change in dose indicated.	Low placental transfer to fetus.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be boosted with low-dose RTV. Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with preexisting cardiac conduction system disease.

[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:** <0.3

Key to Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir

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Tipranavir (Aptivus, TPV)

(Last reviewed June 7, 2016; last updated June 7, 2016)

Tipranavir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

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 tipranavir/ritonavir (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.[1]

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 of TPV/r BID).[1]

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.[1]

Placental and Breast Milk Passage

No animal studies of placental or breast milk passage of tipranavir have been reported.

Human Studies in Pregnancy

Pharmacokinetics

No studies of tipranavir have been completed in pregnant women or neonates.

Placental and Breast Milk Passage

It is unknown if passage of tipranavir through the placenta or breast milk occurs in humans. A single case report described relatively high levels of tipranavir in the third trimester and relatively high placental transfer (0.41), as measured by cord blood.[2]

Teratogenicity/Developmental Toxicity

The four first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry are insufficient to allow conclusions to be drawn regarding risk of birth defects.[3]

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tipranavir (TPV) *Aptivus* **Note:** Must be combined with RTV for PK boosting	Capsules: • 250 mg Oral Solution: • 100 mg/mL	Standard Adult Dose: • TPV 500 mg plus RTV 200 mg twice daily *With RTV Tablets:* • Take with food. *With RTV Capsules or Solution:* • Take without regard to food; however, administering with food may help make the dose more tolerable. PK in Pregnancy: • Limited PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Moderate placental transfer to fetus reported in one patient.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Must be given as low-dose RTV-boosted regimen.

[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:** <0.3

Key to Abbreviations: PK = pharmacokinetic; RTV = ritonavir; TPV = tipranavir

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Entry Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • 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.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

The antiretroviral (ARV) drugs in this class inhibit 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 October 26, 2016; last reviewed October 26, 2016)

Enfuvirtide is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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

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 a body surface area basis).

Teratogenicity/Developmental Toxicity

Studies in rats and rabbits have shown no evidence of teratogenicity or effect on reproductive function with enfuvirtide.[1]

Placental and Breast Milk Passage

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 a body surface area basis). 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 (amino acid and peptide fragments) of enfuvirtide.

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Human Studies in Pregnancy

Pharmacokinetics

Data on the use of enfuvirtide in human pregnancy are limited to case reports of a small number of women treated with the drug.[2-9]

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 eight peripartum patients and their neonates and data from an *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of enfuvirtide.[2,5,10-12]

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry and in a national cohort of pregnant women with HIV infection in Italy, insufficient numbers of first-trimester exposures to enfuvirtide in humans have been monitored to be able to make a risk determination.[13,14]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name.*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Enfuvirtide (T-20) *Fuzeon*	Injectable: • Supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for SQ delivery of approximately 90 mg/1 mL.	T-20 is indicated for advanced HIV disease and must be used in combination with other ARV drugs to which the patient's virus is susceptible by resistance testing. Standard Adult Dose: • 90 mg (1 mL) twice daily without regard to meals PK in Pregnancy: • No PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Minimal to low placental transfer to fetus.[b] No data on human teratogenicity.

[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:** <0.3

Key to Abbreviations: ARV = antiretroviral; PK = pharmacokinetic; SQ = subcutaneous; T-20 = enfuvirtide

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Maraviroc (Selzentry, MVC)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Maraviroc is classified as Food and Drug Administration Pregnancy Category B.[1]

Animal Studies

Carcinogenicity

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

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

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

Minimal placental passage was demonstrated in a study of single-dose maraviroc in rhesus macaques that showed poor placental transfer and rapid clearance from infant monkeys' blood.[2] Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A U.S./European study of intensive, steady-state 12-hour pharmacokinetic profiles in the third trimester and at least 2 weeks postpartum included 18 women taking maraviroc as part of clinical care.[3] Sixty-seven percent were taking 150 mg BID with a protease inhibitor; 11% took 300 mg BID and 22% took an alternative regimen. The geometric mean ratios for third-trimester versus postpartum AUC were 0.72 and 0.70 for maximum maraviroc concentration. Despite the overall 30% decrease in maraviroc exposure during pregnancy and 15% decrease in C_{trough}, C_{trough} exceeded the minimum target concentration of 50 ng/mL, and only one woman had a C_{trough} below that level both during pregnancy and post-partum. These data suggest that the standard adult dose adjusted for concomitant antiretroviral (ARV) drugs seems appropriate in pregnancy. A review of drug interactions between ARV drugs and oral contraceptives found that it is safe to coadminister oral contraceptives with maraviroc.[4]

