

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection *and* Interventions to Reduce Perinatal HIV Transmission in the United States



Developed by the HHS Panel on Treatment of Pregnant Women with HIV Infection 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 Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinataGL.pdf>. Accessed (insert date) [include page numbers, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo website (<http://aidsinfo.nih.gov>).

What's New in the Guidelines

October 25, 2018

On October 25th, 2018, the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents (Adult Panel) updated guidance on the use of dolutegravir in adults and adolescents with HIV who are pregnant or of childbearing potential (see [Women with HIV](#) in the [Adult and Adolescent ARV Guidelines](#)). This guidance was developed in collaboration with the Panel on Treatment of Pregnant Women With HIV Infection and Prevention of Perinatal Transmission (Perinatal Panel). The Perinatal Panel is currently working on updating the guidelines to reflect the guidance given by the Adult Panel. Until the Perinatal Guidelines are published, please refer to the [Adult and Adolescent ARV Guidelines](#).

May 30, 2018

[Recommendations Regarding Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or Of Child Bearing Potential](#), a joint statement from the HHS Antiretroviral Guideline Panels, was released.

November 14, 2017

The guidelines text, appendices, and references were updated to include new data and publications where relevant. To facilitate access to relevant content, the guidelines now include three sections that will also appear in the [Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection: Maternal HIV Testing and Identification of Perinatal HIV Exposure, Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV Infection](#), and [Diagnosis of HIV Infection in Infants and Children](#). In response to community input, edits were made to continue to incorporate People-First Language, which focuses on the person rather than the disease and recognizes the importance of language in empowering individuals and reducing stigma. Language edits to change “HIV-infected women” to “women with HIV” or “women living with HIV” are reflected in the updated title of the Guidelines and the name of the Perinatal Panel. Major content changes are summarized below; all changes are highlighted throughout the guidelines.

Preconception Counseling and Care for Women of Childbearing Age Living with HIV

- [Table 3](#). Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives includes updated recommendations regarding atazanavir, atazanavir/ritonavir, atazanavir/cobicistat, and darunavir/cobicistat.

Reproductive Options for Couples with the Same or Differing HIV Status

- The Panel has updated recommendations regarding safer conception for couples who attempt conception with condomless sexual intercourse.

Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

- The section has been expanded to include maternal outcomes with information about hypertensive disorders of pregnancy in relation to HIV and antiretroviral therapy (ART).

Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Drugs

- This section was updated in accordance with changes in [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) (published October 19, 2017).
 - When a pregnant woman presents on an elvitegravir/cobicistat regimen, providers should consider switching to a more effective regimen. If an elvitegravir/cobicistat regimen is continued, viral load should be monitored frequently and therapeutic drug monitoring may be useful.
 - Drugs not recommended for initial use because of toxicity (stavudine, didanosine, and treatment-

dose ritonavir) should also be stopped in women who present during pregnancy while taking these medications.

Special Populations: HIV/Hepatitis B Virus Coinfection

- If women with HIV/HBV coinfection are virally suppressed on an antiretroviral (ARV) regimen that includes tenofovir alafenamide when they become pregnant, they can be offered the choice of continuing that ARV regimen or switching tenofovir alafenamide to tenofovir disoproxil fumarate in their regimen, since there are limited data about the use of tenofovir alafenamide in pregnancy.

Acute HIV Infection

- In order to rapidly suppress viral load to reduce the risk of perinatal HIV transmission in women with acute HIV infection during pregnancy, the Panel recommends initiating a ritonavir-boosted protease inhibitor-based regimen or a dolutegravir-based regimen with tenofovir disoproxil fumarate/emtricitabine. Dolutegravir-based regimens are not generally recommended as preferred for initial treatment in pregnant women, but they are a preferred option in the setting of acute HIV infection. See [Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women](#).
- Given the high risk of perinatal HIV transmission when acute HIV infection is diagnosed during pregnancy or breastfeeding, the Panel strongly recommends consultation with a pediatric HIV specialist regarding appropriate infant management and ARV prophylaxis regimens. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV Infection](#).

Pregnancy in Women Who Were Infected Perinatally

- The Panel recommends an enhanced focus on adherence interventions during pregnancy and after delivery for women with perinatal HIV infection.

Intrapartum Antiretroviral Therapy/Prophylaxis Care

- The Panel has added information about intrapartum intravenous (IV) zidovudine for women with HIV RNA between 50 and 999 copies/mL. There are inadequate data to determine whether administration of IV zidovudine to women with HIV RNA levels between 50 and 999 copies/mL provides any additional protection against perinatal transmission, but some experts would administer IV zidovudine to women with RNA levels in this range, as the transmission risk is slightly higher when HIV RNA is in the range of 50 to 999 copies/mL compared to <50 copies/mL.

Other Intrapartum Management Considerations

- In women who are receiving a cobicistat, a potent cytochrome P450 (CYP) 3A4 enzyme inhibitor, methergine should be used only if no alternative treatments for postpartum hemorrhage are available and the need for pharmacologic treatment outweighs the risks due to risk of exaggerated vasoconstrictive response.

Postpartum Care

- The Panel recommends discussing potential barriers to formula feeding in order to help mothers follow infant feeding recommendations and avoid breastfeeding.
- The mother should receive ART prescriptions for herself and ARVs for the newborn prior to discharge.

Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV Infection

- This section, formerly titled Infant Antiretroviral Prophylaxis, has been updated to reflect emerging issues in the ARV management of infants born to women with HIV. The Panel recommends that the

selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission. The uses of ARV regimens in newborns include:

- ARV prophylaxis – the administration of one or more ARVs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition.
- Empiric HIV therapy – the administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later confirmed to be HIV-infected, but it also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not become infected with HIV.
- HIV therapy – the administration of three-drug combination ARVs at treatment dosages (ART) to newborns with confirmed HIV infection (see [Diagnosis of HIV Infection](#)).
- The Panel recommends combination ARV prophylaxis or empiric HIV therapy for newborns at higher risk of HIV acquisition and HIV therapy for newborns with confirmed HIV infection.
- Table 7. Antiretroviral Management According to Risk of HIV Infection in the Newborn has been added to provide an overview and guidance about ARV management for different clinical categories.
- Table 8. Newborn Antiretroviral Dosing Recommendations has been revised in accordance with updated Panel recommendations for newborn ARV management.

Initial Postnatal Management of the Neonate Exposed to HIV

- Recommendations and detailed information about infant HIV testing are now available in a new section, [Diagnosis of HIV Infection in Infants and Children](#).

Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs

- The Panel recommends including information about *in utero* and neonatal ARV exposure in the long-term medical record of an uninfected child.

Maternal HIV Testing and Identification of Perinatal HIV Exposure

- The Panel has added a new section, shared with the Pediatric Antiretroviral Guidelines, that details recommendations about maternal HIV testing in relation to pregnancy and identification of perinatal HIV exposure in infants and children.

Diagnosis of HIV Infection in Infants and Children

- The Panel has added a new section, [Diagnosis of HIV Infection in Infants and Children](#), with recommendations and detailed content about the timing and types of tests used to diagnose HIV infection in infants and children or determine that they are uninfected.

Table 9: Antiretroviral Drug Use in Pregnant Women with HIV: 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

- Sections were updated with new data for each drug, including new formulations and fixed-dose combinations. The Panel added a drug section subheading for Infant Safety Outcomes and revised a subheading to Teratogenicity/Adverse Pregnancy Outcomes to facilitate user access to information.

October 19, 2017

Recommendations for Use of Antiretroviral Drugs during Pregnancy and Table 6: What to Start: Initial Combination Regimens for Antiretroviral Naive-Pregnant Women

- This section was updated to include new data and publications where relevant.
- After review of available study findings, the Panel continues to recommend tenofovir as a component of first line therapy and zidovudine as a second-line agent for use in antiretroviral-naive pregnant women living with HIV in the United States.
- Based on limited but increasing experience with use in pregnancy, dolutegravir is now classified as an Alternative agent for antiretroviral-naive pregnant women.
- The Panel has changed its classification of elvitegravir/cobicistat to Not Recommended for Initial Use in Pregnancy based on data showing inadequate levels of both drugs during the 2nd and 3rd trimester as well as viral breakthroughs.
- When a pregnant woman presents on elvitegravir/cobicistat regimens, providers should consider switching to a more effective regimen. If elvitegravir/cobicistat regimens are continued, viral load should be monitored frequently and therapeutic drug monitoring may be useful.
- Maraviroc and enfuvirtide are not recommended for use in antiretroviral-naive pregnant women, in accordance with guidelines for non-pregnant adults and due to lack of pharmacokinetic and safety data in pregnancy.

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 about [tenofovir disoproxil fumarate](#).

October 5, 2017

On October 5, 2017, the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel) released the following statement:

A recent [BMJ](#) clinical practice guideline recommended that pregnant women living with HIV should not be treated with the combination of tenofovir/emtricitabine (TDF/FTC). After fully considering the results of the [PROMISE study](#), both the Panel and the [British HIV Association](#) do not support these recommendations. The Panel found that there were important study design and statistical considerations that limit the generalizability of the PROMISE findings, and in consideration of all available evidence, the Panel concluded that the assessment of expected benefits and harms favored TDF/FTC over ZDV/3TC, leading the Panel to keep TDF/FTC as a Preferred recommendation and ZDV/3TC as an Alternative recommendation for antiretroviral-naive pregnant women living with HIV in the United States.

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Members of the Panel on Treatment of Pregnant Woman with HIV Infection and Prevention of Perinatal Transmission (Last updated November 14, 2017; last reviewed November 14, 2017)

Revisions to the **October 26, 2016** *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection 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 Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (a Working Group of the Office of AIDS Research Advisory Council).

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Key to Acronyms: DSMB = Data Safety Monitoring Board; CC = Panel Co-Chairs; ES = Executive Secretary; ExOM = *Ex Officio* Member; HHS = Member from Department of Health and Human Services; M = Member; N/A = Not applicable; NVO = Nonvoting Observer

Introduction (Last updated November 14, 2017; last reviewed November 14, 2017)

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 both the epidemic and also in the science of prevention and treatment. With the implementation of recommendations for universal prenatal HIV counseling and testing, maternal antiretroviral treatment (ART) for all pregnant women living with HIV, scheduled cesarean delivery for women with HIV RNA >1,000 near delivery, infant antiretroviral (ARV) prophylaxis, 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

It is estimated that 8,700 women living with HIV (95% CI, 8,400–8,800) give birth annually in the United States.⁴ A focus on appropriate overall medical care for women living with HIV 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 women living with HIV 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 October 2016 Perinatal Guidelines. The Department of Health and Human Services Panel on Treatment of Pregnant Women Living with HIV and Prevention of Perinatal Transmission (the Panel), a working group of the Office of AIDS Research Advisory Council, develops these guidelines. The guidelines provide health care providers with information for discussion with pregnant women living with HIV infection to enable collaborative, informed decision-making regarding the use of ARV drugs during pregnancy, use of scheduled cesarean delivery to reduce perinatal transmission of HIV, and decision-making around use of ARV drugs for prophylaxis of infants exposed to HIV. The recommendations in these 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 AIDSinfo website (<http://aidsinfo.nih.gov>). The National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service providing free clinical consultation to providers caring for women living with or at risk for HIV and their children, and serves as a resource for obtaining expert consultation for individual cases.

The Panel supports recommendations to ensure that women receive the full benefit of ART for their own health and for prevention of perinatal transmission. However, the Panel recognizes the right of women to make informed choices about treatment during pregnancy, even when their choices might differ from a health care provider's recommendations.

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 managing the care 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.

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 living with HIV 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 managing the care of pregnant women living with HIV (e.g., training in obstetrics/gynecology, infectious diseases, or women's health), pharmacology of ARV drugs during pregnancy , 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, 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 IV of the guidelines.
Financial Disclosures	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the <i>AIDSinfo</i> website (http://aidsinfo.nih.gov).
Users of the Guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Developer	The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission—a working group of the 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 technical assistance consultant 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 pregnant women living with HIV and their infants. Other Guidelines (all available on the <i>AIDSinfo</i> website http://www.aidsinfo.nih.gov) outline the use of ARV agents in non-pregnant adults and adolescents with HIV; use of ARV agents in infants and children with HIV; treatment and prevention of opportunistic infections (OIs) in adults and adolescents with HIV, including pregnant women; treatment and prevention of OIs in children exposed to HIV or with HIV infection; 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.

Guidelines Development Process

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

Topic	Comment
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 <i>AIDSinfo</i> website until the guidelines can be updated with appropriate changes. Updated guidelines are available on the <i>AIDSinfo</i> website (http://www.aidsinfo.nih.gov).
Public Comments	A 2-week public comment period follows release of the updated guidelines on the <i>AIDSinfo</i> 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@aidinfo.nih.gov .

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** that represents the quality of evidence.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

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Maternal HIV Testing and Identification of Perinatal HIV Exposure

(Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- HIV testing is recommended as standard of care for all sexually active women, and should be a routine component of preconception care **(AII)**.
- All pregnant HIV-negative women in the United States should be tested as early as possible during each pregnancy **(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)**.
- Expedited HIV testing at the time of labor or delivery should be performed for any woman with undocumented HIV status; testing should be available 24 hours a day, and results available within 1 hour **(AII)**. If results are positive, intrapartum and infant postnatal antiretroviral (ARV) drug prophylaxis should be initiated immediately, pending results of supplemental HIV testing **(AII)** see [Perinatal Guidelines](#) for guidance.
- Women who have not been tested for HIV before or during labor should undergo expedited HIV antibody testing during the immediate postpartum period (or their newborns should undergo expedited HIV antibody testing) **(AII)**. If results in mother or infant are positive, an appropriate infant antiretroviral (ARV) drug regimen should be initiated immediately, and the mothers should not breastfeed unless supplemental HIV testing is negative **(AII)**. Infants with initial positive HIV viral tests (RNA, DNA) should have their ARV regimen modified, if necessary, to a three-drug combination of ARV drugs at treatment dosages (antiretroviral therapy) (see [Antiretroviral Management of Exposed Infants](#)) **(AII)**.
- Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
- HIV testing to determine HIV status is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown **(AIII)**.

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

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

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

HIV Testing in Pregnancy

HIV infection should be identified prior to pregnancy (see [Preconception Care in the Perinatal Guidelines](#)) or as early in pregnancy as possible. This provides the best opportunity to prevent infant acquisition of HIV, and to identify and start therapy as soon as possible in infants who acquire HIV. Universal voluntary HIV testing is recommended as the standard of care for all pregnant women in the United States by The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel), the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force.¹⁻⁵ All HIV testing should be performed in a manner consistent with state and local laws (<http://nccc.ucsf.edu/clinical-resources/hiv-aids-resources/state-hiv-testing-laws/>). CDC recommends the “opt-out” approach, which involves notifying pregnant women that HIV testing will be performed as part of routine care unless they choose not to be tested for HIV. The “opt-out” approach during pregnancy is allowed in every jurisdiction. The “opt-in” approach involves obtaining specific consent before testing and has been associated with lower testing rates.^{6,7} The mandatory newborn HIV testing approach, adopted by several states, involves testing of newborns for perinatal HIV exposure with or without maternal consent, if prenatal or intrapartum maternal testing is not performed.

Knowledge of antenatal maternal HIV status enables:

- Women living with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections for their own health.
- **Initiation of treatment in the identified women, which** may also decrease risk of transmission to their partners.^{2,8,9}
- Provision of ART to the mother during pregnancy and labor, and antiretroviral (ARV) drug prophylaxis to the newborn to reduce the risk of perinatal transmission of HIV;
- Counseling of women living with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce perinatal transmission of HIV;¹⁰⁻¹²
- Counseling of women living with HIV about the risks of HIV transmission through breast milk (breastfeeding is not recommended for women with HIV living in the United States);¹³
- Initiation of prophylaxis against *Pneumocystis jirovecii* pneumonia beginning at age 4 to 6 weeks in all infants with HIV and in those infants exposed to HIV whose HIV status remains indeterminate;¹⁴ and
- Early diagnostic evaluation of infants exposed to HIV, **(see Diagnosis section)** as well as testing of partners and other children, to permit prompt initiation of ART in individuals with HIV.^{1,15,16}

Technological improvements have resulted in increased sensitivity to early HIV acquisition and reduced performance time for laboratory-based assays, allowing completion in less than 1 hour. Accordingly, the Panel now incorporates CDC's 2014 HIV Laboratory Testing Recommendations.¹⁷ The guidelines recommend that HIV testing begin with an immunoassay capable of detecting HIV-1 antibodies and HIV-1 p24 antigen (referred to as an antigen/antibody combination immunoassay, **or a fourth-generation HIV antigen/antibody assay**). Individuals with a reactive antigen/antibody combination assay should be tested further with an HIV-1/HIV-2 antibody differentiation assay (supplemental testing). Individuals with a reactive antigen/antibody combination immunoassay and a nonreactive differentiation test should be tested with a Food and Drug Administration-approved HIV nucleic acid test (NAT) to establish diagnosis of acute HIV (see <http://www.cdc.gov/hiv/pdf/hivtestingalgorithmrecommendation-final.pdf#page=11>).

The **antigen/antibody combination** immunoassay is the test of choice and can be done quickly (referred to as expedited), but requires trained laboratory staff and therefore may not be available in some hospitals 24 hours a day. If this test is unavailable, then initial testing should be performed by the most sensitive expedited or rapid test available. Every delivery unit needs to have access to an HIV test that can be done rapidly (i.e., in <1 hour) 24 hours a day. If positive, testing for confirmation of HIV should be done as soon as possible (as with all initial positive assays). Because older tests have lower sensitivity in the context of recent acquisition of HIV, testing following the 2014 CDC algorithm should be considered as soon as feasible if HIV risk cannot be ruled out. Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider.

Repeat HIV Testing in the Third Trimester

Repeat HIV testing during the third trimester, before 36 weeks' gestation, is recommended **(see Acute HIV in the Perinatal Guidelines)**¹⁸ for women who:

- Are receiving health care in a jurisdiction that has a high incidence of HIV or AIDS in women between ages 15 and 45, or who are receiving health care in facilities in which prenatal screening identifies at least 1 pregnant woman with HIV per 1,000 women screened (a list of areas where such screening is recommended is found in the [2006 CDC recommendations](#); a more up-to-date list is forthcoming);
- Are known to be at high risk of acquiring HIV (e.g., those who are injection drug users or partners of

injection drug users, exchange sex for money or drugs, are sex partners of individuals with HIV, have had a new or more than one sex partner during the current pregnancy, or have been diagnosed with a new sexually transmitted disease during pregnancy); or

- Have signs or symptoms of acute HIV.^{2,3,19,20}

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester, using an antigen/antibody **combination** immunoassay, as these tests have a higher sensitivity in the setting of acute **HIV-1**, compared to older antibody tests.^{17,21} When acute retroviral HIV is suspected during pregnancy, in the intrapartum period, or while breastfeeding, a plasma HIV RNA test should be obtained in conjunction with an antigen/antibody combination immunoassay (**see the [Acute and Recent \[Early\] HIV Infection section in the \[Adult and Adolescent Guidelines\]\(#\)](#)**).

HIV Testing During Labor in Women with Unknown HIV Status

HIV testing is recommended to screen women in labor whose HIV status is undocumented and to identify HIV exposure in their infants. HIV testing during labor has been found to be feasible, accurate, timely, and useful both in ensuring prompt initiation of intrapartum and neonatal ARV prophylaxis and in reducing perinatal transmission of HIV (see [Intrapartum Care](#) in the [Perinatal Guidelines](#)).^{1-4,15}

Policies and procedures must be in place to ensure that staff are prepared to provide patient education and expedited HIV testing, that appropriate ARV drugs are available whenever needed, and that follow-up procedures are in place for women diagnosed with HIV and their infants.

If the antigen/antibody combination immunoassay is not available, initial testing should be performed by the most sensitive expedited test available.

A positive expedited HIV test result must be followed by a supplemental test.¹⁷ Immediate initiation of ARV drug prophylaxis (**including intravenous intrapartum zidovudine**) for prevention of perinatal transmission of HIV is recommended pending the supplemental result after an initial positive expedited HIV test (see [Intrapartum Management](#) in the [Perinatal Guidelines](#)).^{1-5,15} No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay.¹⁷

HIV Testing During the Postnatal Period

Women who have not been tested for HIV before or during labor should be offered expedited testing during the immediate postpartum period; **if mothers are unavailable for testing**, their newborns should undergo expedited HIV testing.^{1,3,15} Maternal testing should be done using **the combination** antigen/antibody immunoassay to screen for established and acute HIV-1; results should be obtained in <1 hour. If acute HIV-1 is a possibility, then a plasma HIV NAT test should be sent as well. Use of expedited HIV assays for prompt identification of infants exposed to HIV is essential because neonatal ARV prophylaxis should be initiated as soon as possible after birth—ideally no more than 6 hours after birth—to be effective for the prevention of perinatal transmission. When an initial HIV test is positive in mother or infant, initiation of infant ARV drug prophylaxis and counseling against initiation of breastfeeding is strongly recommended pending results of supplemental HIV tests to confirm and/or differentiate between HIV-1 and HIV-2 (see [ARV Management of Newborns with Perinatal HIV Exposure](#)). If supplemental tests are negative and acute HIV is excluded, infant ARV drug prophylaxis can be discontinued. In the absence of ongoing maternal HIV exposure, breastfeeding can be initiated. Mechanisms should be developed to facilitate HIV screening for infants who have been abandoned and are in the custody of the state.

Infant HIV Testing when Maternal HIV Test Results are Unavailable

When maternal HIV test results are unavailable (e.g., for infants and children who are in foster care) or their accuracy cannot be evaluated (e.g., for infants and children adopted from a country where results are not

reported in English), HIV testing is indicated to identify HIV in those infants or **children.**¹ **The choice of test will vary based on the age of the child (see [Diagnosis of HIV Infection in Infants and Children](#)).**

Acute Maternal HIV Infection During Pregnancy or Breastfeeding

The risk of perinatal transmission of HIV is increased in infants born to women who have acute HIV during pregnancy or lactation.^{18,22-25} The antigen/antibody **combination** immunoassay will detect acute infection more readily than other immunoassays. If acute HIV is suspected, a plasma HIV RNA test should be sent as well. Women with possible acute HIV who are breastfeeding should cease breastfeeding immediately until HIV is confirmed or excluded.¹³ Pumping and temporarily discarding breast milk can be recommended and (if HIV infection is excluded), in the absence of ongoing maternal exposure to HIV, breastfeeding can resume. Care of pregnant or breastfeeding women identified with acute or early HIV, and their infants, should follow the recommendations in the [Perinatal Guidelines](#).

Other Issues

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

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Preconception Counseling and Care for Women of Childbearing Age Living with HIV (Last updated November 14, 2017; last reviewed November 14, 2017)

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) and prevention (e.g., access to syringe services program) should be provided (AII).
- All women living with HIV who are 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 women of childbearing age living with HIV, 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; however, drug-drug interactions between hormonal contraceptives and ART should be considered (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

Overview

The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), 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 women of reproductive age living with HIV 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, women living with HIV 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 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 women living with HIV. 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.^{9,18}

- 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 (see [Reproductive Options](#) section).
- Encourage sexual partners to receive HIV counseling and testing so they can seek HIV care if they have HIV infection and seek advice about oral pre-exposure prophylaxis (PrEP) and other measures to prevent HIV acquisition if they do not have HIV infection.
- Counsel on eliminating alcohol, tobacco, and other drugs of abuse or appropriately treat and prevent when elimination is not feasible (e.g., methadone program, access to syringe services program).
- Counsel women contemplating pregnancy to take a daily multivitamin that contains 400 mcg of folic acid to help prevent certain birth defects. Women who are at higher risk of having a child with a neural tube defect than the baseline population are candidates for higher (1 to 4 mg) dose **folic acid** supplementation.
- 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 women living with HIV 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 virus (HBV) status, the potential for teratogenicity, and possible adverse outcomes for mother and fetus.¹⁹⁻²¹
- Use the preconception period in women who are contemplating pregnancy to modify their ART regimen to optimize virologic suppression and minimize potential adverse effects.
- 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 a partner that does not have HIV infection.
- 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, HBV, and tetanus. All women, including those with HIV infection, should receive Tdap vaccination during each pregnancy.
- Offer all women who do not currently desire pregnancy effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Women living with HIV can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs).²² 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 (see [ACOG Guidelines](#) for emergency contraception). 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.²³ There are no data on potential interactions between ARV drugs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is predominantly metabolized by CYP3A4, so interactions can be expected (see <http://www.hiv-druginteractions.org/checker>).

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

Drug-drug interactions between hormonal contraceptives and ART should be considered (see [Table 3](#)).

Data on drug interactions between ARV agents and hormonal contraceptives primarily come from drug labels and limited studies.²³⁻³⁹ The contraceptive effectiveness of the levonorgestrel IUD (Mirena) is largely through local (i.e., intrauterine) release of levonorgestrel, not through systemic absorption. The [CDC’s U.S. Medical Eligibility Criteria for Contraceptive Use](#) list the levonorgestrel IUD (Mirena) as category 1 (no restrictions) in drug interactions with all ARVs listed in women who already have IUD and category 1/2 (benefits outweigh risk) for those initiating use of an IUD.

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 women with HIV in Swaziland using levonorgestrel implants (Jadelle), 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.³⁵ **In a study using data from 5,153 women with HIV followed prospectively for 1 to 3 years, 9% of women ever used implants (mostly levonorgestrel), 40% used injectables, and 14% used oral contraceptives; 31% of women ever used ART, mostly nevirapine (75%) or EFV (15%). Among women not using contraception, pregnancy rates were 13.2 and 22.5 per 100 person-years for those on and not on ART, respectively. Implants greatly reduced the incidence of pregnancy among women on ART (aHR 0.06, 95% CI, 0.01–0.45) and not on ART (aHR 0.05, 95% CI, 0.02–0.11).** Injectables and oral contraceptives also reduced pregnancy risk, though by lesser degrees. ART use did not significantly diminish contraceptive effectiveness, although all methods showed nonstatistically significant reduced contraceptive effectiveness when concurrently using efavirenz.⁴⁰ Scarsi et al. reported on 3 groups of Ugandan women living with HIV (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, 24, 36, and 48 weeks post-insertion. The geometric mean ratio of levonorgestrel (efavirenz-based vs. ART-naïve patients) was 0.53 at 24 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-naïve or nevirapine groups.³⁹

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 (etonogestrel/levonorgestrel) 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.^{35,41,42} 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.^{25,27,37,43} Nucleoside reverse transcriptase inhibitors have no effect on hormonal contraceptive doses.

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, levonorgestrel 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 on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends use of oral contraceptives containing ≤30 µg ethinyl estradiol. The Panel does 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%).

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	<p><u>COC:</u></p> <ul style="list-style-type: none"> No effect on EE concentrations ↓ active metabolites of norgestimate LN AUC ↓ 83%; norelgestromin AUC ↓ 64%²⁸ Etonogestrel (in COC) C24 ↓ 61%³⁴ <p><u>DMPA:</u></p> <ul style="list-style-type: none"> No effect on DMPA levels^{25,27} <p><u>Etonogestrel Implant:</u></p> <ul style="list-style-type: none"> Etonogestrel AUC ↓ 63% to 82%^{44,45} <p><u>LN Implant:</u></p> <ul style="list-style-type: none"> LN AUC ↓ 47%³⁹ LN (emergency contraception) AUC ↓ 58%²³ <p><u>Changes in ARV Levels and/or Effects on HIV:</u></p> <p><u>COC:</u></p> <ul style="list-style-type: none"> No effect on EFV concentrations²⁸ EFV C12 ↓ 22%; was under therapeutic threshold in 3/16 subjects³⁴ <p><u>DMPA:</u></p> <ul style="list-style-type: none"> No effect on HIV disease progression^{25,46,47} No effect on EFV concentrations²⁵ <p><u>LN Implant:</u></p> <ul style="list-style-type: none"> No effect on HIV disease progression³⁹ 	<p><u>COC:</u></p> <ul style="list-style-type: none"> Pregnancy rates no difference⁴⁰ Pregnancy rate higher (13%) in women using COCs and EFV than COCs alone^{42,48} Progesterone >3 (a surrogate for ovulation) in 3/16⁴⁹ No ovulations²⁸ <p><u>DMPA:</u></p> <ul style="list-style-type: none"> No increase in pregnancy^{25,40,42,47} Low progesterone^{25,27,47} <p><u>Etonogestrel Implant:</u></p> <ul style="list-style-type: none"> Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods⁴² Presumptive ovulation in 5%⁴⁴ <p><u>LN Implant:</u></p> <ul style="list-style-type: none"> 12% pregnancy rate³⁵ 15% pregnancy rate³⁹ Pregnancy rate higher with EFV compared with no ART, but still lower than other hormonal methods⁴² No increase in pregnancy rate⁴⁰ 	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.	<p>For COCs, some studies suggest higher pregnancy rate and ovulation and decreased progestin levels. EFV may decrease, but clinical significance unclear.</p> <p>For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also, no effect on HIV disease progression or EFV levels.</p> <p>For implants, some studies suggest higher pregnancy rate and decreased hormone levels.</p>

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
NNRTIs, continued							
ETR	EE AUC ↑ 22% ⁵⁰ <u>NE:</u> • No significant effect ⁵⁰	<u>COC:</u> • No ovulations ⁵⁰	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, 1 study found no ovulations and no significant change in progestin levels. No evidence on POPs.
NVP	EE AUC ↓ 29%; ⁵¹ EE AUC no change ⁵² NE AUC ↓ 18% ⁵¹ Etonogestrel (in COC) C24 decreased 22% ³⁴ <u>DMPA:</u> • No significant change ²⁵ <u>LN Implant:</u> • LN AUC ↑ 35% ³⁹ <u>Changes in ARV Levels and/or Effects on HIV</u> <u>COC:</u> • NVP no significant effect ^{49,51,53} <u>DMPA:</u> • No effect on HIV disease progression ^{25,46,47,54} <u>LN Implant:</u> • No effect on HIV disease progression ^{39,55}	<u>COC:</u> • No increase in pregnancy rate ^{40,42,48,56,57} • No ovulations ^{49,52,57} <u>DMPA:</u> • No increase in pregnancy rate ^{40,42,47,56} • No ovulations ²⁵ <u>Etonogestrel Implant:</u> • No increase in pregnancy rate ⁴² <u>LN Implant:</u> • No increase in pregnancy rate ^{35,39,40,42,55}	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.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPA ^a	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
NNRTIs, continued							
RPV	EE AUC ↑ 14% ³³ <u>NE:</u> • No significant change ³³ <u>Changes in ARV Levels and/or Effects on HIV</u> <u>COC:</u> • No change in RPV levels compared to historical controls ³³	<u>COC:</u> • No change in progesterone ³³	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 progesterin levels. Also, no change in RPV levels. No evidence on POPs.
RTV-Boosted PIs							
ATV/r	EE AUC ↓ 19% ⁵⁸ Norgestimate AUC ↑ 85% ⁵⁸ <u>POP:</u> • NE AUC ↑ 50% ⁵⁹	N/A	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, increase in progesterin levels but only 1 study. For POPs, increase in progesterin levels but only 1 study. RTV inhibits CYP3A4 which may increase contraceptive hormone levels.
DRV/r	EE AUC ↓ 44% ⁶⁰ NE AUC ↓ 14% ⁶⁰	N/A	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 progesterin levels. No evidence on POPs.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPA ^a	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
RTV-Boosted PIs, continued							
FPV/r	EE AUC ↓ 37% ⁶¹ NE AUC ↓ 34% ⁶¹ FPV/r level: no change ⁶¹	N/A	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 POPs.
LPV/r	EE AUC ↓ 55% ²⁴ NE AUC ↓ 17% <u>Patch:</u> • EE AUC ↓ 45% ²⁴ • Norelgestromin AUC ↑ 83% ²⁴ <u>DMPA:</u> • DMPA AUC ↑ 46% ³⁷ <u>Etonogestrel Implant:</u> • Etonogestrel AUC ↑ 52% ⁴⁴ <u>Changes in ARV Levels and/or Effects on HIV</u> <u>Patch:</u> • LPV/r level ↓ 19% ²⁴ <u>DMPA:</u> • No effect on HIV disease progression ³⁷ • LPV/r no change ³⁷	<u>COC:</u> • Increased pregnancy rate, but CIs overlap ⁴² <u>Patch:</u> • No ovulations ²⁴ <u>DMPA:</u> • No pregnancies, no ovulations ³⁷ • Increased pregnancy rate, but CIs overlap ⁴² <u>Etonogestrel Implant:</u> • No increase in pregnancy rate ⁴² <u>LN Implant:</u> • No increase in pregnancy rate. ^{35,42}	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.

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 for POPs	Dosing Recommendation/ Clinical Comment for DMPA ^a	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants	Justification/Evidence for Recommendation
RTV-Boosted PIs, continued							
SQV/r	<p>↓ EE⁶²</p> <p><u>Changes in ARV Levels and/or Effects on HIV:</u></p> <p>COC:</p> <ul style="list-style-type: none"> • SQV/r no change⁶³ 	N/A	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.	<p>No information on progestin levels for CHCs or POPs.</p> <p>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.</p>
TPV/r	<p>EE AUC ↓ 48%⁶⁴</p> <p><u>NE:</u></p> <ul style="list-style-type: none"> • No significant change⁶⁴ <p><u>Changes in ARV Levels and/or Effects on HIV</u></p> <ul style="list-style-type: none"> • TPV no change⁶⁴ 	N/A	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.	<p>For COCs, no significant change in progestin levels but only from product label.</p> <p>No evidence on POPs.</p> <p>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.</p>

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% ⁶⁵ • NE AUC ↑ 110% ⁶⁵	N/A	Prescribe oral contraceptive that contains no more than 30 mcg of EE, or recommend alternative contraceptive method.	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 POPs.
ATV/c	Drospirenone AUC ↑ 2.3-fold; EE AUC ↓ 22% ⁶⁶	N/A	Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia. Consider alternative or additional contraceptive method.	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 POPs.
DRV/c	Drospirenone AUC ↑ 1.6-fold; EE AUC ↓ 30% ⁶⁶	N/A	In combination with drospirenone containing COCs, clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method.	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 POPs.

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
PIs without RTV, continued							
FPV	<p><u>COC:</u> APV: • EE AUC no change, C_{min} ↑ 32% • NE AUC ↑ 18%, C_{min} ↑ 45%⁶¹</p> <p><u>FPV with EE/Norethindrone:</u> • ↓ APV (AUC 22%, C_{min} 20%)⁶¹</p>	N/A	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 FPV alone with ethinyl estradiol/norethindrone may lead to loss of virologic response. No evidence on POPs.
IDV	<p><u>COC:</u> • EE AUC ↑ 22% • NE AUC ↑ 26%⁶⁷</p>	<p><u>COCs:</u> • No pregnancies among women taking IDV and COCs⁴⁸</p>	No additional contraceptive protection is needed.	For COCs, small increases in EE and progestin, and 1 clinical study did not suggest any efficacy concerns. No evidence on POPs.			
NFV	<p><u>COC:</u> • EE AUC ↓ 47% • NE AUC ↓ 18%⁶⁸</p> <p><u>DMPA:</u> • No change²⁵</p> <p><u>NFV:</u> • AUC ↓ 18%</p>	<p><u>COCs:</u> • 1 small study suggested that women using COCs and NFV may have had higher pregnancy rates than those using COCs alone⁴⁸</p> <p><u>DMPA:</u> • No pregnancies, no ovulations^{25,47} • CD4 count/HIV RNA: no change^{25,47}</p>	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; 1 small clinical study suggests possible higher pregnancy rate with COC and NFV use. DMPA, PK, and clinical data demonstrate no change. However, NFV AUC slightly decreased. No evidence on POPs or implants.
CCR5 Antagonist							
MVC	<p><u>COC:</u> • No significant effect on EE or LN⁶⁹</p>	N/A	No additional contraceptive protection is needed.	For COCs, no change in EE or progestin. No clinical data. No evidence on POPs.			

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	<u>COC:</u> • EE no change • Norgestimate AUC ↑ 14% ⁷⁰	N/A	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 POPs.
DTG	<u>COC:</u> • No significant effect on norgestimate or EE • DTG AUC no change ³⁸	N/A	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 POPs.
EVG/c	<u>EVG/COBI/FTC/TDF</u> <u>COC:</u> • Norgestimate AUC ↑ 126% EE AUC ↓ 25% ⁷¹	N/A	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 EE were observed. No clinical data. No evidence on POPs.

^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/c = atazanavir/cobicistat**; ATV/r = atazanavir/ritonavir; AUC = area under the curve; CHC = combination hormonal contraceptives; **CI = confidence interval**; C_{min} = minimum plasma concentration; COBI = cobicistat; **COC/P/R = combined oral contraceptives/patch/ring**; DMPA = depot medroxyprogesterone acetate; **DRV/c = darunavir/cobicistat**; DRV/r = darunavir/ritonavir; DTG = dolutegravir; e = estrogen; EE = ethinyl estradiol; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; **EVG/c = elvitegravir/cobicistat**; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; IDV = indinavir; LN = levonorgestrel; LPV/r = lopinavir/ritonavir; MVC = maraviroc; **NE = norethindrone**; NFV = nelfinavir; NVP = nevirapine; P = progestin; PI = protease inhibitor; PI/r = ritonavir boosted-protease inhibitor; **PK = pharmacokinetic**; POP = progesterone-only oral contraceptive pills; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; **TDF = tenofovir disoproxil fumarate**; TPV/r = tipranavir/ritonavir

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Tables 15a, 15b, and 15d. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>.

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Reproductive Options for Couples with the Same or Differing HIV Status (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

For Couples Who Want to Conceive When One or Both Partners are Living with HIV:

- 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)**.
- Partners living with HIV infection should attain maximum viral suppression before attempting conception to prevent HIV sexual transmission **(AI)** and, for women living with HIV, to minimize the risk of HIV transmission to the infant **(AII)**.
- For couples with differing HIV status, when the woman is living with HIV, assisted insemination at home or in a provider's office with a partner's semen during the peri-ovulatory period is recommended as a conception strategy that eliminates the risk of HIV transmission to the partner without HIV **(AIII)**.
- For couples with differing HIV status, when the man is living with HIV, the use of donor sperm from a man who is HIV-uninfected can be used as a conception strategy that eliminates the risk of HIV transmission to the partner without HIV **(BIII)**.
- For couples with differing HIV status, when the partner living with HIV is on ART and has achieved sustained viral suppression, sexual intercourse without a condom limited to the 2 to 3 days before and the day of ovulation (peak fertility) is an approach to conception with very low risk of sexual HIV transmission to the partner without HIV **(BII)**.
- For couples with differing HIV status who attempt conception via sexual intercourse without a condom (despite counseling) when the partner living with HIV has not been able to achieve viral suppression or when the viral suppression status is not known, administration of antiretroviral pre-exposure prophylaxis (PrEP) to the partner without HIV is recommended to reduce the risk of sexual transmission of HIV **(AI)**. Couples should still be counseled to limit sex (without condoms) to the period of peak fertility **(AIII)**.
- For couples with differing HIV status who attempt conception (sexual intercourse without a condom limited to peak fertility) when the partner living with HIV has achieved viral suppression, it is unclear whether administering PrEP to the partner without HIV further reduces the risk of sexual transmission **(CIII)**.

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

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

The objective of this section is to provide guidance for safe conception and pregnancy while maximizing efforts to prevent HIV transmission to partners and infants.

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

Couples with Differing HIV Status

Before conception is attempted, the partner living with HIV 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 persons living with HIV with CD4 T lymphocyte (CD4) cell counts of 350 to 550 cells/mm³ could prevent sexual transmission of HIV among couples with differing HIV status. 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 93% reduction in sexual transmission of HIV to the partner. Of 46 cases of HIV infection documented to be genetically linked to the partner living with HIV, 43 occurred in the 877 couples in which the partner living with HIV delayed initiation of ART until the CD4 cell count fell below 250 cells/mm³, whereas 3

cases of HIV infection occurred in the 886 couples with a partner living with HIV who began immediate ART. The majority of transmissions (82%) were observed in participants from Africa. Thus, this randomized trial clearly demonstrated that provision of treatment to persons living with HIV can reduce the risk of transmission of HIV to their sexual partners.⁶ In addition, the PARTNERS trial—which studied 1,166 serodiscordant couples (both heterosexual and men who have sex with men) where the partner with HIV was on suppressive ART and had sex without using a condom—had no cases of transmission after 1.3 years.⁷

In 161 serodiscordant couples (133 with a male partner living with HIV) where the partner living with HIV received suppressive ART, and the couple opted for natural conception, a total of 144 natural pregnancies occurred and 107 babies were born. No case of sexual (to partner) or vertical (to infant) transmission occurred.⁸

It is important to recognize that no single method (including treatment of the partner living with HIV) is fully protective against transmission of HIV, though the risk appears to approach zero when the partner living with HIV maintains consistently undetectable plasma viral load on ART.⁹ 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.¹⁰⁻¹² In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.¹³ In a prospective study of 2,521 African couples with differing HIV status, higher genital HIV RNA concentrations were associated with greater risk of heterosexual HIV-1 transmission and this effect was independent of plasma HIV concentrations.¹⁴ Each log₁₀ increase in genital HIV-1 RNA levels increased the risk of female-to-male or male-to-female HIV transmission by 1.7-fold.¹⁴ However, there was no case of transmission in the context of undetectable plasma viral load but detectable genital tract HIV.

In addition to reducing the risk of HIV transmission between partners, starting ART before conception in women living with HIV may also further reduce the risk of perinatal transmission.¹⁵ Early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission,^{16,17} but did not completely eliminate the risk of perinatal transmission.¹⁷ 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.¹⁸⁻²⁰

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.

Strategies for Safer Conception

For serodiscordant couples where the woman is living with HIV, assisted insemination at home or in a provider's office with a partner's semen during the periovulatory period is recommended as a conception strategy that eliminates the risk of HIV transmission to the partner without HIV. For serodiscordant couples where the man is living with HIV, the use of donor sperm from a man who is HIV-uninfected can be used as a conception strategy that eliminates the risk of HIV transmission to the partner without HIV.

However, as described above, studies have shown that the risk of HIV infection to the partner without HIV is very low when the partner living with HIV is on ART and has demonstrated sustained plasma viral load below the limits of detection. For serodiscordant couples where the partner living with HIV is on ART and has achieved sustained viral suppression, sexual intercourse without a condom limited to the 2 to 3 days before and the day of ovulation (peak fertility) is an approach to conception with low risk of sexual HIV transmission to the partner without HIV. The use of an ovulation kit would be optimal to identify the most fertile time of the cycle.

The use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization with intracytoplasmic sperm injection has been reported. However, the appropriate role of semen preparation techniques in the current context is unclear, particularly given their expense and technical requirements.

These sperm preparation techniques were largely developed prior to the studies demonstrating the efficacy of PrEP and ART in decreasing transmission to sexual partners without HIV. Sperm preparation techniques may be useful in cases of male infertility.

Semen analysis is recommended for men living with HIV 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 female partner without HIV 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.²¹⁻²⁴

For serodiscordant couples who attempt conception via sexual intercourse without a condom (despite counseling), when the partner living with HIV has not been able to achieve viral suppression or when viral suppression status is not known, administration of antiretroviral PrEP to the partner without HIV is recommended to reduce the risk of sexual transmission of HIV. PrEP is the use of ARV medications by an individual who is HIV negative to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. 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. Couples should still be counseled to limit sex without a condom to the period of peak fertility.

One study evaluated timed intercourse with PrEP in 46 heterosexual couples of differing HIV status where the female partner was HIV negative. The male partners living with HIV were receiving ART and had undetectable plasma HIV RNA levels. One dose of oral TDF was taken by the women at luteinizing hormone peak and a second oral dose was taken 24 hours later. None of the women contracted HIV and pregnancy rates were high, reaching a plateau of 75% after 12 attempts.²⁵ Another study from England reported the use of TDF with or without emtricitabine for PrEP by the female partner who was HIV negative with timed intercourse in 13 couples of differing HIV status; PrEP was well tolerated and no HIV transmissions occurred.²⁶

Sun et al. reported on 91 serodiscordant couples (43 with men living with HIV and 48 with women living with HIV) with effective ART being used in the partner with HIV, with PrEP (or post-exposure prophylaxis) administered to the partner without HIV, and with intercourse timed to maximally reduce the risk of HIV transmission. There were 196 acts of intercourse with a condom, 100 natural conceptions, and 97 live births. There were no cases of HIV seroconversion in the sexual partner without HIV.²⁷

Among 1,013 Kenyan and Ugandan, high-risk HIV serodiscordant couples (67% of couples where the woman was living with HIV), where an integrated ART and PrEP strategy for HIV prevention was implemented, there were no HIV transmissions to male partners. Only 2 incident infections were observed in the women (HIV incidence of 0.2 per 100 person years). These 2 infections occurred in the absence of use of ART or PrEP.²⁸

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.^{6,29-34} [Table 4](#) summarizes clinical trials of PrEP.³⁵

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 serodiscordant heterosexual 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	Serodiscordant 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 fertility 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: FTC = emtricitabine; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

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.

Pregnancy and breastfeeding are not contraindications to PrEP.³⁶⁻⁴⁰ There is no evidence of an increase in congenital anomalies among children born to women exposed to [TDF](#) or to [emtricitabine](#) during the first trimester.⁴¹ Data from studies of infants born to mothers living with HIV and exposed to TDF through breast milk suggest limited drug exposure.⁴²⁻⁴⁴ 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.

For couples with differing HIV status who attempt conception (sexual intercourse without a condom limited to peak fertility) when the partner living with HIV has achieved viral suppression, it is unclear if administration of PrEP for the partner without HIV further reduces the risk of sexual transmission. A modeling study analyzed the utility of PrEP under different conditions. Hoffman’s analysis shows that PrEP provides little added benefit when the male partner is on ART with suppressed viral load, sex without a condom is limited to the ovulation window, and other modifiable transmission risks are optimized.⁴⁵

Pre-Exposure Prophylaxis Provision and Monitoring in Couples with Differing HIV Status

If clinicians elect to use PrEP in couples with differing HIV status, 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) has issued guidelines for the use of PrEP in sexually active heterosexual adults.⁴⁶ The CDC recommends that an individual who does not have HIV and is planning pregnancy with a partner living

with HIV start daily oral TDF plus emtricitabine beginning 1 month before conception is attempted and continued for 1 month after conception is attempted.⁴⁶ 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. Individuals without HBV infection 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. Partners who are HIV negative 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.⁴⁷ Clinicians are strongly encouraged to register women who become pregnant while receiving PrEP with the [Antiretroviral Pregnancy Registry](#).

Couples Where Both Partners are Living with HIV

Both partners should be on ART with maximum viral suppression before attempting conception. Perioviulatory 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

Monitoring of Pregnant Women Without HIV who have Partners with HIV

Women without HIV who present during pregnancy and indicate that their partners are living with HIV, 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. Pregnant women without HIV should also be counseled to always use condoms to reduce the risk of HIV acquisition and their partners living with HIV should be virologically suppressed on ART. **These women should be tested for HIV, at least once per trimester, or more often if the partner's viral load is not known.** 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. Pregnant women without HIV with partners living with HIV should **be counseled on methods to prevent acquisition of HIV, including suppressive ART for her partner, PrEP, and condom use.** 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.

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 [Intrapartum Care](#) and [Infant Antiretroviral Prophylaxis](#)).

Women with partners living with HIV who test HIV seronegative should continue to be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV. **They should also be counseled on the importance of their partners' adherence to ART and the need for achievement of sustained virologic suppression to reduce the 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}

Coordination of care across multiple disciplines including HIV primary care, Ob/Gyn, family planning, case management and peer support is advised. Integration of reproductive health counseling including pregnancy desires and/or prevention are all recommended.

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.

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Antepartum Care (Last updated November 14, 2017; last reviewed November 14, 2017)

General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

Panel's Recommendations
<ul style="list-style-type: none">Initial evaluation of pregnant women living with HIV should include assessment of HIV disease status and plans to initiate, continue, or modify antiretroviral therapy (ART) (AI). The National Perinatal HIV Hotline (888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.All pregnant women living with HIV 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). Maintenance of a viral load below the limit of detection throughout pregnancy and lifetime of the individual living with HIV is recommended (AII).To minimize the risk of perinatal transmission, antiretroviral (ARV) drugs should be administered at all time points, including antepartum and intrapartum to the woman as well as postnatally to the neonate (AI).The known benefits and potential risks of all medication use, including ARV drug use during pregnancy and postpartum, should be discussed with all women living with HIV (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 women living with HIV 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, family planning and contraceptive options, infant feeding, infant ARV prophylaxis, timing of infant diagnostic testing, and neonatal circumcision (AIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>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</p>

In addition to the standard antenatal assessments for all pregnant women, the initial evaluation of women living with HIV 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;
- Screening for and treatment of sexually transmitted infections such as syphilis, *Chlamydia trachomatis* and *Neisseria gonorrhoea* and trichomonas;^{1,2}**

- 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;^{3,4}
- Complete blood cell count and renal and liver function testing;
- HLA-B*5701 testing if abacavir use is anticipated (see [Table 9](#));
- 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 antiretroviral therapy (ART);
- Intimate partner violence-related screening and supportive care needs;
- Referral of sexual partner(s) for HIV testing and ARV treatment or prophylaxis; and
- **Referral of children for HIV testing**

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 women living with HIV and their infants.

How Antiretrovirals Prevent Perinatal Transmission

ARV drugs reduce the risk of perinatal transmission of HIV in 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).⁵⁻⁷ Low-level cervicovaginal HIV RNA and DNA shedding has been detected even in women treated with ART who have undetectable plasma viral load.⁸⁻¹⁰ Penetration of ARV drugs into the female genital tract varies by drug.^{11-13,14} Because maternal viremia is not the only risk factor for HIV transmission, another important mechanism of protection is infant pre-exposure prophylaxis achieved by maternal administration of 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 to the infant 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.¹⁵⁻²¹ Therefore, combined preconception ART, confirmation of antepartum plasma viral load suppression, **scheduled surgical delivery (if indicated, based on most recent maternal plasma viral load)**, intrapartum continuation of current regimen with addition of intravenous zidovudine **(if indicated, based on the most recent maternal plasma viral load)**, and infant ARV prophylaxis are all 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 in regimen selection based on concerns about specific drugs or limited experience with newer drugs during pregnancy, where the perinatal guidelines may differ from the adult guidelines.