Other Safety Issues

A retrospective study from an English-Irish cohort of 857 pregnant women showed an increased rate of hepatotoxicity among the 492 who started antiretroviral therapy during pregnancy.[5] Maraviroc was one of three drugs that was associated with an increased risk of liver enzyme elevation during pregnancy with an aHR of 4.19 [1.34–13.1, $P = 0.01$], along with efavirenz and nevirapine. In a model using human placental BeWo cells, maraviroc inhibited transplacental passage of two fluorescent organic cations, suggesting that it might influence placental drug transfer and cause drug-drug interactions.[6]

Placental and Breast Milk Passage

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.[7] In a study in humans of 6 mother/infant pairs, the median ratio of cord blood-to-maternal-plasma drug concentrations was 0.33 (0.03–0.56).[3,8] Whether maraviroc is secreted into human milk is unknown.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to maraviroc in

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humans have been monitored to be able to make a risk determination.[9,10]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Maraviroc (MVC) *Selzentry*	Tablets: • 150 mg • 300 mg	Standard Adult Dose: • 300 mg twice daily with or without food • MVC must be used in combination with other ARVs in HIV-1-infected adults with only CCR5-tropic virus. Dose Adjustments: • Increase to 600 mg BID when used with potent CYP3A inducers: EFV, ETR, and rifampin. • Decrease to 150 mg BID when used with CYP3A inhibitors: all PIs except TPV/r and itraconazole. PK in Pregnancy: • A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in AUC, but C_{trough} exceeded the recommended minimal concentration of 50 ng/mL. Dosing in Pregnancy: • Standard adult dosing adjusted for concomitant ARV use appears appropriate.	No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. MVC placental passage category should be moderate.[b]

[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:

Key to Abbreviations: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetic

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Integrase Inhibitors

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • 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.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

This class of antiretroviral (ARV) drugs inhibits 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 reverse transcription 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 June 7, 2016; last reviewed June 7, 2016)

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

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.

Animal Teratogenicity/Developmental Toxicity

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.

Human Studies in Pregnancy

Pharmacokinetics

Human reports of dolutegravir use in human pregnancy are limited to two published case reports of dolutegravir use in single pregnant women and one presentation of dolutegravir safety, pharmacokinetic, and efficacy data from 21 pregnant women.[1-3] In both case reports, dolutegravir was used safely and effectively in pregnancy.[1,2] In the series of 21 pregnant women, dolutegravir plasma concentrations were lower during

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pregnancy than postpartum but HIV-1 RNA in the third trimester was below 50 copies/mL in all 15 women for whom third-trimester data were available. Dolutegravir was well tolerated by these pregnant women.[3]

Placental and Breast Milk Passage

No human data on placental passage or breast milk excretion are available.

Teratogenicity Data

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to dolutegravir in humans have been monitored to be able to make a risk determination.[4] In the series of pregnant women discussed above, congenital anomalies were reported in 4 infants: total anomalous pulmonary venous return, cystic fibrosis and polycystic right kidney, congenital chin tremor, and sacral dimple with filum terminale fibrolipoma.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Dolutegravir (DTG) *Tivicay* (DTG/ABC/3TC) *Triumeq*	Tablets: • 50 mg Triumeq: • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet	Standard Adult Dose *ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive Patients)* *DTG (Tivicay):* • 1 tablet once daily, without regard to food. *DTG/ABC/3TC (Triumeq):* • 1 tablet once daily, without regard to food. *ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced* *DTG (Tivicay):* • 1 tablet twice daily, without regard to food. PK in Pregnancy: • Limited PK data in human pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Unknown placental transfer to fetus. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult Guidelines, Appendix B, Table 7).