The known benefits and known and unknown risks of ARV drug use during pregnancy should be considered and discussed with women (see [Table 9](#) 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 for reducing the risk of transmission of HIV to infants. Counseling of pregnant women about ARV use should be directive and non-coercive, and providers should help women 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;
- Benefit of ART for preventing perinatal transmission of HIV;⁶
- Benefits of therapy for reducing sexual transmission to partners who do not have HIV when viral suppression is maintained;²²
- 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 after *in utero* drug exposure, **especially for new antiretrovirals.**

Transplacental passage of ARV drugs is thought to be 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 9](#)).²³⁻²⁷

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.²⁸ The ART regimen can be modified, if necessary, based on resistance assay results²⁹ (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 pregnant women living with HIV should initiate or continue ART during pregnancy to minimize the risk of transmission of HIV to their infants and partners. Providers should begin to counsel women living with HIV about what they can expect during labor and delivery and the postnatal period. This includes discussions about the mode of delivery, possible intrapartum zidovudine, **as well as family planning and contraceptive options in the postpartum period. Providers should also discuss possible changes to the pregnant woman's ART regimen post-delivery, because** lifelong ART is recommended for all individuals living with HIV. In addition, **discussions regarding prevention of postnatal transmission to the neonate should include recommendations about infant feeding,** neonatal ARV prophylaxis, infant diagnostic HIV testing, and the avoidance of pre-mastication of food.

Medical care of pregnant women living with HIV 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, and genital tract infections. Besides improving maternal health, cessation of cigarette smoking and drug use, treatment of **sexually transmitted** and other genital tract infections may reduce risk of perinatal transmission. **Women should be assessed for mental health concerns** and the risk of intimate partner violence **and referred to appropriate services** (i.e., depending on a woman's individual circumstances). Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public

assistance programs is essential to ensure that women living with HIV adhere to their ARV drug regimens.

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Teratogenicity (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see <http://www.APRRegistry.com>) (AIII).
- Based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester compared with later ARV drug 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 infants exposed to 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 drug exposure during pregnancy provided by health care providers, prevalence of birth defects was 2.7 per 100 live births among women with a first-trimester exposure to any ARV drug (244 of 8,909 exposures; 95% confidence interval [CI], 2.4–3.1). 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 0.99; 95% CI, 0.83–1.18).⁶

Some individual reports have raised concerns regarding specific ARV agents. Most studies evaluating a possible association between ARV drug 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

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 2-fold increase in the risk of overall birth defects, without any such increase detected; a single case of myelomeningocele and one case of anophthalmia 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 meningomyelocele, 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 2 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 foramen 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 Current Antiretroviral Pregnancy Registry data through July 31, 2017, included defects among 29 of 990 with first-trimester exposures (2.4%, 95% CI 1.4-3.3) and among 3 of 190 (1.6%, 95% CI 0.3-4.6) with later exposure.⁶ 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 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 and tolerated 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% (76/3342) women with first-trimester TDF exposure, similar to that in the general population.⁶ A recent comprehensive review of use of TDF in pregnant women for treatment of HIV or hepatitis B (or for pre-exposure prophylaxis) found no

evidence of an increased risk of pregnancy loss, stillbirth, preterm birth, small for gestational age, or infant mortality compared to similar women receiving placebo or alternate ARV drug regimens.¹⁹

Administration of TDF at high doses to pregnant monkeys (exposure resulting in drug levels 25 times the 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, a study evaluating fetal long bone (femur and humerus) growth by serial ultrasound in women who received different durations of TDF antiretroviral therapy (ART) during pregnancy (<10 weeks, 10–24 weeks, ≥ 25 weeks) found no association between duration of *in utero* TDF exposure per week and change in femur and humerus length z-score ($P = 0.51$ and $P = 0.40$, respectively).²⁰ 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, first trimester ARV drug exposure was found in 5,388 (42%). 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 infants exposed to HIV, 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 congenital heart defects comparing exposure between zidovudine-containing regimens and non-zidovudine ART regimens did not find significant differences between the 2 groups.²¹ Additionally, in a comparison between 417 infants exposed to HIV and ARV drugs who were uninfected 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 drug exposure overall was not associated with an increased risk of birth defects.²² 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-trimester 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 darunavir, didanosine, efavirenz, indinavir, **raltegravir, rilpivirine**, and stavudine; no such increases have been detected to date. For **abacavir**, 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 (2.72%) for the MACDP rate, **but not elevated compared to the Texas Birth Defect Registry rate of 4.17%, an additional comparator now included in the Antiretroviral Pregnancy Registry**. 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.

Antiretroviral Pregnancy Registry Reporting

Health care providers who are caring for pregnant women living with HIV 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 Maternal and Neonatal Outcomes

(Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Clinicians should be aware of a possible small increased risk of preterm delivery 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 outcomes (**All**).

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 (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 summary of the published data regarding ART and adverse neonatal outcomes. **In addition, there are limited data suggesting a potential association between hypertensive disorders of pregnancy and maternal HIV. These data are summarized at the end of this section.**

We have reviewed and summarized studies from 1986 to 2017 reporting on **obstetric and neonatal outcomes** in women with HIV. These studies are conducted in Europe (11), North America (9), sub-Saharan Africa (9), and Latin America (2). Study size and designs vary significantly; the total study participant numbers range from 183 to **10,592**. The ART regimens evaluated in these studies differ and may include:

- No ART (8)
- Monotherapy: Single antiretroviral (ARV) drug (19)
- Dual therapy: Two ARV drugs (13), *and*
- Multi-ARVs: At least 3 ARV drugs; protease inhibitor (PI)-based (23) or non-PI-based (27).

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 preterm birth or delivery, LBW, and SGA are provided. These data are weighted heavily regarding preterm birth or delivery (30), and fewer studies report outcomes of LBW (12), SGA (8), and stillbirth (11).

Pregnancy Outcomes

Preterm Delivery

All the studies reviewed in this section (33) have reported outcomes related to preterm delivery. Among the 19 studies that report an association between ART use and preterm delivery, the relative risks/odds ratios for preterm delivery range from 1.2 to 3.4.¹⁻¹⁸ Conflicting findings regarding preterm delivery and ART use may be influenced by variability in the data available for analysis. For example, some studies have reported increased rates of preterm delivery 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 preterm delivery independent of ART use.¹⁹⁻²¹ In order to control for medical or obstetrical factors associated with preterm delivery, two studies have assessed spontaneous preterm delivery alone. One study included women initiating ART during pregnancy. Neither study reported an association between ART use and preterm delivery.^{22,23} In general, none of the studies reviewed in this section have comprehensively controlled for all potential factors that may be associated with

preterm delivery.

Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Seven of the 31 studies in Table 5 report an association between ART initiation prior to pregnancy and preterm delivery.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 (3) and included various ART regimens (including single-drug, two-drug, and multidrug regimens). A large meta-analysis of 11,224 women in 14 European and American studies did not demonstrate an increased rate of preterm delivery among women using ART during pregnancy.⁴

Antiretroviral Therapy Regimens Associated with Preterm Delivery

PI-Based

Fifteen of the 31 studies in Table 5 investigate an associated risk between PI-based ART and preterm delivery. These studies include populations in Europe (4), North America (9), and Africa (3). The risk of preterm delivery ranges from 1.14 to 3.4.^{1,3-6,8,15,17,18,22,24,25} Five of these studies did not demonstrate a significant association between PI-based ART and preterm delivery.^{15,22,24-26} The recent PROMISE trial study compared zidovudine-alone to lopinavir/ritonavir ART combined with a dual NRTI backbone of either zidovudine/lamivudine or tenofovir disoproxil fumarate (TDF)/emtricitabine. Compared to women receiving zidovudine-alone, higher rates of extremely preterm delivery were reported in women receiving zidovudine/lamivudine/lopinavir/ritonavir ($P < 0.001$) but not TDF/emtricitabine/lopinavir/ritonavir ($P = 0.77$). In contrast, extremely preterm delivery rates were higher among women receiving TDF/emtricitabine/lopinavir/ritonavir than women receiving zidovudine/lamivudine/lopinavir/ritonavir ($P = 0.04$). These rates of very preterm delivery were not significantly different compared to women receiving zidovudine-alone ($P = 0.10$). The use of ritonavir to boost a PI-based regimen may be associated with preterm delivery compared to non-boosted PI regimens. In a small, retrospective Canadian study, women taking non-boosted PI regimens did not have increased rates of preterm delivery.¹⁵ A small meta-analysis of 10 studies (8 prospective cohort, 1 randomized controlled trial, and 1 surveillance study) demonstrated an increased risk of preterm birth associated with PI-based ART, aOR 1.32 (CI 1.04-1.6) with an $I^2 = 47%$ (moderate heterogeneity). When evaluating the effects of initiating PI-based ART in the first and third trimesters of pregnancy, the pooled effect was non-significant.²⁷

Non-PI-Based

Exposure to NRTI single-drug prophylaxis (primarily zidovudine) was not associated with preterm delivery.¹ Other reports have found increased rates of preterm delivery when ART is compared with dual-ARV regimens⁹ and when non-nucleoside reverse transcriptase inhibitor-based ART regimens were compared with other forms of ART.²⁰

Mechanism for Preterm Delivery

The potential mechanism of action by which PIs may increase a woman's risk of preterm delivery is unknown. Papp et al. demonstrated in cell culture, mouse models, and in pregnant women with HIV that exposure to PIs (except for darunavir) can decrease plasma progesterone levels. Low levels of plasma progesterone during pregnancy may potentially be associated with fetal loss, preterm delivery, and LBW.²⁸ Papp et al. subsequently demonstrated that pregnant women with HIV 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.²⁹

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%.^{8,14,16,18,21,24,25,30-33} Of the 15 studies that address

effects of ART on birth weight, **five** demonstrate an association between any ART use and LBW.^{16,31-34} **Seven** studies report the rates of SGA, which range from 7.3% to 31%.^{11,14,16,18,21,26,35,36} 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 **Three** studies in Botswana report a positive association with ART use (both non-PI-based and PI-based) and SGA.^{11,18,37} 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 **When compared to emtricitabine/TDF/efavirenz ART, both nevirapine-based and lopinavir/ritonavir-based ART were associated with increased SGA.**¹⁸ **Ten** studies report rates of stillbirth ranging from 0.5% to 11.4%.^{7,11,12,14,18,21,25,31,33} **Two** studies have evaluated the 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 and (aRR 2.31 [95% CI, 1.64–3.26]).¹⁸ **In the latter study, zidovudine/lamivudine/nevirapine was associated with a significantly increased rate of stillbirth compared to emtricitabine/TDF/efavirenz.**

Maternal Outcomes

Hypertensive Disorders of Pregnancy

Limited data suggest an association of hypertensive disorders of pregnancy and maternal HIV. An earlier meta-analysis³⁸ reported an increased association between maternal HIV and hypertensive disorders of pregnancy, but a more recent meta-analysis³⁹ did not reveal a clear association of maternal HIV with pregnancy-induced hypertension, preeclampsia, or eclampsia. An Italian study demonstrated an increased risk for both early and late-onset preeclampsia (aOR=2.50, 95% CI, 1.51–4.15; aOR=2.64, 95% CI, 1.82–3.85) as well as pre-eclampsia with severe features (aOR=2.03, 95% CI, 1.26–3.28 respectively) when comparing pregnant women living with HIV versus without HIV.⁴⁰

Few studies have evaluated the effect of combination ART on pre-eclampsia. No studies have evaluated the effect of specific ARV drugs on maternal hypertension. In the NISDI cohort, women exposed to ART in the first trimester had an increased risk of preeclampsia when compared to women who were not exposed to ART (aOR = 2.3, 95% CI, 1.1–4.9)^{41,42} A secondary analysis of South African data revealed that amongst women with low CD4 T lymphocyte counts (<200 cells/mm³), there was an increased risk of maternal death from hypertensive disorders of pregnancy when comparing those on combination ART vs. those who received no ART during pregnancy (RR = 1.15, 95% CI, 1.02–1.29).⁴³ It is unclear whether this finding reflects the fact that immune reconstitution associated with ART initiation plays a role in increasing inflammatory responses associated with preeclampsia/eclampsia or whether there is a direct effect of ART on this outcome.

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 preterm delivery 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 preterm delivery. Until more information is available, pregnant women with HIV receiving ART should continue their provider-recommended regimens and receive regular monitoring for pregnancy complications, including preterm delivery.⁴⁴

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

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 Preterm Delivery	Notes
European Collaborative Study and Swiss Mother and Child HIV Cohort Study; 1986–2000 ¹	3,920/896	<ul style="list-style-type: none"> • Mono (573) • Multi, no PI (215) • Multi-PI (108) 	<ul style="list-style-type: none"> • YES (compared with no ARV) • Multi: 1.82 (1.13–2.92) • Multi-PI: 2.60 (1.43–4.7) 	<ul style="list-style-type: none"> • Increase in preterm delivery if ARV begun before pregnancy versus in third trimester
United States; 1990–1998 ²⁴	3,266/2,123	<ul style="list-style-type: none"> • Mono (1,590) • Multi (396) • Multi-PI (137) 	<ul style="list-style-type: none"> • NO (compared with mono) • Multi: 0.95 (0.60–1.48) • Multi-PI: 1.45 (0.81–2.50) 	<ul style="list-style-type: none"> • 7 prospective clinical studies
European Collaborative Study; 1986–2004 ⁴⁵	4,372/2,033	<ul style="list-style-type: none"> • Mono (704) • Dual (254) • Multi (1,075) 	<ul style="list-style-type: none"> • 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 ³⁴	2,543/Not given	<p><u>Early (<25 Weeks):</u></p> <ul style="list-style-type: none"> • Mono (621) • Multi, ≥ 2 without PI or NNRTI, (198) • Multi, with PI or NNRTI (357) <p><u>Late (≥ 32 Weeks):</u></p> <ul style="list-style-type: none"> • Mono (932) • Multi, ≥ 2 without PI or NNRTI (258) • Multi, with PI or NNRTI (588) 	<ul style="list-style-type: none"> • NO (compared with mono) • No association between any ARV and preterm delivery 	<ul style="list-style-type: none"> • Preterm delivery decreased with ARV compared with no ARV.
United States; 1990–2002 ³	1,337/999	<ul style="list-style-type: none"> • Mono (492) • Multi (373) • Multi-PI (134) 	<ul style="list-style-type: none"> • YES (compared with other multi) • Multi-PI: 1.8 (1.1–3.03) 	<ul style="list-style-type: none"> • Multi-PI reserved for advanced disease, those who failed other multi-ARV regimens.
Brazil, Argentina, Mexico, Bahamas; 2002–2005 ³⁰	681/681	<ul style="list-style-type: none"> • Mono/dual NRTI (94) • Multi-NNRTI (257) • Multi-PI (330) 	<ul style="list-style-type: none"> • NO (compared with mono/dual NRTI) • No association between any ARV regimen and preterm delivery 	<ul style="list-style-type: none"> • All on ARV for at least 28 days during pregnancy • Preeclampsia/eclampsia, cesarean delivery, diabetes, low BMI associated with preterm delivery
Meta-Analysis, Europe and United States; 1986–2004 ⁴	11,224/Not given	<ul style="list-style-type: none"> • Multi-no PI (including dual) or multi-PI (2,556) 	<ul style="list-style-type: none"> • YES (only comparing PI with multi) • PI versus multi-no PI: 1.35 (1.08–1.70) 	<ul style="list-style-type: none"> • 14 studies, 5 in preterm-delivery-ARV comparison • No overall increase in preterm delivery with antepartum ARV • Preterm delivery increased in those on ARV pre-pregnancy and in first trimester compared with later use.

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

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 Preterm Delivery	Notes
Italy; 2001–2006 ⁵	419/366	<ul style="list-style-type: none"> • Multi-PI second trimester (97) • Multi-PI third trimester (146) 	<ul style="list-style-type: none"> • YES • Multi-PI second trimester: 2.24 (1.22–4.12) • Multi-PI third trimester: 2.81 (1.46–5.39) 	<ul style="list-style-type: none"> • Multivariate association also with hepatitis C
United States; 1989–2004 ⁶	8,793/6,228	<ul style="list-style-type: none"> • Mono (2,621) • Dual (1,044) • Multi-no-PI (1,781) • Multi-PI (782) 	<ul style="list-style-type: none"> • YES (compared with dual) • Multi-PI associated with preterm delivery: 1.21 (1.04–1.40) 	<ul style="list-style-type: none"> • Lack of antepartum ARV also associated with preterm delivery • Preterm delivery and LBW decreased over time.
United Kingdom, Ireland; 1990–2005 ⁷	5,009/4,445	<ul style="list-style-type: none"> • Mono/dual (1,061) • Multi-NNRTI or multi-PI (3,384) 	<ul style="list-style-type: none"> • YES (compared with mono/dual) • Multi: 1.51 (1.19–1.93) 	<ul style="list-style-type: none"> • Similar increased risk with PI or no-PI multi • No association with duration of use
Germany, Austria; 1995–2001 ⁸	183/183	<ul style="list-style-type: none"> • Mono (77) • Dual (31) • Multi-PI (21) • Multi-NNRTI (54) 	<ul style="list-style-type: none"> • YES (compared with mono) • Multi-PI: 3.40 (1.13–10.2) 	N/A
United States; 2002–2007 ²²	777/777	<ul style="list-style-type: none"> • Mono (6) • Dual (11) • Multi-no-PI (202) • Multi-PI (558) 	<ul style="list-style-type: none"> • NO (compared PI with all non-PI) • Multi-PI: 1.22 (0.70–2.12) 	<ul style="list-style-type: none"> • All started ARV during pregnancy. • Analyzed only spontaneous preterm delivery
Swiss Mother and Child HIV Cohort Study; 1985–2007 ⁹	1,180/941	<ul style="list-style-type: none"> • Mono (94) • Dual (53) • Multi, PI or no PI, (409) • Multi-PI (385) 	<ul style="list-style-type: none"> • YES (compared with no ARV) • Multi: 2.5 (1.4–4.3) 	<ul style="list-style-type: none"> • No association of mono/dual with preterm delivery compared with no ARV • No confounding by duration of ARV or maternal risk factors
Botswana; 2006–2008 ¹⁰	530/530	<ul style="list-style-type: none"> • LPV/r plus ZDV plus 3TC (267) • ABC plus ZDV plus 3TC (263) 	<ul style="list-style-type: none"> • YES • Multi-PI versus multi-NRTI: 2.03 (1.26–3.27) 	<ul style="list-style-type: none"> • 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/mm³
Botswana; 2007–2010 ³⁷	4,347/3,659	<ul style="list-style-type: none"> • ARV, regimen unspecified (70) • Mono (2,473) • Multi, 91% NNRTI (1,116) 	<ul style="list-style-type: none"> • NO • No association between multi-ART and very preterm delivery (<32 weeks' gestation) 	<ul style="list-style-type: none"> • Observational; multi-ART before conception associated with very-small-for-gestational-age and maternal hypertension during pregnancy
Spain; 1986–2010 ²³	519/371	<ul style="list-style-type: none"> • Mono/dual NRTI (73) • All multi (298) • Multi-PI (178) 	<ul style="list-style-type: none"> • NO (compared with no ARV plus mono/dual) • Spontaneous preterm delivery not associated with multi-ARV or multi-PI before or during pregnancy 	<ul style="list-style-type: none"> • Preterm delivery associated with multi-ARV given in second half of pregnancy and with prior preterm delivery

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

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 Preterm Delivery	Notes
Botswana; 2009–2011 ¹¹	9,504/7,915	<ul style="list-style-type: none"> • Mono (4,625) • All multi (3,290) • Multi-PI (312) 	<ul style="list-style-type: none"> • YES (multi-ARV before and during pregnancy compared with mono): 1.2 (1.1–1.4) and 1.4 (1.2–1.8) • YES (multi-PI compared with multi-no PI before pregnancy): 2.0 (1.1–3.6) 	<ul style="list-style-type: none"> • ART group classified by initiation before and during pregnancy
France; ANRS French Perinatal Cohort 1990–2009 ¹²	8,696/8,491	<ul style="list-style-type: none"> • Mono (950) • Dual (590) • Multi-PI (2,414) 	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • Patients on ART before and during pregnancy had increased rates of preterm delivery
United States; 2000–2011 ³⁶	183/183	<ul style="list-style-type: none"> • Multi-PI (183) 	<ul style="list-style-type: none"> • NO (no control group without ART) • Rate of preterm delivery: 18.6% 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Mono/dual (138) • Multi-NRTI (193) • Multi-NNRTI (160) • Multi-PI (1,319) 	<ul style="list-style-type: none"> • YES (compared with no ARV in first trimester) • Multi-PI in first trimester vs. none in first trimester • Preterm delivery 1.55 (1.16–2.07); spontaneous preterm delivery 1.59 (1.10–2.30) 	N/A
Latin America; 2002–2012 ¹⁴	1,512/1,446	<ul style="list-style-type: none"> • Multi-PI (907) • Multi-non-PI (409) • Mono/dual (130) • No ART or ART <28 days (66) 	<ul style="list-style-type: none"> • YES (when on ARVs at conception): preterm delivery 1.53 (1.11–2.09) 	<ul style="list-style-type: none"> • ART for treatment rather than prophylaxis associated with increased rates of LBW (<2,500 g) 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 ⁴⁶	356/356	<ul style="list-style-type: none"> • Multi-PI, LPV/r (179) • Multi-non-PI, EFV (177) 	<ul style="list-style-type: none"> • NO (no control group without ART) 	<ul style="list-style-type: none"> • Trend in increased preterm delivery among women starting ART 24–28 week GA was NS: aOR 1.76 (0.96–3.23)
Italy; 1997–2013 ⁴⁷	158/158	<ul style="list-style-type: none"> • Mono/dual (27) • Multi-PI (114) • Multi-non-PI (17) 	<ul style="list-style-type: none"> • NO (no control group without ART) 	<ul style="list-style-type: none"> • Preterm delivery 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	<ul style="list-style-type: none"> • Multi-non-boosted PI (220) • Multi-boosted PI with RTV (144) • Multi-non-PI (166) • Mono (77) • No ART (59) 	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • Highest risk of preterm delivery among women not taking ART compared to non-boosted PI group: 2.7 (1.2–6.09)

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

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 Preterm Delivery	Notes
United Kingdom; 2007–2012 ²⁵	493/493	<ul style="list-style-type: none"> Multi-PI, LPV/r Multi-PI, ATV/r 	<ul style="list-style-type: none"> NO (comparing two PI-based regimens): aOR 1.87 (0.93–3.75) 	<ul style="list-style-type: none"> Rate of preterm delivery 13% among women who conceived on ART and 14% among women who started ART during pregnancy. In multivariate analysis, a history of preterm delivery was associated with recurrent preterm delivery: aOR 5.23 (1.91–14.34)
Republic of the Congo; 2007–2012 ³¹	188/188	<ul style="list-style-type: none"> Multi-non-PI, EFV-based (31) Multi-non-PI, NVP-based (146) 	<ul style="list-style-type: none"> NO (comparing EFV 13% vs NPV 10%) 	<ul style="list-style-type: none"> Rate of preterm delivery 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	<ul style="list-style-type: none"> Multi (1,094) Mono (1,768) No ART (452-excluded) 	<ul style="list-style-type: none"> YES (Multi before pregnancy vs Mono): 1.24 (1.05–1.47) Very preterm delivery, 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) 	<ul style="list-style-type: none"> Rate of preterm delivery 29%; women who conceived on ART more likely to have preterm delivery compared to women on ZDV monotherapy. Pregnancy-induced hypertension associated with preterm delivery: 1.25 (1.03–1.51)
67 Countries and US Territories; APR 1989–2013 ³³	14,684/12,780 (ZDV), 1,904 (non-ZDV)	<ul style="list-style-type: none"> Multi^a ARV with ZDV ARV without ZDV 	<ul style="list-style-type: none"> NO (any ZDV-ARV vs non-ZDV-ARV exposure): 1.0 (0.9–1.2) 	<ul style="list-style-type: none"> Preterm delivery rate 12% LBW rate 16%, RR of LBW with ZDV-ART vs non-ZDV ART RR: 1.2 (1.0–1.3), $P = 0.02$ Stillbirth rate: 1.5%, RR 0.8 (0.5–1.1)
Texas, United States; 1984–2014 ²⁶	1,004/792	<ul style="list-style-type: none"> Multi, PI ART (597); non-PI ART (230) No ART (177) 	<ul style="list-style-type: none"> NO (non-PI ART vs PI-ART): 0.9 (0.5–1.5) 	<ul style="list-style-type: none"> Rate of preterm delivery: 13% to 21% Rate of SGA: 19% to 23%, OR 1.3 (0.8–1.9)
India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, PROMISE Trial; 2011–2014 ³²	3,490/3,096	<ul style="list-style-type: none"> Mono (1,386) All Multi (2,710) ZDV-based (1,385) TDF-based (325) 	<ul style="list-style-type: none"> YES (Multi after 14 weeks vs mono) 	<ul style="list-style-type: none"> Rate of preterm delivery: 21% on ZDV-based ART compared to ZDV-mono ($P < 0.001$). Rate very preterm delivery: 6% in TDF-based ART and 3% in ZDV-based ART ($P = 0.04$) LBW was more common in ZDV-based ART (23% vs. 12%) in ZDV-alone ($P < 0.001$) and TDF-based ART (17% vs 9%) in ZDV-alone, ($P = 0.004$)

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

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 Preterm Delivery	Notes
United States and Puerto Rico; SMARTT 2007–2016 ¹⁷	1,864/1,491	• Multi (1,491)	• YES: 1.59 (1.2–2.1)	• PI-based ART exposure in first trimester was associated with increased risk of spontaneous preterm delivery compared with no first-trimester ART
South Africa; 2011–2014 ²¹	3,723/3,547	• Dual (974) • Multi (2,573)	• NO • Dual: 0.2 (0.08–0.5) • Multi: 0.3 (0.1–0.9)	• Preterm delivery rate regardless of ART: 22% to 23% • LBW rate on ART: 9% to 15%. Risk of LBW: Dual 0.06 (0.02–0.2) and multi 0.12 (0.04–0.4) • SGA rate on ART: 7% to 9%. Risk of SGA: Dual 0.37 (0.1 to 1.5) and multi 0.3 (0.07 to 0.9) • Stillbirth rate on dual (1.2%) and multi (2.2%). Risk of stillbirth: Dual 0.08 (0.04–0.2) and multi 0.2 (0.1–0.3)
Botswana; 2012–2014 ¹⁸	11,932/10,592	• Multi, PI-based (398) • Multi, NNRTI-based (4,597)	• YES • Multi PI-based: 1.36 (1.06–1.75) • Multi NNRTI-based: 1.14 (1.01–1.29)	• SGA rates were significantly higher in multi PI-based ART (27.7% and 20.4%) and NVP-based ART (24.9% and 28.2%) compared to EFV-based ART (16.9%). • Stillbirth rates were higher in nevirapine-based ART: 2.31 (1.64–3.26).
19 Countries, 5 Continents; 2002–2013 ²⁷	23,490 (meta-analysis 10 studies)	• Multi, PI-based • Multi, PI-sparing	• YES • Multi-PI based ART: 1.3 (1.04–1.6), I ² =47%	• 6 of 10 studies demonstrated increased risk of preterm delivery: aOR (1.2–4.14)

Note: The data presented in the column Association Noted between ARV Regimens and Preterm Delivery represent the published results of the study in the corresponding row. Depending on the study designs, these are adjusted and unadjusted odds ratios and relative risks.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; aOR = adjusted odds ratio; ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; dual = two ARV drugs; EFV = efavirenz; GA = gestational age; LBW = low birth weight; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NS = non-significant; OR = odds ratio; PI = protease inhibitor; RR = relative risk; SGA = small for gestational age; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Recommendations for Use of Antiretroviral Drugs during Pregnancy: Overview (Last updated October 19, 2017; last reviewed October 19, 2017)

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 (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. [Table 6](#) provides specific information about recommended ARV drugs when **initiating** antiretroviral therapy (ART) in treatment-naïve pregnant women, and [Table 9](#) provides dosing and PK data. Additional recommendations for women who have never received ARV drugs (ARV-naïve 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.

ARV drug recommendations for pregnant women living with HIV 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 Pregnant Women with HIV Infection 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 adult women living with HIV, 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 based on several factors that apply to all pregnant women, as well as factors that will vary for individual patients. Pregnancy-related factors include:

- 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,
- PK changes in pregnancy,
- Potential adverse maternal drug effects, especially those that may be exacerbated during pregnancy,

Individual-level factors include:

- Potential drug interactions with other medications,
- Results of genotypic resistance testing and prior ARV exposure,

- Comorbidities,
- 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 in pregnancy, as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short- and long-term drug toxicity of ARV regimens
- Evidence from clinical studies of risk of maternal toxicity, teratogenicity, adverse pregnancy outcomes, and adverse infant outcomes;
- 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 (APR) (and other post-marketing surveillance) data.²

Categories of ARV regimens refer to initial therapy for ARV-naive pregnant women, and include:

- **Preferred:** Drugs or drug combinations are designated as preferred for initial therapy 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 PK, dosing, tolerability, formulation, administration, or interaction concerns.
- **Insufficient Data to Recommend:** The drugs and drug combinations in this category are approved for use in ART-naive 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 **insufficient drug levels and/or** inferior virologic response in pregnancy, potentially serious maternal or fetal safety concerns, or are not recommended for ARV-naive populations regardless of pregnancy status. While this section pertains primarily to initiating ARV drugs, [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, adolescents, and children**, 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.** 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](#)). 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), and may include medications that may increase risk of viral failure in pregnancy (elvitegravir/cobicistat); see [Table 6](#). **Women who are not fully suppressed and currently taking ART should be carefully evaluated for adherence and genotypic resistance, with every effort made to achieve full virologic suppression through adherence interventions or medication changes. Women who have received ARV drugs in the past but are not currently taking ARV drugs will need additional consideration of previous regimens and potential for genotypic resistance.** Specific recommendations for each type of patient are described in the following three sections: Women Living with HIV Who Have Never Received Antiretroviral Drugs (ARV-Naive); Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy; and Pregnant Women Living with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications.

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.³⁻⁵ 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. In general, the PKs of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and non-pregnant women (although data on etravirine are limited), whereas PI and integrase inhibitor PKs are more variable, particularly in the second and third trimesters of pregnancy. Currently available data on the PKs and dosing of ARV drugs in pregnancy are listed for each drug below, and summarized in [Table 9](#).

Nucleoside Reverse Transcriptase Inhibitors

There are two preferred NRTI combinations for use in ARV-naïve 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.⁶ 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. **Testing for hepatitis B virus (HBV) should be performed; for women living with HIV/HBV coinfection, two NRTIs active against HBV should be chosen (e.g., TDF with emtricitabine or lamivudine), in place of abacavir/lamivudine.**

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 HBV, 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](#)).**⁷ Although some authors have suggested that zidovudine/lamivudine be used in place of TDF/emtricitabine,⁸ this suggestion is based on data from a single study, the PROMISE trial.⁹ However, the generalizability of the PROMISE findings is limited by important study design and statistical considerations that limit (for details see the [Tenofovir Disoproxil Fumarate](#) and [Lopinavir/Ritonavir](#) sections). In consideration of all available evidence, the Panel concluded that the

assessment of expected benefits and harms favored TDF/emtricitabine over zidovudine/lamivudine, leading the Panel to maintain TDF/emtricitabine designation as a Preferred recommendation and zidovudine/lamivudine as an Alternative recommendation.

Zidovudine/lamivudine is 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 (see Zidovudine Section).

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.¹⁰⁻¹² 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 infants exposed to ARV drugs, their clinical significance remains uncertain, and they are very likely to be outweighed by the importance of maternal and infant ARV drug use to prevent perinatal HIV transmission.^{13,14} For pregnant women, uncommon but important clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis; **hepatic steatosis and lactic acidosis** may be more common in women than in men.^{15,16} 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 acidosis and hepatic steatosis in pregnant women with HIV 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.¹⁷ 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](#)).

Integrase Inhibitors

Raltegravir is a Preferred integrase inhibitor for use in ARV-naive pregnant women, based on PK, safety, and other data on the use of raltegravir during pregnancy.¹⁸⁻²³ Clinical trial data from non-pregnant adults suggest a more rapid viral decay with the use of raltegravir compared to efavirenz.²⁴ 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.^{18,20,25-33} The rate of viral decay with raltegravir compared to efavirenz **or lopinavir/ritonavir** in late-presenting pregnant women is currently under investigation.^{34,35} 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.³⁶ **Although a once-daily formulation of raltegravir is approved for non-pregnant adults, there are insufficient PK data to support its use in pregnancy; recommended dosing remains twice-daily.**

Dolutegravir is an Alternative integrase inhibitor for use in ARV-naive pregnant women. This is based on both PK and safety data, however, these data have been presented in only abstract form and have not yet been

published at the time of writing. Data from the P1026 study suggest that while dolutegravir levels in the third trimester are lower than in the postpartum period, this is due to higher-than-expected postpartum levels; third-trimester levels were comparable to those observed in non-pregnant adults, and no viral failures occurred.³⁷ Published data reported to the APR through January 2017 include anomalies in 2 of 77 (2.6%) first-trimester and 2 of 56 (3.5%) second- /third-trimester exposures. Additional data presented at the International AIDS Society meeting (not yet published) include 0 anomalies among 116 first-trimester and 729 second- /third-trimester exposures in Botswana, and anomalies in 3 of 42 (7.1%) first-trimester and 1 of 38 (2.6%) second- /third-trimester exposures in a pooled analysis from the EPICC, NEAT-ID, and PANNA cohorts.^{38,39} Including all exposures and outcomes from these 3 reports, the calculated risk would be 2.1% with first-trimester and 0.4% with second- /third-trimester exposure. Data from the Botswana cohort also suggest similar risks of adverse pregnancy outcomes (preterm/very preterm delivery, small/very small for gestational age, stillbirth, neonatal death, or combinations of these outcomes) compared to efavirenz-based ART.³⁸

There are currently limited data on the use of **elvitegravir/cobicistat** in pregnancy.^{29,40} Data from the P1026 study suggest that elvitegravir and cobicistat levels in the third trimester were significantly lower than in the postpartum period (below the levels expected to lead to virologic suppression); viral breakthroughs did occur, with only 74% of women maintaining viral suppression at delivery.³⁷ Based on these data, elvitegravir/cobicistat **is not recommended** for initial use in pregnancy until more data are available. For women who present on elvitegravir/cobicistat, providers should consider switching to more effective, recommended regimens. If an elvitegravir/cobicistat regimen is continued, viral load should be monitored frequently, and therapeutic drug monitoring (TDM) (if available) may be useful.

Protease Inhibitors

Atazanavir/ritonavir and **darunavir/ritonavir** are the Preferred PI drugs for use in ARV-naïve pregnant women, based on efficacy studies in adults and experience with use in pregnancy. Factors impacting the decision between these two medications may include limitations in administering concomitant antacid, H₂ blocker, or proton pump inhibitors (atazanavir) and the requirement for twice-daily dosing (darunavir; although a once-daily formulation is approved for non-pregnant adults, there are insufficient PK data to support its use in pregnancy). 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. Atazanavir is associated with increased indirect bilirubin levels, which theoretically may increase the risk of hyperbilirubinemia in neonates, although pathologic elevations have not been seen in studies to date.⁴¹ In analyses from the PHACS SMARTT study, *in utero* exposure to atazanavir compared to other drugs was associated with statistically significant but small reductions in language and social-emotional scores,⁴² and was associated with risk of late language emergence at 12 months that was no longer significant at 24 months.^{43,44} The clinical significance of these findings associated with *in utero* atazanavir exposure is not known. **Nelfinavir**, **saquinavir**, and **indinavir** are not recommended for initial therapy in pregnancy due to concerns about lower efficacy and higher toxicity than preferred or alternative PIs (Table 6). Data on use in pregnancy are too limited to recommend routine use of **fosamprenavir** or **tipranavir/ritonavir** in pregnant women; these medications are also not recommended for use in ART-naïve non-pregnant adults. As described below, the use of cobicistat as a pharmacologic booster for darunavir is also not recommended.

Current data suggest that with standard adult dosing, plasma concentrations of lopinavir, atazanavir, and darunavir are reduced during the second and/or third trimesters. Dose adjustment is recommended for lopinavir/ritonavir and may be considered for atazanavir (see Table 9).⁴⁵ Specific dosing recommendations depend on the PI, an individual patient's treatment experience, and use (if any) of concomitant medications with potential for drug interactions.⁴⁵⁻⁵³ Clinicians may consider TDM in specific situations.

Non-Nucleoside Reverse Transcriptase Inhibitors

There are no preferred NNRTIs for use in ARV-naïve pregnant women.

Efavirenz is 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.^{54,55} 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.⁵⁴⁻⁵⁶ Both British and World Health Organization guidelines note that efavirenz can be used throughout pregnancy (see [Teratogenicity and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment](#)). Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens, **as is recommended for most regimens (Table 6)**.

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/mm³. 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.⁵⁷ **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 because it is not recommended for ARV-naive non-pregnant patients, and because there are insufficient safety and PK data on etravirine in pregnancy.

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.⁵⁸

Entry and Fusion Inhibitors

Enfuvirtide and **maraviroc** are not recommended for initial ART in pregnancy because they are not recommended as initial ART in non-pregnant adults and because of the lack of safety and PK data in pregnancy. Use of these agents can be considered for women who have failed therapy with several other classes of ARV drugs; however, because there are insufficient data to inform safety or dosing guidance for their use in pregnancy, their use should only be undertaken after consultation with HIV and obstetric specialists.

Pharmacologic Boosters

There are currently limited data on the use of **cobicistat** in pregnancy, therefore, this drug cannot be recommended for ARV-naive pregnant women at this time. **As noted above, both elvitegravir and cobicistat levels in the P1026 study were significantly lower in the third trimester than in the postpartum period.** Low-dose ritonavir as a pharmacologic booster for other PIs, as described above, **is currently the preferred pharmacologic booster for initial ART regimens in pregnancy.**

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Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Antiretroviral therapy (ART) should be recommended to all pregnant women living with HIV to reduce the risk of perinatal transmission of HIV and 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 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 be informed by current adult treatment guidelines, what is known about the use of specific drugs in pregnancy, and the risk of teratogenicity (see [Table 6](#) and [Table 9](#)) and maternal factors such as nausea, 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 strand transfer 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 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, minimizes 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 and 2001 to 0.46% in 2010 and 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 to 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 copies/mL). For details regarding genotypic and phenotypic resistance testing, see the [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. **Either a protease inhibitor (PI)-based or integrase strand transfer inhibitor (INSTI)-based** ART regimen can be considered when the results of resistance testing are not available to inform selection of ARV drugs because clinically significant resistance to PIs **and INSTIs** is uncommon in ARV-naive individuals.

[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 or tenofovir disoproxil fumarate with emtricitabine or lamivudine) in combination with either a ritonavir-boosted PI (atazanavir/ritonavir or darunavir/ritonavir) or an INSTI (raltegravir). **Raltegravir is the preferred INSTI for women who are ARV-naïve and experience with its efficacy and safety in pregnant women is increasing.** Selection of these regimens should be based on individual patient characteristics and needs (see [Table 9](#)).

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 non-transmitters 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 non-transmitters, 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-naïve 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 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 9](#)).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.

All pregnant women living with HIV infection should be counseled that ART is recommended, regardless of viral load, to optimally reduce the risk of perinatal transmission. If, after counseling, a woman chooses to forgo the use of ARV drugs during pregnancy, this decision should be re-addressed during subsequent medical appointments. The Perinatal Hotline is a resource that can be accessed to assist with the discussion (www.hivpregnancyhotline.org).

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).²⁵⁻²⁸ Two 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.²⁹ In the second publication, raltegravir was either initiated as part of an ART regimen in 9 ARV-naïve women or added to an existing ARV regimen in 5 women who conceived on ART but had persistent viremia. Raltegravir was initiated at a gestational age of 34 weeks or later.³⁰ 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 ART regimen.³¹ Although raltegravir is the preferred INSTI for women who are ARV-naïve, the efficacy and safety of this approach has only been described in anecdotal reports and, therefore, cannot be routinely recommended at this time.

The ART regimen initiated during pregnancy can be modified after delivery to include simplified regimens that were not used in pregnancy because safety data were insufficient. Decisions regarding continuation of an ART 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 3)

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 9](#) 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. **In addition, The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) makes no recommendation of one agent or regimen over another within each category (Preferred or Alternative).**

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, **and (until more data are available) elvitegravir/cobicistat.**

Drug	Comments
Preferred Initial Regimens in Pregnancy:	
<ul style="list-style-type: none"> 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; in addition, there have been no established associations with teratogenic effects (from animal and/or human studies), and no 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. Cannot be administered with proton-pump inhibitors; specific timing recommended for dosing with H2 blockers (see Table 9).
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(s)	
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.
Alternative Initial Regimens in Pregnancy:	
<ul style="list-style-type: none"> Regimens with clinical trial data demonstrating efficacy in adults and adequate serum drug levels in pregnancy, 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.
Alternative 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 9). Once-daily LPV/r is not recommended for use in pregnant women.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 2 of 3)

Drug	Comments
Alternative Integrase Inhibitor Regimens	
DTG plus a Preferred Two-NRTI Backbone	PK data available only in abstract form. No safety problems identified in limited but increasing experience in pregnancy. Available as FDC (with ABC, requiring HLA B5701 testing). Administered once daily. Useful when drug interactions with a PI are a concern. In non-pregnant adults, associated with lower rates of INSTI resistance than RAL, and therefore suggested for women with acute infection in pregnancy. Specific timing and/or fasting recommendations if taken with calcium or iron (e.g., in prenatal vitamins; Table 9).
Alternative NNRTI Regimens	
EFV plus a Preferred Two-NRTI Backbone	Concern because of birth defects seen in primate studies, but data not borne out in human studies and extensive experience in pregnancy ; cautionary text remains in package insert (see Teratogenicity and Table 9). Preferred regimen in women who require co-administration of drugs with significant interactions with preferred agents, or who need the convenience of a coformulated, single-tablet, once-daily regimen and are not eligible for RPV . Screening for antenatal and postpartum depression is recommended. Higher rate of adverse events than drugs in Preferred category
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.
Insufficient Data in Pregnancy to Recommend Routine Use in Initial Regimens for ART-Naive Women:	
<ul style="list-style-type: none"> • Drugs that are approved for use in adults but lack adequate pregnancy-specific PK or safety data 	
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:	
<ul style="list-style-type: none"> • Drugs whose use is not recommended as part of initial regimens in pregnancy because of toxicity, lower rate of viral suppression, or pharmacologic data suggesting insufficient serum drug levels in pregnancy, or because these drugs are not recommended in ART-naive populations. <p>Note: Drugs not recommended for initial use because of toxicity (stavudine [d4T], didanosine [ddI], treatment-dose ritonavir [RTV], marked below with *) should also be stopped in women who present during pregnancy while taking these medications. For women who present on drugs not recommended for initial use because of concerns about viral breakthrough (EVG/COBI/TDF/FTC or EVG/COBI/TAF/FTC, marked below with **), providers should consider switching to more effective, recommended regimens. If an EVG/COBI regimen is continued, viral load should be monitored frequently, and therapeutic drug monitoring (if available) may be useful.</p>	
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.	
EVG/COBI/TDF/FTC** Fixed Drug Combination	Limited data on use of EVG/COBI component in pregnancy. Inadequate levels of both EVG and COBI in 2nd and 3rd trimester, as well as viral breakthroughs, have been reported. Specific timing and/or fasting recommendations, especially if taken with calcium or iron (e.g., in prenatal vitamins; see Table 9).
EVG/COBI/TAF/FTC** Fixed Drug Combination	Limited data on use of EVG/COBI as above; additionally, no data on use of TAF in pregnancy. Inadequate levels of both EVG and COBI in 2nd and 3rd trimester, as well as viral breakthroughs, have been reported. Specific timing and/or fasting recommendations, especially if taken with calcium or iron (e.g., in prenatal vitamins; see Table 9).
ABC/3TC/ZDV As a complete regimen, in absence of other antiretroviral medications	Generally not recommended due to inferior virologic efficacy.
COBI	Limited data on use of COBI (including coformulations with ATV or DRV) in pregnancy.
d4T*	Not recommended due to toxicity.
ddI*	Not recommended due to toxicity.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 3 of 3)

Drug	Comments
FPV	Limited data on use in pregnancy. Not recommended in ART-naive populations.
IDV/r	Nephrolithiasis, maternal hyperbilirubinemia.
MVC	MVC requires tropism testing before use. Few case reports of use in pregnancy. Not recommended in ART-naive populations.
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 Acronyms: 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

Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- In general, women living with HIV receiving antiretroviral therapy (ART) who present for pregnancy care generally should continue their ART during pregnancy, provided the regimen is tolerated and effective in suppressing viral replication (HIV viral load less than lower limits of detection of the assay) **(AII)**.
- Certain drugs should not be continued in pregnant women because of toxicity risk (stavudine, didanosine, and treatment-dose ritonavir, which are also recommended for non-pregnant individuals). Additionally, consider replacing certain drugs that have low drug exposure in pregnancy associated with potential increase in virologic failure (i.e., elvitegravir/cobicistat). These drugs should be replaced with ARVs recommended in pregnancy (see [Table 6](#)) **(BIII)**. More frequent virologic monitoring is warranted when an antiretroviral (ARV) regimen is altered during pregnancy **(CIII)**.
- HIV 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 generally continue their ART regimen during pregnancy, provided it is well-tolerated and effective in suppressing viral replication.

As newer, highly effective antiretroviral (ARV) drugs are approved, women living with HIV 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 pharmacokinetics and safety. There are certain drugs which should not be continued in pregnant women because of toxicity risk (stavudine, didanosine, and treatment-dose ritonavir, which are also recommended for non-pregnant individuals). Additionally, consider replacing certain drugs that have low drug exposure in pregnant women associated with potential increase in virologic failure (i.e., elvitegravir/cobicistat). These drugs should be replaced with ARVs recommended in pregnancy (see [Table 6](#)). However, discontinuation or alteration 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.¹ Maintenance of viral suppression is paramount for both maternal health and prevention of perinatal transmission. Thus, if questions arise about specific 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. In addition, more frequent virologic monitoring is warranted when an ARV regimen is altered during pregnancy. 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](#).

Women with HIV 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 [Efavirenz](#) section). 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% CI, 0.56–1.08). The Panel on Treatment of Pregnant Women Living with HIV and Prevention of Perinatal Transmission recommends that efavirenz be continued in pregnant women receiving efavirenz-based ART, provided that the ARV regimen is well tolerated and

results in virologic suppression.

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

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Pregnant Women Living with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications (Last updated November 14, 2017; last reviewed November 14, 2017)

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 of 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, prior ARV use, concurrent medical conditions, and current recommendations for ART in pregnancy, 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 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 resistance studies because longer ART has been associated with reduced transmission rates compared to shorter treatment periods (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 women living with HIV 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 resistance and, thus, reduced efficacy if these antiretroviral (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.⁶⁻¹¹ 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.^{8,12}

Increased risk of treatment failure has not been demonstrated with re-initiation 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 women when compared with those who received ART during previous pregnancies or according to type of ART previously received.¹³ 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.¹⁴ 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.¹⁵

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, prior medical conditions, and the results of resistance testing should be taken into consideration. In general, ART should be initiated prior to receiving results of ARV drug-resistance studies, especially because **longer** duration of ART has been associated with reduced transmission rates compared to shorter treatment periods.^{16,17} 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, **has no evidence of resistance to that ART, and (preferably)** is currently recommended as first-line or an alternate ART regimen for initial ART in pregnancy (see [Table 6: What to Start](#)). **Drugs not recommended for initial use because of toxicity (stavudine, didanosine, treatment-dose ritonavir) should not be used; drugs not recommended for initial use because of concerns about viral breakthrough during pregnancy should also generally be avoided.** 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 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 November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Plasma HIV RNA levels of pregnant women with HIV 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 [Antiretroviral Management of Newborns](#)) (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 recently been tested for ARV resistance (AIII). HIV drug-resistance studies should be performed before modifying the ARV regimens of patients with detectable HIV RNA levels that are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) or who have suboptimal virologic response to ARV drugs started during pregnancy; however, **therapy should not be delayed while waiting for resistance testing results (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).
- 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).
- Women taking ART during pregnancy should undergo standard glucose screening at 24 to 28 weeks' gestation (AIII). Some experts suggest earlier glucose screening for 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](#).
- An ultrasound, performed as soon as possible, is recommended to confirm gestational age and, if scheduled cesarean delivery is necessary, to guide the timing of the procedure (see [Transmission and Mode of Delivery](#)) (AI).
- Amniocentesis should be performed on women living with HIV 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 should be achieved in 12 to 24 weeks. **Individuals with higher viral loads and lower CD4 T lymphocyte (CD4) cell counts are more likely to achieve viral suppression later within this range,¹ while those with lower values and those using integrase strand transfer inhibitors (INSTIs) are more likely to achieve suppression in much shorter time frames.** 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.^{2,3} Viral load should be monitored in pregnant women living with HIV 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.⁴ **Similarly, more frequent testing may be required for women on regimens for which there is less confidence in adequate drug exposure or efficacy in pregnancy (Table 6).**

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 pregnant women living with HIV, 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.^{2,5,6}

ARV drug-resistance testing—including transmitted INSTI resistance genotype testing, if INSTI resistance is a concern—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 while waiting for resistance testing results (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)). If the results demonstrate resistance, then the regimen can subsequently be adjusted. ARV drug resistance testing also should be performed on women taking an ARV regimen who have suboptimal viral suppression (i.e., failure to achieve undetectable levels of virus after an appropriate time frame, as noted above) or who have sustained 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.

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.^{7,8}

Pregnancy increases the risk of glucose intolerance. PI drugs have been associated with increased risk of hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis.⁹⁻¹² However, the majority of studies in pregnant women with HIV have not shown an increased risk of glucose intolerance with PI-based regimens during pregnancy.¹³ A prospective study including detailed evaluations for glucose intolerance and insulin resistance among pregnant women living with HIV did not find differences between women on PI-containing and non-PI-containing regimens.¹⁴ 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. Women living with HIV 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 scheduled cesarean deliveries at 38 weeks' gestation to prevent perinatal transmission in women living with HIV 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](#)).¹⁵⁻¹⁷ 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.^{18,19} 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.²⁰⁻²³ Although no transmissions have occurred among 159 cases reported of amniocentesis or other invasive diagnostic procedures among women on effective ART, a small increase in risk of transmission cannot be ruled out.²⁴⁻²⁷ Women living with HIV 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 women living with HIV, and they recommend limiting invasive procedures to amniocentesis. At a minimum, pregnant women living with HIV 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.^{28,29} 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 November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- HIV drug-resistance studies should be performed in women living with HIV whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before:
 - Starting antiretroviral (ARV) regimens in all ARV-naive pregnant women unless they have already been tested for ARV resistance (AIII).
 - Initiating antiretroviral therapy (ART) in ARV-experienced pregnant women, or.
 - Modifying ART regimens for women entering pregnancy while receiving ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy (AII).
- 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).
- If an integrase strand transfer inhibitor (INSTI) is being considered for an ART-naive patient and INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay (BIII).
- Documented zidovudine resistance does not affect the indications for use of intrapartum zidovudine (BIII).
- Choice of ARV regimen 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 [Antiretroviral Management of Newborns](#)) (AIII).
- Pregnant women living with HIV 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 Pregnant Women Living with HIV

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 for women living with HIV who have HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before:

- Initiating antiretroviral therapy (ART) in ARV-naive pregnant women who have not been previously tested for ARV resistance,
- Initiating ART in ARV-experienced pregnant women, or
- Modifying ARV regimens in pregnant women living with HIV who are entering pregnancy 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 or ARV-experienced women not presently on ART, ART should be initiated without waiting for the results of resistance testing, with modification of the regimen, if required, when test results return.