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DTG = dolutegravir; EFV = efavirenz; FPV/r = fosamprenavir/ritonavir; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

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Elvitegravir (Viteka, EVG)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Elvitegravir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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 with human systemic exposure at the recommended dose.[1]

Reproduction/Fertility

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.[1]

Teratogenicity/Developmental Toxicity

Studies in rats and rabbits have shown no evidence of teratogenicity or effect on reproductive function with elvitegravir.[1]

Placental and Breast Milk Passage

No data on placental passage are available for elvitegravir. Studies in rats have demonstrated that elvitegravir is secreted in breast milk.

Human Studies in Pregnancy

Pharmacokinetics

Pharmacokinetic (PK) studies of elvitegravir in human pregnancy are limited to a single case report of elvitegravir and cobicistat PK, safety, and efficacy in a single pregnant woman. Elvitegravir and cobicistat pharmacokinetics were assessed in this woman at 34 weeks' gestation and repeated at 6 weeks postpartum. Elvitegravir area under the curve (AUC) was similar during pregnancy and postpartum, but C_{min} was reduced by 60% during pregnancy compared to postpartum (and was below the suggested target concentration of 0.13 mg/L). Cobicistat AUC was reduced by 44% during pregnancy compared to postpartum. Despite the low elvitegravir C_{min}, viral load remained undetectable throughout the pregnancy.[2]

Placental and Breast Milk Passage

The only data available on placental passage of elvitegravir in humans are from the single case report cited above. At delivery, maternal and cord blood plasma elvitegravir concentrations were both 0.30 mg/L.[2] No data are available on human breast milk transfer of elvitegravir.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to elvitegravir in humans have been monitored to be able to make a risk determination.[3]

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Elvitegravir (EVG) *Vitekta* **Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate** (EVG/COBI/ FTC/TDF) *Stribild* **Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide** (EVG/COBI/FTC/ TAF) *Genvoya*	EVG Tablet (Vitekta): • 85 mg • 150 mg Tablet (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg Tablet (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg	Standard Adult Dose (Vitekta): • EVG (as Vitekta) must be used in combination with an HIV PI co-administered with RTV and another ARV drug. **Recommended Elvitegravir Dosage Taken Once Daily with Food (All Drugs Administered Orally)** **Dosage of Elvitegravir** / **Dosage of Concomitant PI** / **Dosage of Concomitant RTV** **85 mg once daily**: ATV 300 mg once daily / 100 mg once daily LPV 400 mg twice daily / 100 mg twice daily **150 mg once daily**: DRV 600 mg twice daily / 100 mg twice daily FPV 700 mg twice daily / 100 mg twice daily TPV 500 mg twice daily / 200 mg twice daily Standard Adult Dose (Stribild and Genvoya): • One tablet once daily with food. PK in Pregnancy: • PK studies in human pregnancy limited to case report of 1 woman. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Insufficient data are available on placental transfer of EVG/COBI. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 7).

Key to Abbreviations: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; DRV = darunavir; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

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Raltegravir (Isentress, RAL)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Raltegravir is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

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 the 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.[1]

Reproduction/Fertility

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

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).[1]

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.[1]

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.[1]

Human Studies

Pharmacokinetics

Raltegravir pharmacokinetics (PK) were evaluated in 42 women during pregnancy in the IMPAACT P1026s study. Raltegravir PKs in these women showed extensive variability as is also seen in non-pregnant individuals. Median raltegravir area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen between the third trimester and postpartum trough concentrations. Plasma HIV RNA levels were under 400 copies/mL in 92% of women at delivery. Given the high rates of virologic suppression and the lack of clear relationship between raltegravir concentration and virologic effect in non-pregnant adults, no change in dosing was recommended during pregnancy.[2] In a study of 22 women with paired third-trimester and postpartum data from the PANNA Network, the geometric mean ratios of third trimester/postpartum values were $AUC_{0\text{-}12hr}$ 0.71 (0.53–0.96), C_{max} 0.82 (0.55–1.253), and C_{12hr} 0.64 (0.34–1.22). One patient was below the target C_{12hr} in the third trimester and none were below