Use of integrase strand transfer inhibitors (INSTIs) as part of the ART regimen for pregnant women is becoming increasingly common.¹ Resistance to INSTIs is uncommon among ARV-naive individuals in the United States;² therefore, routine INSTI resistance testing is generally not indicated in pregnant women. However, such testing can be considered in the following circumstances:

- A patient received prior treatment that included an INSTI
- A patient has a history with a sexual partner on INSTI therapy, *or*
- A patient is starting or changing her ART regimen late in pregnancy, in which case an INSTI might be selected because of its ability to rapidly decrease viral load.

The usual order for HIV drug resistance genotype testing detects mutations that confer resistance to protease inhibitors (PIs), nucleos(t)ide reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). At some intuitions, testing for INSTI resistance may require a separate order.

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 individuals living with HIV. In addition, pre-existing resistance to a drug in an ART regimen may diminish the 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. Resistance to ARV drugs appears to be more common in women who acquired HIV perinatally than in other women with HIV.³ The complexities of managing pregnant women with perinatally acquired HIV warrant consultation with an expert in HIV.

Several factors unique to pregnancy may increase the risk of development of 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

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 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;⁴ however, women in this cohort had characteristics that would indicate a need for ART under current recommendations from the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel). 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,⁵ and other studies have suggested that drug-resistance mutations may diminish viral fitness,⁶ possibly leading to a decrease in transmissibility.

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.⁷

In another study, prevalence of ARV drug resistance among newborns diagnosed with HIV 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.^{8,9}

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 2009.¹⁰ 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 PI-based in 48%, non-PI-based in 4%, NRTI 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.¹¹ 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.^{12,13}

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 (for HIV RNA >1,000 copies/mL near delivery; see [Intrapartum Antiretroviral Drug Therapy/Prophylaxis](#)). Other ARVs should be continued orally during labor to the extent possible. The rationale for including zidovudine intrapartum when a woman is known to harbor virus with zidovudine resistance is based on several factors. 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.⁵ Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.⁶ 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.¹⁴⁻¹⁶ 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,^{17,18} 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.^{19,20} Thus, intrapartum IV administration of zidovudine, when indicated, is recommended even in the presence of known **zidovudine** 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 adhere to an effective ARV regimen that achieves maximal viral suppression.

Several studies have demonstrated that women's adherence to ART may worsen in the postpartum period.²¹⁻²⁶

Previous versions of the Perinatal Guidelines have provided guidance about the situation in which women stop their ART regimen post-partum. However, the Panel strongly recommends that ART, 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 November 14, 2017; last reviewed November 14, 2017)

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 perform tests for resistance if HIV RNA level is > 500 copies/mL (AII).
 - Consult an HIV treatment expert and consider possible antiretroviral regimen modification (AIII).
- Scheduled cesarean delivery at 38 weeks' gestation is recommended for pregnant women living with HIV 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. In addition, an analysis from the Women's Interagency HIV Study cohort found that higher viral loads were associated with an increased risk of pregnancy loss (miscarriage or stillbirth).⁴

Issues associated with adherence are frequently associated with lack of virologic suppression and should be assessed when viral load does not decline as expected. A systematic review and meta-analysis of adherence to antiretroviral therapy (ART) during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the United States) found that only 73.5% of pregnant women achieved adequate (>80%) ART adherence.⁵ Evaluation of and support for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

The lack of virologic suppression by late pregnancy may indicate virologic failure but may also represent inadequate time on 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 treatment-naive pregnant women with HIV 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.⁶ A 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.⁷

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 lymphocyte (CD4) counts after ART initiation (non-nucleoside reverse transcriptase inhibitor-based) in 25 women with acute HIV infection and 30 women with chronic HIV infection 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).⁸ Strategies to accelerate viral decline may be considered in this situation, in consultation with HIV treatment experts (see [Acute HIV Infection](#) section).

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:

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

The role of therapeutic drug monitoring (TDM) in reducing the risk of virologic failure is still undefined.⁹ In a cohort of pregnant women with HIV, 66 (39%) underwent TDM.¹⁰ Comparing women who had and did not have TDM, multivariate analysis found that it was associated with medication alterations during pregnancy but was not associated with any difference in viral breakthrough during pregnancy or detectable viral load at birth; there were no transmissions in either group.

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. Other possible interventions include adherence education, treatment of comorbidities such as nausea or vomiting, and directly-observed drug administration in the home or hospital setting.¹¹

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.¹² These findings also highlight the importance, as much as possible, of avoiding changing effective ARV regimens in women who become pregnant on ART (see Pregnant Women Currently Receiving ART).

The integrase strand transfer inhibitor (INSTI) class of drugs has been associated with rapid viral load reduction. Raltegravir has been shown to reduce viral load by approximately 2 log copies/mL by week 2 of therapy in ART-naïve patients.^{13,14} Because of these data, the addition of raltegravir or another INSTI 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.¹⁵⁻¹⁷ However, the efficacy and safety of this approach in pregnancy have not been evaluated in clinical trials, and only case series and a retrospective cohort are available, primarily involving raltegravir.^{18,19} 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. In addition, if the reason for viremia is poor adherence, it is unclear that adding a new drug to the existing regimen would improve adherence. There have been 2 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.^{18,20} Furthermore, data in 19 mother-infant pairs enrolled in a multicenter trial to determine washout pharmacokinetics and safety of *in utero*/intrapartum exposure to raltegravir in infants born to pregnant women receiving raltegravir-based ART found that, while raltegravir readily crossed the placenta, elimination was highly variable and extremely prolonged in some infants, raising potential infant safety concerns.²¹ At the current time, although this approach is increasingly being used in clinical practice, data are

insufficient to recommend routinely adding raltegravir alone to a regimen for women in whom ART is failing in late pregnancy.

Scheduled cesarean **delivery at 38 weeks' gestation** is recommended for pregnant women living with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery (see [Transmission and Mode of Delivery](#)).^{22,23}

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Stopping Antiretroviral Drugs during Pregnancy (Last updated November 14, 2017; last reviewed November 14, 2017)

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 antiemetics, 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 antiretroviral therapy (ART) 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 mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated with perinatal transmission of HIV. 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% confidence interval [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 ART administered during the antepartum or intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert and a clinical pharmacologist experienced with ARV medications.

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Panel's Recommendations

- All pregnant women living with HIV should be screened during the current pregnancy for hepatitis B virus (HBV) and unless they are known to have HIV/HBV coinfection and for hepatitis C virus (HCV) infection unless they are known to have HIV/HCV coinfection (see [HIV/Hepatitis C Virus Coinfection](#)) (AIII).
- All pregnant women living with HIV 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. If they screen negative for HAV antibody, they should receive HAV vaccine, which is safe to use in pregnancy (AIII).
- All pregnant and postpartum women with HIV/HBV coinfection should receive antiretroviral therapy (ART). Antepartum ART in pregnant women with HIV/HBV coinfection should include tenofovir disoproxil fumarate (TDF) plus lamivudine or emtricitabine (AI). If women with HIV/HBV are virally suppressed on a tenofovir alafenamide (TAF) plus lamivudine or emtricitabine-based ART and become pregnant, they can be offered the choice of continuing that ART regimen or switching TAF to TDF in their ART regimen (BIII).
- 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 HBV if a flare is suspected (BIII).
- Decisions concerning mode of delivery in pregnant women with HIV/HBV coinfection should be based on standard obstetric and HIV-related indications alone; HIV/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 women living with HIV should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All pregnant women living with HIV should be screened during each pregnancy for HBV unless they are known to have HIV/HBV coinfection and for HCV unless they are known to have HIV/HCV coinfection. 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 polymerase chain reaction.¹

To prevent horizontal transmission of HIV and HBV from women with HIV/HBV coinfection to their male partners, their sexual contacts should be counseled and tested for HIV and HBV. All HBV susceptible contacts should receive the HBV vaccine series, and all partners who do not have HIV infection should be counseled about condom use and the potential benefits and risks of starting pre-exposure prophylaxis.^{2,3}

Pregnant women living with HIV who screen negative for HBV (i.e., HBsAg-negative, anti-HBc-negative, and anti-HBs-negative) should receive the HBV vaccine series. Women living with HIV 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 Women with HIV infection whose anti-HBs titers are below 10 IU/mL despite having received the HBV vaccine series should receive a second HBV vaccine series; some experts advise using a double dose of HBV vaccine (i.e., a 40-mg dose) and delaying revaccination until after a sustained increase in CD4 T lymphocyte (CD4) cell count $>350 \text{ cells/mm}^3$ is achieved on antiretroviral therapy (ART).² There is no evidence of adverse events from hepatitis B vaccine for developing fetuses **or newborns**, and current vaccines contain noninfectious HBsAg.⁴ Anti-HBs titers should be obtained 1 month after completion of the vaccine series in patients with HIV infection; 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 $>350 \text{ cells/mm}^3$ is achieved on ART). There is no consensus for management of patients whose anti-HBs titers remain below 10 IU/mL following a second HBV vaccine series.²

A positive test for anti-HBc alone can be false-positive; alternatively, it may signify remote infection 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 patients with HIV infection 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 individuals with HIV infection **and** 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). Pregnant women with HIV infection 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 have HBV infection and who have not already received the HAV vaccine series should also be screened for hepatitis A virus (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 (note that some labs only provide a combined IgG and IgM HAV titer, which is acceptable). Women with chronic HBV infection who have not already received the HAV vaccine series and are HAV IgG antibody-negative should receive the HAV vaccine series, which is safe in pregnancy. Responses to the HAV vaccine are reduced in patients living with HIV with CD4 counts $<200 \text{ cells/mm}^3$. Antibody response should be assessed in such patients 1 month after HAV vaccine series is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is $>200 \text{ cells/mm}^3$.² Women who have already received the HAV vaccine series when their CD4 cell count was $\geq 200 \text{ cells/mm}^3$ do not need to be revaccinated for HAV 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 directly evaluated, 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, 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 **miscarriage¹¹ and** preterm labor and delivery may be increased¹² with acute HBV infection (see [Hepatitis B Infection](#) in the [Adult and Adolescent OI Guidelines](#)).

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.¹³ High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.¹⁴⁻¹⁶

Several studies and a meta-analysis suggest that lamivudine or telbivudine may reduce the risk of perinatal transmission of HBV if given during the third trimester to HIV-seronegative women with HBV infection and high HBV DNA levels.¹⁷⁻²⁵ In addition to HBV viral load, the presence of certain HBV variants is also a risk factor for failure of HBV prophylaxis.^{9,26} In a study of 2,048 pregnant women living with HIV in Malawi, 103 women (5%) were HBsAg-positive, 70 of whom also had HBV viremia. Nearly 10% of infants born to mothers with HIV/HBV coinfection had HBV DNA detected by age 48 weeks despite being immunized according to national recommendations at ages 6, 10, and 14 weeks.²⁷

Lamivudine, TDF, TAF (a prodrug of TDF), and emtricitabine have activity against both HIV and HBV. TDF or TAF with emtricitabine or lamivudine is the preferred dual nucleoside reverse transcriptase inhibitor backbone in women with HIV/HBV coinfection. However, only lamivudine, TDF, and emtricitabine are recommended for use in pregnancy (see Table 6). There is no pharmacokinetic information and there are few reports of use of TAF in human pregnancy. In animal studies, there were no developmental effects when TAF was administered during the period of organogenesis at exposure equal to or 51 times the usual therapeutic dosage (rats and rabbits, respectively).^{28,29} 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>).

Some pregnant women may already be receiving TAF-containing ART prior to pregnancy. TAF is effective against HBV in non-pregnant adults,^{30,31} but has not been studied in pregnancy. In this case, the woman can be offered a choice of continuing that ART regimen or switching TAF to TDF in their ART regimen. Please see individual drug sections for TDF, TAF, emtricitabine, and lamivudine for detailed review of safety, pharmacologic, and other clinical data for use in pregnancy.

Consultation with an expert in HIV and HBV is strongly recommended for a pregnant woman with HIV/HBV coinfection who continues to have detectable HBV DNA viremia despite receiving an ART regimen with 2 anti-HBV nucleos(t)ides.

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. Seventy-nine cases of exposure to entecavir, 77 during the first trimester and 2 in the second trimester, have been reported to the Antiretroviral Pregnancy Registry with no birth defects noted, but this number of exposures is too few to assess overall risk.²⁸ Seventy-nine cases of exposure to telbivudine have been reported to the Antiretroviral Pregnancy Registry, with 68 during the first trimester, 7 in the second trimester, and 4 in the third trimester. Telbivudine was given during the third trimester to 135 women with HBV infection and without HIV infection; it was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers than in the comparison group not on telbivudine (0% vs. 8%; $P = 0.002$).^{20,32} In a recent systematic review and meta-analysis of single-drug anti-HBV therapy during pregnancy in chronic HBV mono-infection, antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. 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.³³ For pregnant women with HIV/HBV coinfection, 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, their use in the absence of a fully suppressive ART regimen may lead to development of 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

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.³⁴

Monitoring Women With HIV/Hepatitis B Virus Coinfection 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 and Adolescent OI Guidelines](#)).

Following initiation of ART, an elevation in hepatic enzymes can occur in women with HIV/HBV coinfection—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 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, lifelong treatment is recommended.^{1,2} Discontinuation of anti-HBV agents may be associated with hepatocellular damage resulting from reactivation of HBV. If anti-HBV-active drugs are discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter, with prompt re-initiation of HBV treatment if a flare is suspected.²

Mode of Delivery

Decisions concerning mode of delivery in pregnant women with HIV/HBV coinfection 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 women with HIV/HBV coinfection. Current guidelines for women with HBV monoinfection advise that cesarean delivery is not indicated to prevent perinatal transmission of HBV.³⁵⁻³⁷

Evaluating and Managing Infants Exposed to Hepatitis B Virus

Within 12 hours of birth, all infants born to mothers with chronic HBV infection, including those with HIV, should receive HBIG and the first dose of the HBV vaccination series. For infants weighing $\geq 2,000$ 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 3 additional doses at ages 1, 2–3, and 6 months.^{38,39} This regimen is $>95\%$ effective in preventing HBV infection in these infants. **ART that includes nucleos(t)ides with anti-HBV activity will result in low or suppressed HBV viral loads near delivery, which should further reduce risk of HBV perinatal transmission in women with HIV/HBV coinfection.**

Infant post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at ages 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 mothers with HBV infection up to age 24 months. HBsAg-negative infants with anti-HBs levels >10 mIU/mL are protected and need no further medical management. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1 to 2 months after the final dose of vaccine.

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HIV/Hepatitis C Virus Coinfection (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- All pregnant women living with HIV should be screened during the current pregnancy for hepatitis B virus (HBV) unless they are known to have HIV/HBV coinfection and for hepatitis C virus (HCV) infection unless they are known to have HIV/HCV coinfection (see [HIV/Hepatitis B Virus Coinfection](#) section) (AIII).
- All pregnant women living with HIV and/or HCV who screen negative for HBV infection (i.e., HBV surface antigen-negative and HBV core antibody-negative) and lack HBV immunity (i.e., HBV surface antibody-negative) should receive the HBV vaccine series (AII).
- Women with chronic HCV 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). If they screen negative for HAV antibody, they should receive HAV vaccine, which is safe to use in pregnancy (AIII).
- If considering initiation or continuation of HCV treatment in a pregnant woman with HIV coinfection, consultation with an expert in HIV and HCV is strongly recommended (AIII).
- Recommendations for antiretroviral (ARV) drug use during pregnancy are the same for women living with HIV whether they have chronic HCV or not (AIII).
- 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 pregnant women with HIV/HCV coinfection 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 (AIII). The specific type and timing of assays for HCV in children should be performed after consultation with an expert in pediatric HCV infection (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 maintains updated information about treating patients with HIV/HCV coinfection. The guidelines are available online at HCVguidelines.org. The management of HIV/HCV coinfection in pregnancy is complex and none of the approved HCV oral medications/direct-acting antivirals (DAAs) have yet been fully evaluated in pregnant women; thus, 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 pregnant women living with HIV should be screened for HCV at entry into general HIV care and during each pregnancy for hepatitis B virus (HBV) unless they are known to have HIV/HBV coinfection, and for hepatitis C virus (HCV) infection unless they are known to have HIV/HCV coinfection. Among women with HIV, the observed HCV seroprevalence rate was 12% in a European cohort of pregnant women with HIV¹ and 3.8% among women with HIV in New York State.² Although data about secular trends in HCV risk among women living with HIV are limited in the U.S., the prevalence of HCV among women of childbearing age in the general population has increased substantially in recent years.^{3,4} The male partners of all patients with HIV/HCV coinfection 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 partners who do not

have HIV infection should be counseled about the potential benefits and risks of starting oral pre-exposure prophylaxis to prevent HIV acquisition (see [Preconception Counseling](#)).

Newly available DAAs have dramatically improved HCV therapy; it is now possible to cure HCV infection in most patients. Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection. The management of HIV/HCV coinfection in pregnancy is complex, however. Although one study is now evaluating HCV treatment in pregnancy,³ none of the approved DAAs have been fully evaluated in pregnant women; the use of ribavirin, although rarely required with DAAs, is also contraindicated in pregnancy.⁸ If considering initiation or continuation of treatment of HCV in a pregnant woman with HIV/HCV coinfection, consultation with an expert in HIV and HCV is strongly recommended. In addition, the risks of perinatal HCV transmission are much lower than those of perinatal HIV transmission, and many children will clear HCV infection spontaneously,⁷ making the balance of risks and benefits for treating HCV in pregnancy different from that for treating HIV.

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

- To identify women with HIV/HCV coinfection 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 monitor for the increased risk of HCV-related hepatotoxicity related to antiretroviral (ARV) use⁸ and potential for increased risk of preterm birth with HCV infection^{9,10} in women with HIV/HCV coinfection;
- To ensure vaccination against other viral hepatitis (hepatitis A virus [HAV] and HBV) if needed; and
- To ensure appropriate follow-up and evaluation of infants exposed to HCV.

Screening for chronic HCV infection using a sensitive immunoassay for HCV antibody is recommended for all individuals living with HIV, including pregnant women. False-negative anti-HCV immunoassay results can occur in individuals with HIV, 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.¹¹

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. Women with chronic HCV infection who have not already received the HAV vaccine series should be screened for immunity to HAV; if they screen negative for HAV antibody, they should receive the HAV vaccine series. Although the safety of HAV vaccination during pregnancy has not been directly evaluated, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.¹² In women with CD4 T lymphocyte (CD4) count <200 cells/mm³, antibody responses to HAV vaccine should be assessed 1 month after completion of vaccination series; those who are HAV Ab IgG negative should be revaccinated when the CD4 count is >200 cells/mm³.¹³ Women with HIV/HCV coinfection 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. Women with HIV/HCV coinfection who are HBsAb negative despite having received the HBV vaccine series may benefit from revaccination (see [HIV/HBV](#)).¹⁴ There is no apparent risk to developing fetuses from hepatitis B vaccination, as current vaccines contain noninfectious HBsAg.¹²

Impact of HIV/HCV Coinfection on Progression and Perinatal Transmission of Both Viruses

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 well during pregnancy, provided that

they have not progressed to decompensated cirrhosis.^{15,16} HCV infection may increase the risk of intrahepatic cholestasis of pregnancy;¹⁷ there are no data about the risk among women with HIV/HCV coinfection.

In most studies of women with HIV/HCV coinfection who are not receiving treatment for either infection, the incidence of perinatal HCV transmission is approximately 2-fold higher among women with HIV/HCV coinfection (10% to 20% transmission risk), compared to HCV mono-infection.¹⁸⁻²¹ These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impact on HCV disease activity.^{10,22} However, early and sustained control of HIV viremia with ART may reduce HCV transmission to infants.^{16,23,24} A European study of perinatal transmission of HCV found that use of effective ART for HIV was associated with a strong trend toward reduced HCV transmission (odds ratio 0.26, 95% CI, 0.07–1.01).²³ In an Italian cohort, HCV transmission in infants of mostly ART-treated HIV/HCV-coinfected women occurred in 9%, but no HCV transmissions occurred among women with HCV viral loads <5 log IU/mL.¹⁰

In the absence of ART, maternal HIV/HCV coinfection also may increase the risk of perinatal transmission of HIV.^{25,26} Perinatal HIV transmission will likely be reduced in pregnant women with HIV/HCV coinfection by following standard recommendations for ART for all women living with HIV.

Impact of Hepatitis C Virus on HIV Management

Few data exist on the optimal management of pregnant women with HIV/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 with HIV mono-infection (see [HIV/Hepatitis C Coinfection](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)).

Hepatitis C Virus-Specific Therapy in Pregnancy

All currently available DAAs lack sufficient safety data to be recommended during pregnancy. In the past, 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.²⁷ Some DAA regimens are approved for use with ribavirin in specific non-pregnant populations, due to suboptimal treatment response with DAAs alone. Combination regimens of DAAs plus ribavirin are **contraindicated** in pregnant women due to teratogenic and embryocidal effects observed in all animal species exposed to ribavirin. Ribavirin-associated defects in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Concerns have also 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.²⁸ Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or <http://www.ribavirinpregnancyregistry.com>).

There are many interferon-free DAA regimens approved for the treatment of HCV. Determination of the optimal regimen for an individual patient is based on many factors, including HCV genotype (GT), prior treatment experience, and stage of liver disease (e.g., compensated or decompensated cirrhosis). There are three main classes of DAAs:^{29,30}

- NS5A inhibitors: Daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, and velpatasvir
- NS5B polymerase inhibitors: Dasabuvir and sofosbuvir
- NS3/4A protease inhibitors: Glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir.

DAAs are not yet recommended for use in pregnancy because of the lack of pharmacokinetic and safety data, although at least one study of ledipasvir/sofosbuvir in pregnancy is ongoing (see <https://clinicaltrials.gov/ct2/show/NCT02683005>). In addition, potential drug interactions exist between these newer anti-HCV drugs and ARV drugs that may produce clinically significant changes in serum levels of both ARVs and anti-HCV

medications. For detailed information on HIV/HCV drug interactions, see [Adult and Adolescent Guidelines, Adult and Adolescent Opportunistic Infections Guidelines](#) and the HCV treatment guidelines (<http://www.hcvguidelines.org>) or <http://www.hep-druginteractions.org/>.

Monitoring of Women with HIV/HCV Coinfection during Pregnancy

An elevation in hepatic enzymes following initiation of ART can occur in women with HIV/HCV coinfection—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.

Rates of preterm delivery are also high among HIV/HCV-coinfected women. In an Italian cohort of mostly ART-treated women with HIV/HCV coinfection, preterm delivery occurred in 41% of women overall (29% of women with HCV RNA <5 log IU/ml and 43% of women with HCV RNA >5 log IU/ml; the difference between the two groups was not statistically significant, although women with preterm delivery had statistically significantly higher levels of HCV RNA than those who delivered at term).¹⁰

Mode of Delivery

The majority of studies of scheduled cesarean delivery in women with HCV infection, with or without HIV coinfection, have found that the procedure does not reduce the risk of perinatal transmission of HCV.^{23,31-33} 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 Infants Exposed to HCV

Infants born to women with HIV/HCV coinfection should be assessed for HCV infection. Testing with anti-HCV antibody should be performed after age 18 months, when maternal anti-HCV antibody has waned.³⁴ Sensitivity of HCV RNA testing is low at birth and viremia can be intermittent; thus, HCV RNA testing should not be performed before age 2 months and a single negative test is not conclusive evidence of lack of infection.³⁵ The Pediatric Opportunistic Infections Guidelines provide further details about diagnostic evaluation of HCV-exposed infants.

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HIV-2 (Last updated November 14, 2017; last reviewed November 14, 2017)

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 **have only HIV-2 infection, the test will** show negative HIV-1 antibodies and positive HIV-2 antibodies (**AII**).
- Pregnant women with HIV-1/HIV-2 coinfection should be treated as per guidelines for HIV-1 mono-infection, but using antiretroviral drugs that are active against HIV-2 (see below).
- No randomized clinical trials have been performed to address when to start treatment or what the optimal treatment is for HIV-2 infection (**AIII**). **A regimen with two nucleoside reverse transcriptase inhibitors and certain boosted protease inhibitors or integrase strand transfer inhibitors is recommended for all pregnant women with HIV-2 infection (AIII).**
- Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used (**AIII**).
- All infants born to mothers with HIV-2 infection should receive the 6-week zidovudine prophylactic regimen (**BIII**).
- In the United States, where safe infant formula is readily available, breastfeeding is not recommended for infants of mothers with HIV-2 infection (**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, The 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 indeed have HIV-2 mono-infection 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, 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 antibody assay to distinguish HIV-1 from HIV-2 antibodies. **The FDA approved HIV-2 antibody supplemental test Geenius (Bio-Rad Laboratories) is** used as part of the CDC-recommended HIV laboratory testing algorithm. 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 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

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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 women with HIV-1 infection.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 patients with HIV-1 monoinfection, making sure that the antiretroviral therapy (ART) regimen chosen is also appropriate for treatment of HIV-2 (see below). Once treatment is started, ART should be continued postpartum, as is recommended for all patients with HIV-1 infection. In a systematic review of non-pregnant patients with HIV-2 infection from 1996 to 2012, Ekouevi et al. noted a heterogeneity of treatment outcomes among patients with HIV-2 infection 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 susceptibility to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity.²² The integrase strand transfer inhibitors (INSTIs) 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 pregnant women with HIV-2 monoinfection has been based on expert opinion. A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted PI or an INSTI currently is recommended for all pregnant women with HIV-2 infection. Based on efficacy and available data on safety in pregnant women with HIV-1 infection, 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.