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the threshold postpartum. No change in dosing during pregnancy was recommended based on these data.[3]

In a single-center observational study of pregnant women who were started on raltegravir as part of intensification of an antiretroviral (ARV) regimen or part of triple ARV regimens, the raltegravir C_{12h} in the second and third trimester were similar to historical data in non-pregnant population and the cord blood/maternal plasma concentration ratio was 1.03.[4]

In the P1097 study of washout pharmacokinetics (PK) in 21 neonates born to women receiving ongoing raltegravir in pregnancy, raltegravir elimination was highly variable and extremely prolonged in some infants (median $t_{1/2}$ 26.6 hours, range 9.3–184 hours).[8] In a case report of an infant born at 30 weeks' gestation after the mother had received three doses of raltegravir, the cord blood level of raltegravir was 145 ng/mL; the level at age 2 days was 106 ng/mL and at 1 month was 29 ng/mL, still above the IC95 of 15 ng/mL.[5] In a report of 14 infants exposed to raltegravir *in utero*, the infants had no adverse effects and the raltegravir level had been within therapeutic range.[6]

Teratogenicity/Developmental Toxicity

As of July 31, 2015, six cases with defects have been reported among 192 infants with first-trimester exposure to raltegravir included in the Antiretroviral Pregnancy Registry—too few first-trimester exposures to be able to accurately calculate the prevalence of birth defects in exposed cases.[7]

Placental and Breast Milk Passage

In humans, raltegravir appears to readily cross the placenta. In the IMPAACT P1026s study, the ratio of cord blood-to-maternal-plasma was 1.5.[2] In the P1097 study, the median cord blood/maternal delivery plasma raltegravir concentration ratio was 1.48 (range 0.32–4.33), and in the PANNA study it was 1.21.[3,8] Other case reports have shown cord blood/maternal blood drug level ratios of 1.00 to 1.06.[9,10,11] In a series of three cases with preterm deliveries at 29 to 33 weeks' gestation (in 2 cases raltegravir was added to the maternal ARV regimen shortly before anticipated preterm delivery), cord blood-to-maternal-plasma ratios ranged from 0.44 to 1.88.[12]

Whether raltegravir is secreted in human breast milk is unknown.

Safety

In the P1026s Study and the PANNA study, raltegravir was well tolerated, with no treatment-related serious adverse events (AEs) in pregnant women, and all infants were at least 36 weeks' gestation at delivery.[2,3] In the P1097 study, no infant AEs were determined to be related to maternal raltegravir exposure; one (4.6%) infant received phototherapy for treatment of hyperbilirubinemia.[8] In multiple case reports and case series of 4, 5, and 14 pregnant women treated with raltegravir in combination with 2 or 3 other ARV drugs because of persistent viremia or late presentation, the drug was well tolerated and led to rapid reduction in HIV RNA levels.[13-18] However, in one case of similar use, 10- to 23-fold increases in maternal liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.[19] Drug levels were not measured in any of those studies. One case has been reported of drug reaction with eosinophilia and systemic symptoms syndrome with extensive pulmonary involvement in a postpartum woman that resolved with discontinuation of raltegravir. Such reactions have been reported in non-pregnant adults receiving raltegravir and should be considered in the differential diagnosis of fever during pregnancy or postpartum period in women on raltegravir.[20] In a study of 155 adult HIV-infected adults, mean age 49.2 years, started on raltegravir-containing therapy, skeletal muscle toxicity frequency was 23.9% and isolated creatine kinase (CK) elevation was reported in 21.3% (grade 1–2 and self-limiting); fewer than 3% of patients complained of myalgia or muscle weakness. Skeletal muscle toxicity and CK elevation were significantly associated with prior use of zidovudine, higher baseline CK levels, and a higher body mass index.[21]

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

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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.[22] 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_{max} of 4.5 µM, median C_{max} of 6.5 µM and maximum observed C_{max} of 10.2 µM).[22] Raltegravir should not be used in neonates until PK and toxicity studies have been completed.[8]

Chewable tablets contain phenylalanine.

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Raltegravir (RAL) *Isentress*	Film-Coated Tablets: • 400 mg Chewable Tablets: • 25 mg • 100 mg	Standard Adult Dose: • 400-mg film-coated tablets twice daily without regard to food. • Chewable and oral suspension doses are not interchangeable to either film-coated tablets or to each other. *With Rifampin:* • 800-mg film-coated tablets twice daily without regard to food. PK in Pregnancy: • Decreased levels in third trimester not of sufficient magnitude to warrant change in dosing. Dosing in Pregnancy: • No change in dose indicated.	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.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Antiretroviral 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:** <0.3

Key to Abbreviations: PK = pharmacokinetic; RAL = raltegravir

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Pharmacoenhancers

Glossary of Terms for Supplement
Carcinogenic: Producing or tending to produce cancer • 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.
Clastogenic: Causing disruption of or breakages in chromosomes
Genotoxic: Damaging to genetic material such as DNA and chromosomes
Mutagenic: Inducing or capable of inducing genetic mutation
Teratogenic: Interfering with fetal development and resulting in birth defects

Cobicistat (Tybost, COBI)

(Last updated October 26, 2016, last reviewed October 26, 2016)

Cobicistat is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

At cobicistat exposures 7 times and 16 times the human systemic exposure, no increases in tumor incidence were seen in male and female mice. In rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses up to twice the typical human exposure. The follicular cell findings are considered rat-specific, and not relevant to humans.[1]

Reproduction/Fertility

No effect has been seen on fertility in male or female rats.[1]

Teratogenicity/Developmental Toxicity

Rats and rabbits treated with cobicistat during pregnancy at 1.4 and 3.3 times higher than the recommended human exposure have shown no evidence of teratogenicity.[1]

Placental and Breast Milk Passage

No information is available on placental passage of cobicistat. Studies in rats have shown that cobicistat is secreted in breast milk.[2]

Human Studies in Pregnancy

Pharmacokinetics

Pharmacokinetic studies in pregnancy are limited to a single case report, which found that cobicistat area under the curve was reduced by 44% during the third trimester of pregnancy.[3]

Placental and Breast Milk Passage

No data are available on placental or breast milk passage of cobicistat in humans.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, no birth defects have been reported in 32 live births with first trimester exposure and 18 live births with second- or third-trimester exposure to cobicistat. The numbers of first-trimester exposures to cobicistat in humans are insufficient to be able to make a risk determination.[2]

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Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name.*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Cobicistat (COBI) *Tybost* **Elvitegravir/Cobicistat/ Tenofovir Disoproxil Fumarate/Emtricitabine** (EVG/COBI/ TDF/FTC) *Stribild* **Elvitegravir/Cobicistat/ Tenofovir Alafenamide/ Emtricitabine** (EVG/COBI/TAF/FTC) *Genvoya* **Atazanavir/Cobicistat** (ATV/COBI) *Evotaz* **Darunavir/Cobicistat** (DRV/COBI) *Prezcobix*	Tablet (Tybost): • 150mg Tablet (Stribild): • EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg Tablet (Genvoya): • EVG 150 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg Tablet (Evotaz): • ATV 300 mg plus COBI 150 mg Tablet (Prezcobix): • DRV 800 mg plus COBI 150 mg	Standard Adult Dose *Tybost:* • As an alternative PK booster with ATV or DRV: 1 tablet (150 mg) once daily with food. *Stribild, Genvoya, Evotaz, Prezcobix:* • 1 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 COBI are available. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

[a] Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 7).

Key to Abbreviations: ATV = atazanavir; COBI = cobicistat; DRV = darunavir; EVG = elvitegravir; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Ritonavir (Norvir, RTV)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Ritonavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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.[1]

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.[1]

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).[1]

Placental and Breast Milk Passage

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.