There are no data to address whether treatment should be continued after pregnancy in women with HIV-2 monoinfection. 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.³⁵ For pregnant women with HIV-2 infection with CD4 cell counts >500 cells/mm³ 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 with HIV-2 should receive a 6-week zidovudine prophylaxis regimen.³⁴ The possible risks and benefits of ARV prophylaxis should be discussed with the mothers. **The rationale for zidovudine prophylaxis in this clinical situation is based on the inability to monitor HIV-2 plasma viral load in the mother and the lack of nevirapine activity against HIV-2, which precludes its use as prophylaxis.**

There is no evidence for the role of scheduled cesarean delivery in women for prevention of HIV-2 vertical transmission. 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 countries where safe infant formula is readily available.¹⁵

Infants born to mothers with HIV-2 infection should be tested for HIV-2 infection with HIV-2-specific virologic assays at time points similar to those used for HIV-1 testing.³⁶ 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 Antibody testing of infants (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) **can also be performed at age 18 months** 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 with Perinatal HIV Infection (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- The management of prenatal care and general principles of antiretroviral therapy (ART) and HIV management do not differ between pregnant women with perinatally acquired HIV and those who acquired HIV infection postnatally. With effective ART and prenatal management, the risk of perinatal transmission does not appear to be increased in women who acquired HIV perinatally compared with those who acquired HIV infection postnatally (AII).
- Using the same guiding principles that are used for heavily ART-experienced adults, optimal ART regimens should be selected based on resistance testing, prior ART history, and pill burden (AII).
- Consultation with experts in HIV and pregnancy is recommended when the presence of extensive drug resistance warrants the use of antiretroviral drugs for which there is limited experience in pregnancy (AIII).
- Pregnant women with perinatally acquired HIV warrant enhanced focus on adherence interventions during and after delivery (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 individuals living with HIV, including those with perinatally acquired HIV. An increasing number of women with perinatal 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 with perinatally acquired HIV and those who acquired HIV infection in other ways (e.g., acquired through sexual contact or injection drug use). 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 women with perinatal HIV. In addition, because most of these women are still adolescents and young adults, they may be at higher risk of certain pregnancy complications such as preterm delivery, low birthweight, and preeclampsia.⁴⁻⁸

As many as 30% to 70% of pregnant women with perinatal HIV have evidence of HIV drug resistance.⁸⁻¹¹ 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 ART-experienced adults. Because of the potential for known or suspected complex drug-resistance mutation patterns in individuals who acquired HIV perinatally, clinicians may consider phenotypic resistance testing in these women during pregnancy when resistance testing is indicated. Consideration should be given to regimens that optimize dosing intervals and minimize pill burden. Consultation with experts in HIV and pregnancy is recommended. Regimens should be constructed using antiretroviral (ARV) drugs recommended for use in pregnancy whenever possible. However, in many cases, 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 in such cases.

Women with perinatal HIV are more likely to have lower median CD4 T lymphocyte counts, detectable viral loads, and genotypic drug resistance (40% vs 12%) than women with non-perinatally acquired HIV.^{8,11,12} In a retrospective analysis of 37 pregnancies among women with perinatal HIV and 40 pregnancies among age-matched women with non-perinatally acquired HIV who delivered during the same time period, the viral load decline achieved during pregnancy in women with perinatal HIV was not sustained during postpartum follow-up in contrast to the age-matched comparison group. During 4 years of follow-up, there were 4 deaths

due to AIDS-related complications in women with perinatal HIV but none in the women with non-perinatally acquired HIV.¹² Although genotypic mutations were more common in women with perinatal HIV, loss of viral suppression resulting in the progression of disease postpartum was more likely related to adherence difficulties, highlighting the need for special focus on adherence interventions after delivery.

Evidence from studies is conflicting as to whether women with perinatally acquired HIV have higher rates of preterm and small-for-gestational-age (SGA) infants when compared with women with non-perinatally acquired infection.^{13,14} Several studies have demonstrated no associations between perinatal route of maternal HIV infection and preterm birth, SGA, or low birth weight.^{8,11,13-15} Other studies have reported conflicting results:

- A case series reported high rates of preterm birth (31%) among women with perinatally acquired HIV.⁹
- Jao et al. reported a four-fold increased risk for SGA births among the women with perinatal infection compared to those with non-perinatally acquired infection.¹⁶
- Munjal et al. reported earlier gestational age at delivery and lower average birthweights in infants born to women with perinatal compared to those with non-perinatally acquired infection.¹²
- Jao et al. found that infants born to women with perinatally acquired HIV had lower mean length-for-age throughout the first year of life.⁷

Several studies have suggested that pregnant women with perinatally acquired HIV are more likely to have a cesarean delivery most commonly indicated for prevention of HIV infection due to lack of viral load suppression.^{9,12} Cesarean delivery in these young women raises concerns for increased risk of adverse obstetric outcomes if repeated cesarean deliveries are required for future pregnancies. Reassuringly, despite prolonged HIV infection, receipt of multiple ART regimens, and increased likelihood of drug-resistant virus in women who acquired HIV perinatally, with appropriate prenatal management and ART that results in viral suppression, the risk of perinatal transmission does not appear to be increased in this population.^{8,9,11,12,17-19}

Psychosocial challenges may be magnified due to the presence of a lifelong chronic illness, high rates of depression,²⁰ 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 individuals living with HIV 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 youth with HIV. Youth from U.S. studies had the lowest average rate of adherence at 53%.²¹ In a 2014 study of 1,596 people with perinatal HIV living in New York City, only 61% were virally suppressed. The authors attributed poor ART adherence to social, behavioral and developmental factors.²² A history of depression has also been associated with nonadherence to ART among pregnant women with perinatal HIV.²³ Focused attention on diagnosis and treatment of depression in the preconception period may lead to more optimal medication adherence. Self-motivation and social support were key to medication adherence in a study of adolescents living with HIV in the United Kingdom.²⁴

Among adolescents with perinatal HIV, pregnancy may create additional complications in the transition from pediatric/adolescent HIV care to adult care due to the complexity of navigating an adult healthcare system with multiple providers. However, pregnancy may also be an opportune time for a young woman to transition to adult care. Studies have noted reduced rates of retention in care and viral suppression among pediatric and adolescent persons with HIV who are transitioning to adult health care.²⁵ Continuing support for adherence to treatment is needed in this population. 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 November 14, 2017; last reviewed November 14, 2017)

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 antiretroviral therapy (ART) 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 ART, and the regimen should be adjusted, if necessary, to optimize virologic response (AIII).
- In women with acute HIV infection, a ritonavir-boosted protease-inhibitor-based regimen or a dolutegravir-based regimen with tenofovir disoproxil fumarate/emtricitabine should be initiated (AIII) (see [Table 6](#)).
- When acute HIV infection is diagnosed during pregnancy or breastfeeding, given the high risk of transmission to the infant, consultation with a pediatric HIV specialist regarding appropriate infant management and antiretroviral prophylaxis regimen is strongly recommended (see [Infant Management](#) section) (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 From 2002 to 2006, of 3,396 neonates exposed to HIV 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).² Among 70 infants born with perinatal HIV infection in Florida during 2007 through 2014, 12 (17%) of their mothers had evidence of acute infection during pregnancy.³ In the United States, of 10,308 pregnant women with HIV 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 seroconverted 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 infection⁵ 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/artralgias, 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.

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. [More specific guidance on HIV testing can be found](#) in the [Acute and Recent \(Early\) HIV](#) section of the [Adult and Adolescent Antiretroviral Guidelines](#), the CDC HIV testing algorithm (<http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf>) and the [Maternal HIV Testing and Identification of Perinatal HIV Exposure](#) sections.

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.⁸ A report from the Mother-Infant Rapid Intervention at Delivery study found that 6 of 54 (11%) women whose HIV was identified with rapid HIV testing during labor had primary infection. 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](#), <http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf>, and [Maternal HIV testing and Identification of Perinatal HIV Exposure](#)).⁹ Despite this recommendation, a retrospective cohort study at a large metropolitan hospital in a high-prevalence jurisdiction reported that repeat prenatal HIV testing was performed in only 28.4% of women.¹⁰

Acute or recent HIV infection during pregnancy and breastfeeding is associated with a high risk of perinatal transmission of HIV. Therefore, all pregnant women with acute or recent HIV infection should start antiretroviral therapy (ART) as soon as possible, with the goal of preventing perinatal transmission by optimal suppression of plasma HIV RNA below detectable levels.¹¹ Data from the United States and Europe demonstrate that in 6% to 16% of patients, transmitted virus may be resistant to at least 1 antiretroviral (ARV) drug.^{12,13} 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. [The choice of PI for treatment of acute infection during pregnancy should be based on recommendations for use of ARV drugs in pregnancy](#) (see [Table 6](#) and [Table 9](#)) and includes atazanavir/ritonavir and darunavir/ritonavir.¹⁴

However, recent data suggest that integrase strand transfer inhibitor (INSTI)-based regimens may be associated with shorter time to viral suppression. An observational study evaluated time to viral suppression among 86 non-pregnant adults with newly-diagnosed HIV infection: 36 (42%) had acute, 27 (31%) early and 23 (27%) had established HIV infection. ART was initiated within 30 days of diagnosis and the median time to documented viral suppression was 12 weeks. Time to viral suppression was significantly shorter in those receiving an integrase inhibitor- versus a PI-based regimen (median weeks to viral suppression: 12 and IQR 4–24 weeks in those with INSTI vs. median weeks to viral suppression 24 and IQR 12–24 in those with protease inhibitors; $P = 0.022$; baseline viral loads did not differ between those 2 groups).¹⁵ Due to the lower resistance barrier raltegravir is not recommended in this situation as viral loads are expected to be high.¹⁶ Dolutegravir plus tenofovir disoproxil fumarate (TDF)/emtricitabine is considered a reasonable ARV regimen for treatment of acute infection in non-pregnant adults but data are limited regarding efficacy of this regimen in treatment of early infection. [Although dolutegravir is not a preferred INSTI for ART initiation in pregnant women due to the limited data supporting safety and dosing of dolutegravir in pregnancy, dolutegravir may be considered for acute infection during pregnancy because of the high viral load in acute/early infection, higher barrier to resistance of dolutegravir \(compared with raltegravir\), once-a-day dosing and the goal of achieving maternal virologic suppression promptly with minimal risk of needing to adjust the treatment regimen.](#)

[TDF/emtricitabine is the preferred nucleoside reverse transcriptase inhibitor backbone for treatment of acute](#)

infection; abacavir is not recommended for empiric treatment of acute infection unless the patient is known to be HLA-B*5701-negative.

When acute HIV infection is diagnosed during pregnancy, and particularly if it is documented in late pregnancy, cesarean delivery may be necessary if there is 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](#)). Women can continue to express and store breast milk while awaiting confirmation of infection status. When acute HIV infection is diagnosed during pregnancy or breastfeeding, given the high risk of transmission to the infant with acute maternal infection, consultation with a pediatric HIV specialist regarding appropriate infant management and ARV prophylaxis regimen is strongly recommended (see [Infant Prophylaxis](#)). All women diagnosed with acute infection should be asked whether they know the HIV status of their partner. HIV testing of the sexual partners of all pregnant women testing HIV positive should be encouraged.

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Intrapartum Care (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Women should continue taking their antepartum combination antiretroviral therapy (ART) on schedule as much as possible during labor and before scheduled cesarean delivery (AIII).
- Intravenous (IV) zidovudine:
 - Should be administered to women living with HIV with HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery (AI).
 - Is not required for women receiving ART regimens who have HIV RNA ≤50 copies/mL during late pregnancy and near delivery and no concerns regarding adherence to the ART regimen (BII).
 - May be considered for women with HIV RNA between 50 and 999 copies/mL. There are inadequate data to determine whether administration of IV zidovudine to women with HIV RNA levels between 50 and 999 copies/mL provides any additional protection against perinatal transmission. However, some experts would administer IV zidovudine to women with RNA levels in this range, as the transmission risk is slightly higher when HIV RNA is in the range of 50 and 999 copies/mL compared to <50 copies/mL (CII).
- 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 and an HIV-1 RNA assay 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 or the HIV RNA suggests acute infection, infant ARV drugs should be managed as discussed in the [Antiretroviral Management of Newborns](#) section (AI).
 - If the maternal HIV differentiation test is negative and acute HIV infection has been reasonably 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

Intrapartum Antiretroviral Therapy/Prophylaxis

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 pregnant women with HIV 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, $P = .06$) 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, $P > .20$) 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 ($P < .01$) if neonates received only zidovudine for prophylaxis, but was no different (4.8% vs. 4.1%, $P = .83$) without or

with intrapartum zidovudine if the neonate received intensified prophylaxis with 2 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% CI, 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

Based on these studies, IV zidovudine should continue to be administered to women with HIV RNA >1,000 copies/mL near delivery (or for women living with HIV with unknown HIV RNA levels), regardless of antepartum regimen. While IV zidovudine is not required for women with HIV receiving ART with HIV RNA ≤1,000 copies/mL in late pregnancy and/or near delivery with no concerns about adherence to or tolerance of their ART regimens, many experts feel that there are inadequate data to determine whether administration of intrapartum IV zidovudine to such women provides any additional protection against perinatal transmission. **They recommend intrapartum IV zidovudine administration to women with RNA levels in this range, as the transmission risk is slightly higher (approximately 1% to 2%) when HIV RNA is in the range of 50 to 999 copies/mL compared to <50 copies/mL (1% or less).**^{1,5,6} However, regardless of viral load, in these circumstances the clinician may elect to use or not use intrapartum IV zidovudine based on clinical judgment.

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.⁷ Systemic and intracellular zidovudine levels increased from baseline but appeared to stabilize after 3 hours of infusion; cord blood zidovudine levels were associated with maternal levels and maternal infusion duration. If cesarean 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 versus 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.^{8,9} 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 hours⁹ 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 **is to receive IV zidovudine** 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 <24 hours) during the peripartum period, all drugs should be stopped and reinstated 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. Regardless of the reason, all women who have HIV RNA levels >1,000 copies/mL or presumed >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 8](#)).

Women Who Have Not Received Antepartum Antiretroviral Drugs

Women Who Present in Labor without Documentation of HIV Status

All women without documentation of HIV status at the time of labor should be screened for HIV with expedited testing unless they decline (i.e., “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.¹⁰ 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.¹⁰ 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, and an HIV RNA assay to screen for both acute and established 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-Care Settings](#) and the resource page for laboratory testing for HIV). Those with high HIV-1 RNA and a negative confirmatory HIV assay most likely have acute HIV infection.

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 have HIV 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 following-up on confirmatory HIV-1/HIV-2 antibody differentiation immunoassay and HIV-1 RNA testing, these women should receive appropriate assessments as soon as possible to determine their health status, including CD4 cell count, and HIV genotype for resistance.

Arrangements also should be made for establishing HIV care and providing ongoing psychosocial support after discharge. **The infant should receive enhanced prophylaxis as outlined in the section on Infant Prophylaxis.** If the follow-up antibody testing is negative, results of the HIV RNA test should be reviewed 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 women with HIV who have not received antepartum ARV drugs should have IV zidovudine started immediately to prevent perinatal transmission of HIV. Although intrapartum/neonatal ARV medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to or during labor and delivery. Pre-exposure prophylaxis for the fetus can be provided by giving mothers a drug that rapidly crosses the placenta, producing fetal systemic ARV drug levels during intensive exposure to HIV in maternal genital secretions and in blood during birth. In general, zidovudine and other nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and the integrase inhibitor raltegravir cross the placenta well, whereas protease inhibitors do not (see [Table 9](#)). **A small PK study and placental perfusion data suggest moderate to high placental transfer of elvitegravir.¹¹ Limited data from case reports and placental perfusion models also suggest moderate to high transplacental transfer of dolutegravir.^{12,13}**

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.¹⁴ 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.¹⁵ 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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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 (**AII**).
- 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 trial¹ and from a large individual patient data meta-analysis.² These two studies were conducted at a time when the majority of women with HIV 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.

HIV RNA Level of >1000 copies/mL as a Threshold for Recommendation of Scheduled Cesarean Delivery

The American Congress 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.

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 born with HIV. 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 born with HIV, some of which appear to represent *in utero* transmission.⁶

Some 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 women with HIV compared with women without HIV.⁷ Therefore, decisions about mode of delivery for women receiving ART with HIV RNA levels $\leq 1,000$ copies/mL should be individualized based on discussion between an obstetrician and a pregnant woman. 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 $\leq 1,000$ copies/mL and that it is not routinely recommended in this group.

Scheduled Cesarean Delivery in the 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 trial¹ and meta-analysis² documenting the benefits of cesarean delivery included mostly women who were receiving either no ARV drugs or zidovudine alone. However, other data partially address this issue.

In a report on births to women with HIV 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 (13/3814; 0.3%) were not significantly different than those in similar women with planned vaginal delivery (6/2238; 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 $> 1,000$ 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 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

Women with HIV who present late in pregnancy and are not receiving ARV drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be $\leq 1,000$ copies/mL at baseline. Even if ART was begun immediately, reduction in plasma HIV RNA to undetectable levels may take several weeks, depending on the **baseline viral load and** 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. **Although some experts would recommend a cesarean delivery in a woman who has been virologically**

suppressed for a brief period of time (e.g., less than 2 weeks), many others would support a vaginal delivery in this scenario, as long as the plasma HIV RNA level was <1000 copies/mL by the day of delivery.

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 women with HIV and is rarely indicated before scheduled cesarean section for prevention of HIV transmission.

Among 1,194 infants born to mothers with HIV, 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 women with HIV with an HIV RNA $\leq 1,000$ copies/mL for an indication other than decreasing HIV transmission, cesarean delivery should be scheduled based on ACOG guidelines for women without HIV.

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 women with HIV have increased rates of postoperative complications, mostly infectious, compared with women without HIV 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 women with HIV 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.^{23,24} Complication rates in most studies^{1,25-29} were within the range reported in populations of women without HIV 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 women with HIV compared to women without HIV.⁷ The rate of any complication associated with cesarean delivery was 117 per 1,000 deliveries among women with HIV compared with 67 per 1,000 deliveries among women without HIV. Therefore, women with HIV should be counseled regarding the specific risks associated with undergoing cesarean delivery in the setting of HIV infection.

In addition, caution should be exercised in proceeding with a cesarean delivery in circumstances where there is no clear evidence of benefit, especially in younger women who are likely to have additional pregnancies and perhaps multiple cesarean deliveries. Increased risk of abnormal placentation (e.g., placenta previa, placenta accrete, placenta increta, placenta percreta) and intrapartum hemorrhage are associated with increasing numbers of cesarean deliveries. These risks should be considered and discussed with the woman before proceeding with a cesarean delivery.^{30,31}

Managing Women Who Present in Early Labor or with Ruptured Membranes

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 women with HIV, most of whom were receiving no ARV drugs or only zidovudine, demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes.³² However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.³³ A prospective study of 707 women in Ireland showed that among the 493 women on ART with HIV RNA levels <1,000 copies/mL, 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.³⁴ A prospective review of 2,398 women with HIV 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.”^{35,36} 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 woman’s oral ARV drug regimen should be continued, and IV zidovudine initiated (if previously planned) regardless of the mode of delivery.

When membrane rupture occurs before 37 weeks’ gestation, decisions about timing of delivery should be based on best obstetrical practices, considering 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 women with HIV. When the decision is made to deliver, route of delivery should be according to obstetrical indications.

Operative Vaginal Delivery

In the past HIV was considered a relative contraindication to operative vaginal delivery with forceps or vacuum, but data from the era of ART had been lacking. Peters et al. reviewed 9,072 deliveries of women living with HIV in the UK between 2008 and 2016, where 80% of women had viral suppression from 2007 through 2011 and 90% from 2012 through 2014. Among the 3,023/3,663 vaginal deliveries with data as to whether forceps/vacuum were used, 249 (8.2%) involved operative delivery (5.6% forceps, 2.4% vacuum, 0.1% both, and 0.2% type not known). Among the 222 infants with known HIV status at 18 months of age, there was 1 case of HIV transmission with multiple possible causes and not enough evidence to confirm intrapartum transmission. The authors concluded that operative delivery is a safe option among women who are virally suppressed.³⁷

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Other Intrapartum Management Considerations (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Artificial rupture of membranes (ROM) performed in the setting of antiretroviral therapy (ART) 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**)
- 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 P450 (CYP) 3A4 enzyme inhibitor (e.g., a protease inhibitor, **cobicistat**), 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 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 from 2007 through 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 \geq 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 \geq 4 hours, compared with <4 hours (0.14% for \geq 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 women with HIV with viral suppression. **Women with detectable HIV viral loads should not undergo** artificial ROM unless there is a clear obstetric indication.

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 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 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} **and are mostly from the pre-ART era. A prospective, population-based surveillance study in the UK and Ireland reported 251 operative deliveries (forceps or vacuum) from January 2008 through March 2016; 1 infant delivered**

operatively is known to have acquired HIV, although there were other significant risk factors that may have contributed to this transmission.⁷ Although information on HIV-RNA levels was not included in this report, during this time period 80% to 90% of pregnant women living with HIV in the UK achieved viral suppression by the time of delivery.^{7,8} These procedures should be performed only if there are clear obstetric indications. There are no data in the ART era regarding risk of perinatal HIV transmission with episiotomy or with vaginal or perineal tears, specifically in the absence of maternal viremia; indications for episiotomy should be the same as they are for women without HIV (e.g., need for expedited vaginal delivery, need for operative vaginal delivery, shoulder dystocia). Delayed cord clamping has been associated with improved iron stores in both term and preterm infants as well as a lower incidence of necrotizing enterocolitis and intraventricular hemorrhage in preterm infants born to mothers without HIV infection. The American College of Obstetricians and Gynecologists now recommends this practice in vigorous term and preterm infants, with clamping delayed for at least 30 to 60 seconds after birth.⁹⁻¹¹ Even though HIV-specific data on the practice are lacking, there is no reason to modify it in mothers with HIV.

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 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.¹² 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 with PIs **and/or cobicistat have** been associated with exaggerated vasoconstrictive responses.¹³ When uterine atony results in excessive postpartum bleeding in women receiving PIs **or cobicistat**, methergine should be used only if alternative treatments such as prostaglandin F₂-alpha, misoprostol, or oxytocin are unavailable **or are contraindicated**. 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 Follow-Up of Women Living with HIV (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Antiretroviral therapy (ART) is currently recommended for all individuals living with HIV to reduce the risk of disease progression and to prevent the sexual transmission of HIV (AI).
- Plans for 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 (AIII).
- Because the immediate postpartum period poses unique challenges to antiretroviral (ARV) adherence, arrangements for new or continued supportive services should be made before hospital discharge (AII).
- Contraceptive counseling should start during the prenatal period; a contraceptive plan should be developed prior to hospital discharge (AIII).
- 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 (AII).
- Prior to hospital discharge, the woman should be given ARV medications for herself and her newborn to take at home (AIII).
- Infant feeding counseling, including a discussion of potential barriers to formula feeding, should begin in the prenatal period and this information should be reviewed after delivery (AIII).
- Breastfeeding is not recommended for women in the United States with confirmed or presumed HIV infection, because safe alternatives are available (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

The postpartum period provides an opportunity to review and optimize women's health care. Comprehensive medical care and supportive services are particularly important for women living with HIV 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 woman with HIV;
- 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 partner with HIV (i.e., Treatment as Prevention), and **potential** use of pre-exposure prophylaxis by the partner without HIV.

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.

Immediate linkage to care, comprehensive medical assessment, counseling, and follow-up are required for women who have a positive HIV test during labor or at delivery. Women who have an initially positive HIV

test should not breastfeed unless a confirmatory HIV test is negative (for detailed guidance on maternal HIV testing, please see the [Identification of Perinatal HIV Exposure](#) section). If HIV is confirmed, a full health assessment is warranted, including counseling related to newly diagnosed HIV infections, a discussion of the need for lifelong ART, an assessment of the need for opportunistic infection prophylaxis, and an evaluation for associated medical conditions. The newborn should receive appropriate testing and antiretroviral (ARV) drug management. Other children and partner(s) should be referred for HIV testing.

When care is not co-located or not within the same health care system, a case manager can facilitate care coordination. Women receiving case management are also more likely to be virologically suppressed and retained in care.¹ It is especially critical to ensure continuity of ART between the antepartum and postpartum periods, so prior to discharge the mother should receive a follow-up appointment with her HIV care provider and HIV medications for herself and her newborn. Special hospital programs may need to be established to support dispensing of ART to mothers before discharge.

Decisions about any changes to an ART regimen after delivery should be made in consultation between the woman and her HIV care provider, ideally prior to delivery.

ART is currently recommended for all individuals living with HIV to reduce the risk of disease progression and to prevent HIV sexual transmission.² 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/mm³, and the HPTN 052 randomized clinical trial demonstrated that early ART can reduce risk of sexual transmission to a discordant partner by 96%.³⁻⁵ It is important to counsel a woman that no single method (including treatment) is 100% protective against HIV transmission; however, with full, sustained HIV suppression, the possibility of sexual transmission is extremely low.