Human Studies in Pregnancy

Pharmacokinetics

A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in combination with zidovudine and lamivudine in pregnant HIV-infected women showed lower levels of ritonavir during pregnancy than postpartum.[2] 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.[3,4]

Placental and Breast Milk Passage

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.[5] In a Phase I study of pregnant women and their infants (PACTG 354), transplacental passage of ritonavir was minimal, with an average cord blood-to-maternal-delivery concentration ratio of 5.3%.[2] In a study of cord blood samples from 6 women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 5 of the women and was only 0.38 micrograms/mL in the remaining woman.[6] In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving lopinavir/ritonavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested *in*

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utero transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth while mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.47 for ritonavir.[7] However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

Teratogenicity/Developmental Toxicity

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 1.5-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% (63 of 2,720 births; 95% CI, 1.8% to 3.0%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[8]

Excerpt from Table 8[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Ritonavir (RTV) *Norvir*	Capsules: • 100 mg Tablets: • 100 mg Oral Solution: • 80 mg/mL	Standard Adult Dose as PK Booster for Other PIs: • 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) *Tablet:* • Take with food. *Capsule or Oral Solution:* • To improve tolerability, recommended to take with food if possible. PK in Pregnancy: • Lower levels during pregnancy compared with postpartum. Dosing in Pregnancy: No dosage adjustment necessary when used as booster.	Low placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Should only be used as low-dose booster for other PIs. Oral solution contains 43% alcohol and therefore may not be optimal for use in pregnancy.

[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:** <0.3

Key to Abbreviations: PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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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

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Appendix C: Acronyms (Last updated October 26, 2016; last reviewed October 26, 2016)

Acronym/Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ACOG	American College of Obstetricians and Gynecologists
ALT	alanine aminotransferase
anti-HBc	anti-hepatitis B core antibody
anti-HBS	hepatitis B surface antibody
AOR	adjusted odds ratio
AP	antepartum
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AUC	area under the curve
AZT	zidovudine
BID	twice daily
BMI	body mass index
CBC	complete blood count
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
COBI	cobicistat
CVS	chorionic villus sampling
CYP	cytochrome P
CYP3A4	cytochrome P450 3A4
d4T	stavudine
ddI	didanosine
DMPA	depot medroxyprogesterone acetate
DRV	darunavir
DRV/r	darunavir/ritonavir
DSMB	Data and Safety Monitoring Board

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DTG	dolutegravir
EC	enteric coated
ECG	electrocardiogram
EFV	efavirenz
EMS	ethyl methane sulfonate
ETR	etravirine
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed drug combination
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
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
IC_{50}	inhibitory concentration 50%
IDV	indinavir
IDV/r	indinavir/ritonavir
IGF	insulin-like growth factor
IgG	Immunoglobulin G
IP	intrapartum
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
IUD	intrauterine device
IV	intravenous/intravenously
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MAC	*Mycobacterium avium* complex
mtDNA	mitochondrial DNA
MVC	maraviroc

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NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor/non-nucleoside analogue reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor/nucleoside analogue reverse transcriptase inhibitor
NtRTI	nucleotide analogue reverse transcriptase inhibitor
NVP	nevirapine
OC	oral contraceptive
OI	opportunistic infection
OR	odds ratio
The Panel	The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PI	protease inhibitor
PK	pharmacokinetic
PO	orally
PP	postpartum
PPI	proton pump inhibitor
PrEP	pre-exposure prophylaxis
PTD	preterm delivery
RAL	raltegravir
RDS	respiratory distress syndrome
RPV	rilpivirine
RR	relative risk
RTV	ritonavir
SD	single dose
SQ	subcutaneous
SQV	saquinavir
SQV/r	saquinavir/ritonavir
STD	sexually transmitted disease
T20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TID	three times daily
TPV	tipranavir
TPV/r	tipranavir/ritonavir

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UGT	uridine diphosphate glucuronosyltransferase
WHO	World Health Organization
ZDV	zidovudine

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