Understanding the need for lifelong ART is a priority for postpartum care, but does present several specific challenges. Studies have demonstrated significant decreases in ART adherence postpartum.⁶⁻¹⁰ 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 individuals living with HIV, but special attention is warranted during the postpartum period. A number of studies have suggested that postpartum depression is common among women with HIV.¹¹⁻¹⁹ The U.S Preventive Services Task Force recommends screening all women for postpartum depression²⁰ using a validated tool; this is especially important for women living with HIV who appear to be at increased risk for postpartum depression and for poorer ART adherence during the postpartum period. 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.^{1,21-24}

Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of ART.²⁵⁻²⁷ In women who achieve viral suppression by the time of delivery, postpartum simplification to once-daily coformulated regimens—which are often the preferred initial regimens for non-pregnant adults—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 reduction to standard doses can be initiated beginning immediately after delivery.

The postpartum period is a critical time for addressing safer sex practices in order to reduce sexual transmission of HIV to partners²⁸ and should begin to be addressed during the prenatal period. Counseling on prevention of secondary transmission to the partner without HIV should include condoms, ART for the partner with HIV to maintain viral suppression below the limit of detection, and the potential use of pre-exposure prophylaxis (PrEP) by the partner without HIV. With full, sustained HIV suppression in the woman—with or without reliable PrEP use by her partner without HIV—the possibility of transmission is extremely low (for additional information, see [Reproductive Options](#)).

It is important that comprehensive family planning and preconception care be integrated into routine prenatal, postpartum and all 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.²⁹ Long-acting reversible contraceptives (LARC), such as injectables, implants, and intrauterine devices (IUDs), should be inserted **prior to hospital discharge or during the health visit at 6 weeks postpartum**. If LARC is postponed to the postpartum visit, Depo-Provera is an option to be given as a bridge to avoid unplanned pregnancy in the interim, particularly if the postpartum appointment is missed. Interpregnancy intervals of less than 18 months have been associated with increased risk of poor perinatal and maternal outcomes in women without HIV infection.³⁰ 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.³¹

The potential for drug-drug interactions between a number of antiretroviral (ARV) drugs and hormonal contraceptives is discussed in [Preconception Counseling and Care for Women of Childbearing Age Living with HIV](#) 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.^{32,33} Findings from a systematic review of hormonal contraceptive methods and risk of HIV transmission to partners without HIV 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 methodological issues.³⁴ 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 women living with HIV in the United States, because maternal ART dramatically reduces but does not eliminate breastmilk transmission, and 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; **this may be particularly problematic for women from cultures where breastfeeding is important, as they may fear that formula feeding would reveal their HIV status**.^{35,36} It is therefore important to address these possible barriers to formula feeding during the antenatal period. Similarly, **women with HIV infection should be made aware of the** risks of HIV transmission via pre-mastication (prechewing **or prewarming**) of infant food.³⁷

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Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last Updated September 21, 2018; last reviewed November 14, 2017)

Panel's Recommendations

- All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV (AI).
- Newborn ARV regimens—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).
- The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission (AIII). The uses of ARV regimens in newborns include:
 - **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition
 - **Empiric HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later confirmed to have HIV but also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process or during breastfeeding and who do not acquire HIV
 - **HIV Therapy:** The administration of a three-drug combination ARV regimen at treatment dosages (antiretroviral therapy [ART]) to newborns with confirmed HIV infection (see [Diagnosis of HIV Infection](#)).
- For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week zidovudine ARV prophylaxis regimen can be used (BII).
- Newborns at higher risk of HIV acquisition should receive a combination ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk), including those born to women with HIV 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 have not achieved viral suppression near delivery (AII), or
 - Have primary or acute HIV infection during pregnancy (AII), or
 - Have primary or acute HIV infection during breastfeeding (AII).
- Newborns of women with unknown HIV status who test positive on expedited testing performed during labor or shortly after birth should initiate an ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk) (AII). If supplemental testing is negative, the ARV regimen can be discontinued (AII).
- For newborns with confirmed HIV, ART should be initiated (AI).
- In the United States, the use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data (BIII).
- Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care (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

General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

All newborns exposed to HIV should receive antiretroviral (ARV) drugs in the neonatal period to reduce perinatal transmission of HIV, with selection of the appropriate type of ARV regimen guided by the level of transmission risk. The most important contributors to the risk of HIV transmission to a newborn exposed to HIV are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. The risk of transmission is increased in the absence of maternal ART or if maternal

antepartum/intrapartum treatment was started after early pregnancy or was ineffective in producing virologic suppression; higher maternal viral load, especially in later pregnancy, correlates with higher risk of transmission. 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. Also, HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis since it primarily focused on protection against newborn HIV acquisition. More recently, clinicians have begun to identify newborns at highest risk for HIV acquisition and initiate combination ARV regimens as empiric treatment of HIV. In this guideline, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition. ARV prophylaxis includes administration of a single agent, usually zidovudine, as well as combinations of two or three ARV drugs.
- **Empiric HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later confirmed to have acquired HIV, but also serves as ARV prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns with confirmed HIV (see [Diagnosis of HIV Infection](#)). HIV therapy is lifelong.

It is noteworthy that, with the important exception of nevirapine, the neonatal ARV dosing for prophylaxis is the same as that for treatment for all ARV drugs currently recommended for newborns. The terms ARV prophylaxis and empiric HIV therapy describe the clinician's intent in prescribing ARV drugs. At this time, the only difference between ARV prophylaxis containing three ARV drugs and empiric HIV therapy would be the dosage of nevirapine. As newer agents are available for use in newborns, additional differences will emerge. The interval during which newborn ARV prophylaxis or empiric HIV therapy can be initiated and still be of benefit is undefined; however, most studies support providing prophylaxis as early as possible after delivery.¹⁻⁶

Table 7 provides an overview of neonatal ARV management according to risk of perinatal HIV in the newborn. Data supporting these recommendations are presented later in this section. Table 8 summarizes the dosing recommendations for ARV dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks gestational age), can be found in [Pediatric Antiretroviral Drug Information](#). In addition, the [National Perinatal HIV Hotline](#) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Table 7. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (888-448-8765).

Category	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence	4 weeks of ZDV
Higher Risk of Perinatal HIV Transmission^{a,b}	<ul style="list-style-type: none"> • Mothers who received neither antepartum nor intrapartum ARV drugs • Mothers who received only intrapartum ARV drugs • Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal • Mothers with acute or primary HIV infection during pregnancy or breastfeeding^c 	Combination ARV prophylaxis with 6 weeks ZDV and 3 doses of NVP (prophylaxis dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) or Empiric HIV therapy consisting of ZDV, 3TC, and NVP (treatment dosage) ^d
Presumed Newborn HIV Exposure	Mothers with unknown HIV status who test positive at delivery or postpartum or whose newborns have a positive HIV antibody test	ARV management as above (for higher risk of perinatal HIV transmission). ARV management should be discontinued immediately if supplemental testing confirms that mother does not have HIV.
Newborn with Confirmed HIV^e	Confirmed positive newborn HIV virologic test/NAT	3 drug combination ARV regimen at treatment dosage

^a See text for evidence supporting combination ARV prophylaxis and empiric HIV therapy.

^b See the [Intrapartum Care](#) section for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with elevated viral load at delivery.

^c Most experts would opt to administer empiric HIV therapy to infants with acute HIV during pregnancy because of the high risk for *in utero* infection. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.

^d The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue NVP and/or 3TC after the return of negative newborn testing. ZDV should be continued for 6 weeks.

^e Most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See [Table 8](#) for dosing specifics.

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; ZDV = zidovudine

Table 8. Newborn Antiretroviral Dosing Recommendations

Drug	Dosing								
<p>ZDV Treatment and Prophylaxis Dosage</p> <p>Note: For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</p>	<p><u>≥35 Weeks' Gestation at Birth</u> <i>Birth to Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> • 4 mg/kg/dose orally twice daily <p>Simplified Weight-Band Dosing for Newborns ≥35 Weeks:</p> <table border="1" data-bbox="597 369 1239 575"> <thead> <tr> <th data-bbox="597 369 862 474">Weight Band (kg)</th> <th data-bbox="862 369 1239 474">*Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th> </tr> </thead> <tbody> <tr> <td data-bbox="597 474 862 510">2 to <3 kg</td> <td data-bbox="862 474 1239 510">1 mL</td> </tr> <tr> <td data-bbox="597 510 862 546">3 to <4 kg</td> <td data-bbox="862 510 1239 546">1.5 mL</td> </tr> <tr> <td data-bbox="597 546 862 575">4 to <5 kg</td> <td data-bbox="862 546 1239 575">2 mL</td> </tr> </tbody> </table> <p><u>≥30 to <35 Weeks' Gestation at Birth</u> <i>Birth–Age 2 Weeks:</i></p> <ul style="list-style-type: none"> • 2 mg/kg/dose orally twice daily <p><i>Age 2 Weeks to 4–6 Weeks:</i></p> <ul style="list-style-type: none"> • 3 mg/kg/dose orally twice daily <p><u><30 Weeks' Gestation at Birth</u> <i>Birth–Age 4 Weeks:</i></p> <ul style="list-style-type: none"> • 2 mg/kg/dose orally twice daily <p><i>Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> • 3 mg/kg/dose orally twice daily 	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
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								
<p>3TC Treatment and Prophylaxis Dosage</p>	<p><u>≥32 Weeks' Gestation at Birth</u> <i>Birth–Age 4 Weeks:</i></p> <ul style="list-style-type: none"> • 2 mg/kg/dose orally twice daily <p><i>Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> • 4 mg/kg/dose orally twice daily 								
<p>NVP Prophylaxis Dosage</p>	<p><u>≥32 Weeks Gestation at Birth:</u></p> <p>3 doses given (1) within 48 hours of birth, (2) 48 hours after the 1st dose, and (3) 96 hours after the 2nd dose</p> <p><u>Birth Weight 1.5–2 kg:</u></p> <ul style="list-style-type: none"> • 8-mg dose orally • Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose. <p><u>Birth Weight >2 kg:</u></p> <ul style="list-style-type: none"> • 12-mg dose orally • Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose. 								
<p>NVP Treatment Dosage</p>	<p><u>≥37 Weeks' Gestation at Birth</u> <i>Birth–Age 6 Weeks:</i></p> <ul style="list-style-type: none"> • 6 mg/kg/dose orally twice daily <p><u>34 to <37 Weeks' Gestation at Birth</u> <i>Birth–Age 1 Week:</i></p> <ul style="list-style-type: none"> • 4 mg/kg/dose orally twice daily <p><i>Age 1–6 Weeks:</i></p> <ul style="list-style-type: none"> • 6 mg/kg/dose orally twice daily 								

Key to Acronyms: 3TC=lamivudine; IV= intravenous; NVP = nevirapine; ZDV = zidovudine

Recommendations for Antiretrovirals in Specific Clinical Situations

In the following sections and Table 7, we present available data and recommendations for management of **newborns with confirmed HIV** and newborns born to mothers who:

- Received antepartum/intrapartum ARV drugs with effective viral suppression
- Are at higher risk of transmitting HIV to their newborn, 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 near delivery, particularly if delivery was vaginal
- Have acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression

The risk of HIV acquisition in newborns born to women who received standard ARV treatment regimens during pregnancy and labor and had undetectable viral loads at delivery is <1%. Zidovudine alone was shown in the PACTG 076 study to effectively reduce perinatal HIV transmission and is recommended as prophylaxis for **neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy**. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week newborn zidovudine regimen was studied in PACTG 076. However, in the United Kingdom and many other European countries, where a 4-week neonatal zidovudine prophylaxis regimen has been recommended for newborns born to mothers who have received ART regimens during pregnancy and have viral suppression, there has been 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 newborns compared with the 6-week zidovudine regimen.⁹

Therefore, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends a 4-week neonatal zidovudine prophylaxis regimen for newborns 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) near delivery and there are no concerns related to maternal adherence. Dosing recommendations for zidovudine are available for premature newborns and an intravenous preparation is available. [Table 8](#) shows recommended neonatal zidovudine dosing based on gestational age and birthweight.

Newborns Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Intrapartum Antiretroviral Drugs Only, Who Have Received Combination Antiretroviral Drugs and Do Not Have Viral Suppression Near Delivery, or **Who Have Acquired HIV During Pregnancy or Breastfeeding**

All newborns born to mothers with detectable viral load at the time of delivery, who received only intrapartum ARV drugs, or who have received no ARV drugs during pregnancy or delivery, are at higher risk of HIV acquisition and should receive combination ARV prophylaxis **or empiric HIV therapy**.^{5,10-14} **The experience with combination ARV prophylaxis and empiric HIV therapy is described below. At this time, the optimal duration of combination ARV regimens or empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of negative newborn testing but continue**

zidovudine for 6 weeks.

For those women who received ARV drugs during pregnancy, but have a detectable viral load near delivery, the level of viremia in the mother that would trigger the use of combination newborn 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 to 399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.^{15,16} However, there has been no study to demonstrate relative efficacy of combination **ARV regimens, including prophylaxis regimens and empiric HIV therapy**, compared to standard newborn prophylaxis at these different thresholds of maternal viremia. While some experts would recommend a combination ARV regimen or empiric HIV therapy with any level of detectable viremia, others reserve combination regimens and empiric HIV therapy until higher levels of maternal viral load are documented. The decision to administer a combination prophylaxis regimen or empiric therapy should be made following discussion with the parents weighing the risks and benefits of **the proposed regimen**.

Primary or acute HIV infection during pregnancy is associated with an increased risk of perinatal transmission of HIV. Combination ARV prophylaxis or empiric HIV therapy should be administered to the infant until HIV can be confirmed or ruled out. (see [Acute HIV Infection](#)).

In summary, in these scenarios where the infant is at higher risk of HIV transmission, the Panel recommends either combination ARV prophylaxis or empiric HIV therapy. The data supporting the use of combination ARV prophylaxis regimens and empiric HIV therapy are summarized below. Choosing between combination ARV prophylaxis and empiric HIV treatment will depend on the clinician assessment of the likelihood of HIV transmission.

Combination Antiretroviral Prophylaxis

There is a paucity of data from randomized clinical trials to guide the optimal selection of a newborn combination prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of combination prophylaxis in newborns at high risk of HIV acquisition. In this study, 1,746 formula-fed newborns born to women with HIV who did not receive any ARV drugs during pregnancy were randomized to 1 of 3 newborn 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 **The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in 3/53 (5.7%) participants with *in utero* infection who were treated with zidovudine alone and in 6/33 (18.2%) participants treated with zidovudine plus nevirapine ($P > 0.05$). In addition, the third drug in the three-arm regimen was nelfinavir, which has highly variable kinetics in this age group and did not reach the kinetic target in 46% of study participants.**¹⁷ Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or zidovudine-alone regimen (27.5% vs. 15%, $P < 0.0001$).

Data from Europe and the United States indicate increasing use of combination ARV prophylaxis in newborns exposed to HIV. In the United Kingdom and Ireland, use increased from 9% of newborns exposed to HIV 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 newborns.¹⁸⁻²⁰ However, interpretation of these observational studies is complicated by the definition of combination ARV prophylaxis, **use of prophylaxis versus treatment dosing of nevirapine**, and combining heterogeneous combination ARV prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many studies include single-dose nevirapine in combination with another ARV, usually zidovudine, as combination therapy. Most do not report whether nevirapine was

administered at the recommended prophylaxis dose or at a higher dose as part of empiric HIV therapy. So, despite increasing utilization of various combination ARV prophylaxis regimens, comprehensive data on efficacy and safety are lacking. Therefore, based on the NICHD-HPTN 040/PACTG 1043 trial, the 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine is the combination ARV prophylaxis regimen recommended by the Panel for newborns at higher risk of HIV acquisition (Tables 7 and 8).

Empiric HIV Therapy

A three-drug ARV regimen including zidovudine, lamivudine, and the treatment dose of nevirapine (empiric HIV therapy) is the other option recommended by the Panel for newborns at high risk of HIV acquisition.

Enthusiasm for this approach followed a case of a “functional cure” of HIV in a newborn reported in 2013.²¹ The newborn was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and was diagnosed as having HIV by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. At age 30 hours, the newborn initiated a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher treatment dose rather than standard prophylactic dosing). The newborn 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 newborn was continued on treatment for HIV, thought to be acquired *in utero*. At age 18 months, the mother discontinued ART; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for over 2 years without ART. 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 a newborn treated since birth has subsequently been reported.²²

Further support of empiric HIV therapy comes from Canadian investigators who have reported outcomes in 136 newborns considered at high risk of HIV acquisition (i.e., born to women with HIV who had detectable viral load and/or poor adherence to therapy prior to delivery) who received a triple-ARV regimen within 72 hours of birth. Of these 136 newborns, 12 (9%) were found to have acquired HIV and no major toxicities were identified.²³ However, there was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug regimens. Another Canadian study compared the safety of empiric HIV therapy in 148 newborns with high-risk exposure (i.e., 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 newborns who received only zidovudine. Thirteen newborns in the empiric HIV therapy group acquired HIV, including 5 with a positive HIV nucleic acid test (NAT) within the first 48 hours of life, suggesting *in utero* infection. No newborn in the low-risk zidovudine-only group acquired HIV. The newborns receiving empiric HIV therapy 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 newborns receiving zidovudine only (10.2% vs. 0%, $P < 0.001$). ARV drugs were also more likely to be discontinued prematurely in the newborns receiving empiric HIV therapy (9.5% vs. 2.1%, $P = 0.01$).²⁴

Empiric HIV therapy in newborns is consistent with the Centers 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 newborns at high risk of HIV acquisition.^{25,26} However, there are two key safety issues related to the choice and dose of ARV drugs in these newborns. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels at least 10-fold lower than targeted therapeutic levels. The optimal dose for empiric HIV therapy in newborns has not been sufficiently studied but studies are ongoing. 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 empiric HIV therapy in terms of newborn toxicity (particularly in preterm newborns) and efficacy require further study before a general recommendation can be made.

There are three ongoing clinical trials investigating newborn empiric HIV therapy containing nevirapine at

treatment doses, zidovudine, and lamivudine shortly after birth in newborns at high risk of HIV infection (international multisite IMPAACT P1115, ClinicalTrials.gov identifier NCT02140255), or those known to have HIV (BHP-074 in Botswana, NCT02369406, and the Leopard Study in South Africa, NCT02431975). Additional safety and pharmacokinetic (PK) data from these studies will guide future recommendations.

At this time, if an empiric HIV therapy regimen is selected, the Panel recommends a combination of zidovudine, lamivudine, and nevirapine (treatment dosage) (see Tables 7 and 8). The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of a negative newborn testing. Zidovudine should be continued for 6 weeks.

Newborns Born to Mothers with Unknown HIV Status at Presentation in Labor

Expedited HIV testing of mothers is recommended during labor for women with unknown HIV status and for mothers and/or newborns as soon as possible after birth if expedited HIV testing was not performed during labor (see Identification of Perinatal Exposure). Expedited test results should be available within 60 minutes. If expedited testing is positive, newborn combination ARV prophylaxis or empiric HIV therapy should be initiated immediately, without waiting for the results of supplemental tests as described below. 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 newborns should be presumed to indicate maternal HIV until standard supplemental testing clarifies maternal and newborn status. If appropriate test results on a mother (or newborn) are negative, newborn ARV drugs can be discontinued. 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 is confirmed or ruled out in a woman who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.²⁷

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns delivered by women with ARV drug-resistant virus is unknown. It is also unknown whether resistant virus in the mother increases the risk of HIV acquisition by the infant. The ARV regimen for newborns 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). 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.

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.^{28,29} Thus, the selection of the newborn ARV regimen should be based on other risk factors (Table 7).

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.²⁹ However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.³⁰⁻³⁴

Newborns with Confirmed HIV

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT testing results meant that neonatal infections were generally not diagnosed in the first weeks of life. HIV NAT test results now often are available within a few days and newborns with HIV are being diagnosed as early as the first days of life. A positive HIV NAT

test must be repeated to confirm HIV. However, most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing. However, evidence that very early treatment (before age 2 weeks) will produce a prolonged remission or lead to better outcomes in newborns with HIV is lacking. Earlier diagnosis of HIV in newborns and the increasing use of empiric HIV therapy in newborns at high risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same with the important exception of nevirapine (see [Pediatric Antiretroviral Drug Information](#)).

Sufficient data exist to provide dosing recommendations appropriate for the treatment of HIV in neonates using the following medications (see [Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection](#)):

- From birth in term and preterm newborns: [zidovudine](#), [lamivudine](#), [nevirapine](#)
- From birth in term neonates: [emtricitabine](#), [raltegravir](#)
- From age 2 weeks in term neonates: [lopinavir/ritonavir](#)

Dosing recommendations for *premature* newborns are available for only zidovudine, [lamivudine](#), and nevirapine. Neonatal dosing advice, including for premature newborns, is summarized in [Table 8](#). For more detailed information about neonatal dosing recommendations and considerations of these drugs, please see the [Pediatric Antiretroviral Drug Information](#) for these drugs.

Newborns of Mothers Diagnosed with HIV while Breastfeeding

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding is not recommended for women with confirmed HIV in the United States, including those receiving ART (see [Newborn Feeding Practices and Risk of HIV Transmission](#)).³⁵

The risk of HIV acquisition associated with breastfeeding depends on multiple newborn and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.³⁶ Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than are those whose mothers have chronic HIV infection³⁷ because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.³⁸

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a mother with HIV (often because the mother just learned of her own HIV diagnosis) have yet to be defined. Some experts would consider the use of post-exposure prophylaxis in newborns 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.³⁹

Several studies of newborns breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn nevirapine, lamivudine, lopinavir/ritonavir or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.⁴⁰⁻⁴⁴ No trials have evaluated the use of combination regimens for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection.

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 empiric HIV therapy until infant status

can be determined. If the infant's initial HIV NAT is negative, the optimal duration of empiric HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.³⁹ As in other situations, decisions regarding ARV management should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach. The [National Perinatal HIV Hotline](#) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Newborns should be tested for HIV prior to initiation of empiric HIV therapy and 4 to 6 weeks, 3 months, and 6 months after recognition of maternal HIV and cessation of breastfeeding to determine HIV status. (see Diagnosis section). If a newborn is already receiving an ARV prophylaxis regimen other than empiric HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV initiated. Resistance testing should be performed, and the ART regimen modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

Short-Term Antiretroviral Drug Safety

Newborn 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 newborns of exposure to multiple ARV drugs.

Other than zidovudine, lamivudine is the NRTI with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1^{3,45,46} or 2 weeks.⁵ Six weeks of newborn zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the newborns also had *in utero* exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in newborns exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and newborn zidovudine. Anemia was reported in 15% and neutropenia in 18% of newborns exposed to zidovudine/lamivudine, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.⁴⁷ Similarly, in a Brazilian study of maternal antepartum and 6-week newborn zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of newborns.⁴⁸

Experience with other NRTI drugs for neonatal prophylaxis is more limited.^{49,50} Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.^{47,51-54}

In rare cases, chronic multiple-dose nevirapine prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.⁵⁵ These toxicities have not been observed in newborns 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 newborns receiving nevirapine prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.^{5,40-42,44,56}

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 newborns. Four premature newborns (2 sets of twins) started on lopinavir/ritonavir from birth, developed heart block that resolved after drug discontinuation.^{57,58} 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 newborns who were also exposed to lopinavir/ritonavir *in utero* compared with those exposed only in the neonatal period. Term newborns were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.⁵⁹ 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,⁶⁰ predominantly in preterm neonates, the U.S. 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.⁶¹ However, a recent study (ANRS 12174) randomized 1,273 newborns, 615 assigned to lopinavir/ritonavir and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life and only newborns 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 newborns, 7 days of age and older.⁶² At this time, the Panel does not recommend the use of lopinavir/ritonavir before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

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Diagnosis of HIV Infection in Infants and Children (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendations

- Virologic assays (i.e., HIV RNA and HIV DNA nucleic acid tests [NAT]) that directly detect HIV must be used to diagnose HIV in infants and children younger than 18 months with perinatal **and postnatal** HIV exposure; HIV antibody tests should not be used **(AII)**.
- **RNA or DNA polymerase chain reaction (PCR) testing are recommended equally for most patients; RNA PCR is recommended for known maternal non-subtype B virus (AII).**
- Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:
 - 14 to 21 days **(AII)**
 - 1 to 2 months **(AII)**
 - 4 to 6 months **(AII)**
- Additional virologic diagnostic testing at birth should be considered for infants at higher risk of perinatal HIV transmission **(AIII)** and at 2 to 4 weeks after cessation of antiretroviral prophylaxis **(BIII)**.
- A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
- Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with 1 obtained at age ≥ 1 month and 1 at age ≥ 4 months, or 2 negative HIV antibody tests from separate specimens obtained at age ≥ 6 months **(AII)**.
- Some experts confirm the absence of HIV at 12 to 18 months of age in children with prior negative virologic tests by performing an HIV antibody test to document loss of maternal HIV antibodies **(BIII)**.
- Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV in children in this age group who are HIV antibody-positive should be based on an HIV NAT **(AII)**.
- Diagnostic testing in children with non-perinatal exposure only or children with perinatal exposure aged >24 months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV NAT may be necessary to diagnose HIV **(AII)**.

Note: The National Clinical Consultation Center provides consultations on issues related to the management of perinatal HIV infection (1-888-448-8765; 24 hours a day, 7 days a week).

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

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

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

HIV can be definitively diagnosed through use of virologic assays in most non-breastfed infants with HIV exposure by age 1 to 2 months and in virtually all infants with HIV infection by age 4 to 6 months. Antibody tests, including the newer **antigen-antibody combination immunoassays (sometimes referred to as fourth- and fifth-generation tests)**, do not establish the presence of HIV in infants because of transplacental transfer of maternal antibodies to HIV; therefore, a virologic test must be used.^{1,2} Positive virologic tests (i.e., nucleic acid tests [NAT]—a class of tests that includes HIV RNA and DNA polymerase chain reaction [PCR] assays, and related RNA qualitative or quantitative assays) indicate likely HIV infection. The first test result should be confirmed as soon as possible by a repeat virologic test on a second specimen, because false-positive results can occur with both RNA and DNA assays.³ **For additional information on HIV and RNA assays and diagnosis of Group M non-subtype B and Group O HIV-1 infections and HIV-2 infections, see the [Virologic Assays to Diagnose HIV Infection in Infants Younger Than 18 Months With Perinatal HIV-1 Exposure](#)**

section and [Other Issues](#) section below.

Antigen/antibody combination immunoassays which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are not recommended for infant diagnosis. The sensitivity of the antigen component in the first months of life is less than that of an HIV NAT, and antibody tests should not be used for diagnosis **in infants and children <18 months of age**.⁴⁻⁶ Children with perinatal HIV exposure aged 18 to 24 months occasionally have residual maternal HIV antibodies; definitive confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on a NAT (see [Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations](#)). Diagnosis in children aged >24 months relies primarily on HIV antibody and antigen/antibody tests (see [Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months](#)).¹

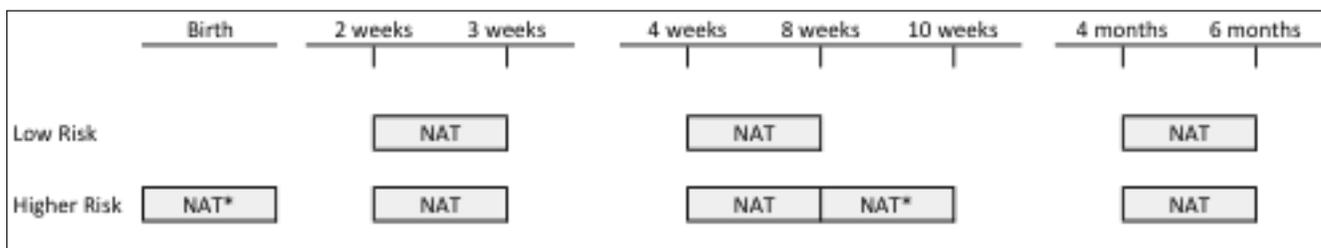
Infants who are found to have positive HIV antibody tests but whose mothers' HIV status is unknown (see [Identification of Perinatal HIV Exposure](#)) should be assumed to be exposed to HIV and undergo HIV diagnostic testing as described below.⁷

For antiretroviral (ARV) management of HIV-exposed newborns and newborns with HIV, see the [Antiretroviral Management of Newborns with Perinatal HIV Exposure](#).^{8,9}

Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

Confirmation of HIV infection is based on two positive virologic tests from separate blood samples in infants and children younger than 18 months. Figure 1 summarizes the timing of **recommended virologic** diagnostic testing **for infants at low risk of transmission (based on maternal antiretroviral therapy [ART] and viral suppression)** with additional time points to be considered for infants at higher risk and those on combination ARV prophylaxis regimens.

Figure 1. Recommended Virologic Testing Schedules for Infants Exposed to HIV by Perinatal HIV Transmission Risk



Low Risk: Infants born to mothers who 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 no concerns related to maternal adherence.

Higher Risk: Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, **mothers who initiated ART late in pregnancy (late second or third trimester)**, were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.

* For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of life).

NAT= nucleic acid test

HIV infection can be **presumptively** excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥ 14 days and one at age ≥ 4 weeks) or one negative virologic test (i.e., negative NAT [RNA

or DNA]) at age ≥ 8 weeks, or one negative HIV antibody test at age ≥ 6 months.^{1,7}

Definitive exclusion of HIV infection in a non-breastfed infant is based on two or more negative virologic tests (i.e., negative NATs [RNA or DNA]), one at age ≥ 1 month and one at age ≥ 4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥ 6 months.

For both **presumptive** and **definitive** exclusion of HIV infection, a child must have no other laboratory (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and not be breastfeeding. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody-negative status.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at age 4 to 6 weeks until they are determined to be without HIV or **presumptively** without HIV.¹⁰ Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see the [Pediatric Opportunistic Infections Guidelines](#) and [Initial Postnatal Management of the Neonate Exposed to HIV](#) section).

Virologic Testing at Birth for Newborns at Higher Risk of Perinatal HIV Transmission

Virologic testing at birth should be considered **for newborns at higher risk of perinatal HIV transmission**,¹¹⁻¹⁶ such as infants born to mothers living with HIV who:

- Did not receive prenatal care
- Did not receive antepartum or intrapartum ARV drugs
- Received intrapartum ARV drugs only
- **Initiated ART late in pregnancy (late second or third trimester)**
- Were diagnosed with acute HIV infection during pregnancy
- Had detectable HIV viral load close to the time of delivery
- Received combination ARV drugs and did not have sustained viral suppression

Testing infants exposed to HIV close to the time of birth identifies 20% to 58% of infants with HIV infection; however, in one study that specifically evaluated infants born to mothers who had not received ARV drugs during pregnancy and hence were at higher risk of *in utero* infection, birth testing identified 66.4% of infants with HIV infection.¹⁷ Prompt diagnosis of infant HIV infection is critical to allow for discontinuing ARV prophylaxis and instituting early ART (see [When to Initiate Therapy](#)). Blood samples from the umbilical cord should not be used for diagnostic evaluations because of the potential for contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection *in utero* from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection.^{11,12,18}

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,⁷ and early identification of infection would permit discontinuation of neonatal ARV prophylaxis and initiation of ART (see [Infants Younger than Age 12 Months](#) and [Table 5](#) in [When to Initiate Therapy](#)).

Virologic Testing at Age 1 to 2 Months

Testing performed at age **1 to 2 months** is intended to maximize the detection of infants with HIV infection.^{19,20} Two studies found that although the sensitivity during prophylaxis was not associated with the type of

maternal or neonatal ARV prophylaxis, the sensitivity of diagnostic HIV testing during the period of infant ARV prophylaxis was lower compared to the sensitivity during the subsequent testing interval at 3 months of age. Overall, in both studies, 89% of infants with HIV infection were identified by 4 to 6 weeks of age. Of those infants who had negative testing in the first 7 days of life, repeat testing at 4 weeks to 6 weeks of age during the period of neonatal ARV prophylaxis identified 76% of infants with HIV infection in one study,¹⁹ and 68% of infants with HIV infection in the second study.¹⁷ In both studies, infants with negative testing in the first 7 days of life were diagnosed when the next diagnostic test was performed at 3 months of age.

For infants at **higher risk of perinatal HIV transmission**, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission suggests an additional virologic test 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of age) given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis, may reduce the sensitivity of testing during prophylaxis.^{7,17,19} In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt recognition of infants with HIV, with an additional test at 8 weeks of life (2 weeks after cessation of prophylaxis at 6 weeks of life) to capture additional cases. For infants at low risk of transmission, a single test obtained at 1 to 2 months of age may be timed to occur 2 to 4 weeks after cessation of ARV prophylaxis.

An infant with two negative virologic tests (one at age ≥ 14 days and the other at age ≥ 4 weeks) or one negative test at age ≥ 8 weeks can be viewed as **presumptively** without HIV, assuming the child has not had a positive virologic test, CD4 immunosuppression, or clinical evidence of HIV infection.

Virologic Testing at Age 4 to 6 Months

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

Antibody Testing at Age 6 Months and Older

Two or more negative HIV antibody tests performed in non-breastfed infants at age ≥ 6 months can also be used to **definitively** exclude HIV infection in children with no clinical or virologic laboratory-documented evidence of HIV infection.^{21,22}

Antibody Testing at Age 12 to 18 Months to Document Seroreversion

Some experts confirm the absence of HIV infection in infants and children with negative virologic tests (when there has not been prior confirmation of two negative antibody tests) by repeat serologic testing between 12 and 18 months of age to confirm that maternal HIV antibodies transferred *in utero* have disappeared.¹ In a recent study, the median age at seroreversion was 13.9 months.²³ Although the majority of infants who are without HIV will serorevert by age 15 to 18 months, there are reports of late seroreversion after 18 months (see below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.²³⁻²⁶

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion (≤ 24 Months of Age)

Non-breastfed children with HIV exposure with no other HIV transmission risk and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies up to age 24 months (these children are called late seroreverters).²³⁻²⁶ In one study, 14% of children with HIV exposure who were uninfected seroreverted after age 18 months.²³ These children may have positive immunoassay results but indeterminate supplemental antibody tests (using Western blot or IFA). In such cases, repeat antibody testing at a later time would document seroreversion. Due to the possibility of residual HIV antibodies, virologic testing (i.e., with a NAT) is necessary to definitively exclude or confirm HIV in children with perinatal HIV exposure **who**

have a positive HIV antibody (or antigen/antibody) test at age 18 to 24 months.

Postnatal HIV Infection in Children with Perinatal HIV Exposure with Prior Negative Virologic Tests for Whom There Are Additional HIV Transmission Risks

In contrast to late seroreverters, in rare situations postnatal HIV infections have been reported in children with HIV exposure who had prior negative HIV virologic tests. This occurs in children who contract HIV through an additional risk after completion of testing (see [Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months](#)). If an HIV antibody test is positive at age 18 to 24 months, repeated virologic testing will distinguish residual antibodies in late-seroreverting (uninfected) children from children with antibodies due to true infection.

Suspicion of HIV-2 or Non-Subtype B HIV-1 Infections with False-Negative Virologic Test Results

Children with non-subtype B HIV-1 and children with HIV-2 may have false-negative virologic tests but persistent positive immunoassay results and indeterminate HIV-1 Western blot results.²⁷⁻²⁹ The diagnostic approach in these situations is discussed below in the sections on Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and on Virologic Assays to Diagnose HIV-2 Infections.

Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months

Breastfeeding

Breastfeeding is a known route of postnatal HIV transmission. Typical scenarios in the United States include women who have not been adequately counseled about infant feeding, women who breastfeed despite being counseled not to (e.g., women from communities where breastfeeding is the norm and women who fear that not breastfeeding would be stigmatizing, including those where avoidance of breastfeeding raise suspicions about maternal HIV infection), and women who learn of their HIV diagnosis only after initiating breastfeeding (e.g., women who were HIV negative during pregnancy but who acquire HIV infection postnatally; breastfeeding during acute HIV infection is associated with an increased risk of perinatal HIV transmission).³⁰⁻³³ Breast milk from a donor with unrecognized HIV infection at the time of donation is an additional risk factor. Infants who are breastfed by women living with HIV should undergo immediate HIV diagnostic testing, and counseling to discontinue breastfeeding should be provided. Follow-up, age-appropriate testing should be performed at 4 to 6 weeks, 3 months, and 6 months after breastfeeding cessation if the initial tests are negative. Diagnostic testing may be influenced by factors that include the transplacental transfer of maternal antibody resulting in residual antibody in children aged up to 24 months (women who acquired HIV infection before delivery), as well as the possibility of performing the test during acute HIV infection; thus, a NAT would be the choice for initial testing. The receipt of postnatal ARV prophylaxis may delay the detection of HIV infection (see [Antiretroviral Management of Newborns with Perinatal HIV Exposure](#)).³⁴⁻³⁶

Premastication

Receipt of solid food premasticated, prechewed, or prewarmed by a caregiver living with HIV has been documented to be associated with risk of HIV transmission.³⁷⁻⁴² If this occurs in children with perinatal HIV exposure aged 24 months or younger with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing, as they may have residual maternal HIV antibodies (see [Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations](#)).

Additional Routes of HIV Transmission

Additional routes of HIV transmission in children include sexual abuse or receipt of contaminated blood

products. In such cases, maternal HIV status may be negative. If the maternal HIV status is unknown, age-appropriate testing should be performed as described for children with perinatal HIV exposure.

Acquisition of HIV is possible through accidental needlestick injuries, sexual transmission, or injection drug use in older children. Medical procedures performed in settings with inadequate infection control practices may pose a potential risk; although tattooing or body piercing presents a potential risk of HIV transmission, no cases of HIV transmission from these activities have been documented.⁴³

Diagnostic Testing

Diagnosis of HIV-1 in infants and children with non-perinatal HIV exposure only or children with perinatal HIV exposure aged >24 months relies primarily on HIV antibody and antigen/antibody tests.^{1,44} Food and Drug Administration (FDA)-approved diagnostic tests include:

- Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen (fourth and fifth generation tests [the fifth generation test differentiates between HIV-1 and HIV-2 antibodies as well as HIV-1 p24 antigen]): Recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection (p24 antigen from HIV-1 non-B, non-M and HIV-2 strains may not be detected).⁴⁵
- HIV-1/2 immunoassays (third-generation antibody tests): Alternative for initial testing.
- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies: Recommended for supplemental testing.
- HIV-1 NAT may be necessary as an additional test to diagnose acute HIV infection.
- HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests): Alternative for supplemental testing but will not detect acute HIV infection.

Diagnosis of HIV-2 in children with non-perinatal exposure or children with perinatal exposure aged >24 months relies on the Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories (APHL) 2014 laboratory testing guidelines, which recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies for supplemental testing. This is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test; more than 60% of individuals with HIV-2 are misclassified as having HIV-1 by the HIV-1 Western blot.^{1,46} All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department; additional HIV-2 DNA PCR testing can be arranged by their public health laboratory or the CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is not conclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis (this assay is not commercially available).^{47,48}

Virologic Assays to Diagnose HIV in Infants Younger than 18 Months with Perinatal HIV-1 Exposure

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in plasma. Their specificity has been shown to be 100% at birth and at 1, 3, and 6 months of age and is comparable to HIV DNA PCR.¹⁹ HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before being interpreted as documentation of HIV infection in an infant.^{49,50} Testing at birth will detect infants who acquire HIV *in utero* and not those who contract HIV from exposure during or immediately prior to delivery (i.e., in the intrapartum period). Studies have shown that HIV RNA assays identify 25% to 58% of infants with HIV infection from birth through the first week of life, 89% at age 1 month, and 90% to 100% by age 2 to 3 months (similar to results of HIV DNA PCR for early diagnosis of HIV).^{3,7,19,51}

HIV RNA undergoes reverse transcription to double-stranded DNA, which persists intracellularly within an infected cell. HIV DNA PCR assays detect intracellular DNA, and usually remain positive in individuals receiving ARV treatment. In contrast, HIV RNA assays are affected by maternal antenatal treatment or infant combination ARV prophylaxis.⁵² In one study, the sensitivity of HIV RNA assays were not associated with the type of maternal or infant ARV prophylaxis, but HIV RNA levels at 1 month were significantly lower in infants with HIV infection receiving multidrug prophylaxis (n = 9) compared to levels among infants receiving single-drug zidovudine prophylaxis (n = 47) (median HIV RNA 2.5 log copies/mL vs. 5.4 log copies/mL, respectively). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log copies/mL) by age 3 months in both groups after stopping prophylaxis.¹⁹ Further studies are necessary to evaluate the sensitivity and predictive value of HIV RNA assays during and after receipt of infant ARV prophylaxis.

An HIV quantitative RNA assay can be used as a supplemental test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. This viral load can also be used to determine HIV genotype and guide initial ARV treatment in an infant with HIV. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting non-subtype B HIV (see [Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections](#)).

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing. It is the only qualitative RNA test that is FDA-approved.^{18,53-56}

HIV DNA PCR And Related Assays

HIV DNA PCR is a sensitive technique used to detect intracellular HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at ages 1, 3, and 6 months. Studies have shown that HIV DNA PCR assays identify 20% to 55% of infants with HIV infection from birth through the first week of life, with the same caveat as for RNA testing that testing at birth will detect infants who contracted HIV *in utero* and not those who contracted HIV during the intrapartum period, but the percentage increases to more than 90% by 2 to 4 weeks of age and to 100% at ages 3 months and 6 months.^{7,18,19,51}

Two studies provided data on diagnostic testing at different time points in infants with confirmed HIV infection including those who had negative testing at birth (i.e., infants considered to have acquired HIV during the intrapartum period). A randomized, international study of 1,684 infants evaluated the efficacy of three different regimens of neonatal prophylaxis containing 6 weeks of zidovudine either alone or with two or three other ARV drugs; none of their mothers had received prenatal ARV drugs. Infant testing was performed at birth, 10 to 14 days, 4 to 6 weeks, and 3 and 6 months (no testing was performed between 6 weeks and 3 months). Ninety-three (66.4%) of 140 infants with HIV infection were identified at birth, and by 4 to 6 weeks of age, 89% of the 140 infants were identified. Of the 47 infants with HIV infection who had negative DNA PCR tests at birth, 68% were identified during the period of neonatal ARV prophylaxis at 4 to 6 weeks; by 3 months, all 47 infants were identified.¹⁷ More recent data from Thailand showed that, in non-breastfed infants, receiving an ARV prophylaxis regimen of zidovudine/lamivudine/nevirapine for 6 weeks was associated with a delay in first HIV DNA detection. In this cohort, up to 20% of HIV-exposed infants had their first positive DNA PCR test after 2 months of age, prompting the authors to recommend infant testing at 4 months of age, having discontinued neonatal prophylaxis for at least 4 to 6 weeks.⁵⁷

Although the AMPLICOR® HIV-1 DNA test has been widely used for diagnosis of infants born to mothers with HIV-1 infection since it was introduced in 1992, it is no longer commercially available in the United States. The sensitivity and specificity of non-commercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the FDA-approved commercial test.

The COBAS AmpliPrep/COBAS TaqMan HIV-1 qualitative test which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots may be used for infant diagnosis but is not FDA-approved.⁵⁸

Other Issues

Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections

Although HIV-1 Group M subtype B is the predominant viral subtype found in the United States, multiple subtypes and recombinant forms are found in the United States with a widespread geographic distribution.⁵⁹ In an evaluation of infants with perinatal HIV infection diagnosed in New York state in 2001 and 2002, 16.7% of infants acquired HIV with a non-subtype B strain of HIV, compared with 4.4% of infants born in 1998 and 1999.⁶⁰ Among a group of 40 children attending a pediatric HIV clinic in Rhode Island during 1991 through 2012, 14 (35%) contracted HIV with non-B HIV-1 subtypes. All 14 children with non-B subtypes were either born outside the United States or their parents were of foreign origin.⁶¹

In an analysis of 1,277 unique sequences collected in Rhode Island from 2004 to 2011, 8.3% were non-B subtypes (including recombinant forms). Twenty-two percent of non-B subtypes formed transmission clusters, including individuals with perinatally-acquired infection.⁶² In an analysis of 3,895 HIV-1 sequences collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms). Among individual states, the percentage of non-B subtypes ranged from 0% (in 12 states) to 28.6% in South Dakota, with seven states having greater than 10%.⁶³ Evolving immigration patterns may be contributing to local and regional increases in HIV-1 subtype diversity. Non-subtype B viruses predominate in other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia. Group O HIV strains are seen in West-Central Africa.⁶⁴ Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.⁶⁵⁻⁶⁹ Geographical distribution of HIV groups is available at [the HIV Sequence Database](#).

Currently available real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay have improved sensitivity for detection of non-subtype B HIV infection and the less common Group O strains, compared to older RNA assays that did not detect or appropriately amplify many non-B subtypes and Group O HIV⁷⁰⁻⁷⁵ (see [HIV RNA Monitoring in Children: General Considerations in Clinical and Laboratory Monitoring](#)).

Thus, a real-time PCR assay or qualitative RNA assay, [rather than a DNA PCR assay](#), should be used for infant testing when evaluating an infant born to a mother whose HIV infection is linked to an area endemic for non-subtype B HIV or Group O strains, such as Africa or Southeast Asia. Another indication is when initial testing is negative using a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody tests obtained at age ≥ 6 months provide further evidence to definitively rule out HIV infection. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or the CDC may be able to assist in obtaining referrals for diagnostic testing.

Virologic Assays to Diagnose HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and parts of India.⁷⁶⁻⁷⁸ It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.^{79,80} HIV-1 and HIV-2 coinfections may also occur, but these are rare outside areas where HIV-2 is endemic. HIV-2 is rare in the United States. Although accurate diagnosis of HIV-2 can be problematic, it is clinically important because HIV-2 strains are resistant to several ARV drugs developed to suppress HIV-1.⁸¹⁻⁸³

Infant testing with HIV-2-specific DNA PCR tests should be performed at time points similar to those used for HIV-1 testing when evaluating an infant born to a mother with a known or suspected HIV-2 infection. A mother should be suspected of having HIV-2 if her infection is linked to an area endemic for HIV-2 infection or if her HIV testing results are suggestive of HIV-2 infection (i.e., positive initial HIV 1/2 immunoassay test, repeatedly indeterminate results on HIV-1 Western blot, and HIV-1 RNA viral loads at or below the limit of detection; however, the current recommendation to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test as described below).^{1,84} HIV-2 DNA PCR testing can be arranged by the HIV surveillance

program of the state or local health department through their public health laboratory or the CDC, because this assay is not commercially available.^{47,48} Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.^{76,85}

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Initial Postnatal Management of the Neonate Exposed to HIV (Last updated November 14, 2017; last reviewed November 14, 2017)

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 infant, 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 (see [Diagnosis of HIV Infection in Infants and Children](#)) (All).
- To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV 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](#)) (All).
- Health care providers should routinely inquire about breastfeeding and pre-mastication; instruct caregivers living with HIV to avoid these practices, and advise on safer feeding options (All).

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 newborns exposed to HIV 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 infant, 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. Hematologic safety data are limited on administration of 4 mg/kg of zidovudine twice daily in infants. 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.²⁻⁴ 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 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.

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.⁵⁻⁷ 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.⁸

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 maternal history of ARV prophylaxis, viral load near delivery, and mode of delivery). 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.⁹ **A 4-week (instead of 6-week) zidovudine neonatal chemoprophylaxis regimen is recommended** when a mother has received standard antiretroviral therapy (ART) during pregnancy with consistent viral suppression and no concerns related to maternal adherence; **the shorter regimen will mitigate the risk of anemia in such infants, who are at low risk of acquiring HIV (see [Antiretroviral Management of Newborns](#)).**^{10,11}

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.^{12,13} 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.^{12,13} 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 levels are significantly abnormal (i.e., >5 mmol/L), ARV prophylaxis should be discontinued and an expert in pediatric HIV infection consulted regarding alternate prophylaxis.

Prophylaxis Against *Pneumocystis jirovecii* Pneumonia

To prevent *Pneumocystis jirovecii* pneumonia, all infants born to women with HIV should begin trimethoprim-sulfamethoxazole (TMP-SMX) 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](#)).¹⁴

HIV Testing of the Infant

All infants perinatally exposed to HIV require virologic HIV testing to diagnose HIV or determine that they have not acquired HIV. For a detailed discussion, including types of tests and recommended HIV testing schedule, see [Diagnosis of HIV Infection in Infants and Children](#).

Postnatal Management

Following birth, infants exposed to HIV should have a detailed physical examination, and a thorough maternal history should be obtained. Mothers living with HIV may be coinfecting 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 exclude the possibility of transmission of additional infectious agents. The routine primary immunization schedule should be followed for exposed infants born to mothers with HIV. Modifications in the schedule may be required for infants with known HIV (see the [Pediatric OI Guidelines](#) for more information).

No evidence is available to enable the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission to assess whether any changes in routine bathing practices, or timing of

circumcision, are indicated for newborns with perinatal HIV exposure.

Infant Feeding Practices and Risk of HIV Transmission

In the United States, where safe infant feeding alternatives are available, **it is recommended that** women with HIV not breastfeed their infants.¹⁵ 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 may continue to pose a transmission risk.¹⁶ However, clinicians should be aware that some women may face considerable social, familial, and personal pressures to breastfeed despite this recommendation. It is important to address possible barriers to formula feeding beginning as early as possible in the antenatal period (see [Postpartum Follow Up](#)).

Some HIV transmission events in later infancy **are thought to have resulted from infants being fed solid food that has been premasticated (prechewed or prewarmed) by caregivers with HIV.** 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 caregivers living with HIV against this feeding practice, and advise on safer feeding options.^{17,18}

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Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel's Recommendation

- Children with *in utero*/neonatal exposure to antiretroviral (ARV) 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).
- It is important that the long-term medical record of a child without HIV includes information about *in utero* and neonatal ARV exposure (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

Available evidence does not permit definitive conclusions about whether exposure to antiretroviral (ARV) agents *in utero* might affect the long-term risk of neoplasia or organ system toxicities in children; however, the balance of evidence accumulated over the past 2 decades, particularly related to zidovudine exposure, is reassuring. Potential toxicities require further, long-term investigation, especially as individual antenatal ARV drugs and ARV drug 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, or 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 ARV drugs may have long-term effects on mitochondrial and immunologic function. Ongoing studies within the PHACS and other cohorts of children who are HIV-exposed but uninfected may help to identify the long-term risks of ARV drug exposure in infancy.

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.⁶⁻¹⁰ 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.^{8,10-13} 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 infants who are HIV exposed but uninfected compared with infants without HIV exposure.¹⁴ 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.^{8,15}

Evidence of clinically apparent effects of mitochondrial toxicity are also conflicting. A low rate of hyperlactatemia (3.4%) is documented among HIV-exposed but uninfected infants born to U.S. women receiving antiretroviral therapy (ART).¹⁶ 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 infants without HIV born to women with HIV (who received or did not receive ARV drugs during pregnancy: 12/2,644 vs. 0/1,748, respectively, $P = 0.002$).^{17,18} Further clinical studies from the United States and Europe

have not duplicated these French reports.¹⁹⁻²⁵ 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 but uninfected infants.²⁴ Definitive diagnosis was not possible 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.^{26,27}

Given the above data, mitochondrial dysfunction should be considered in children without HIV, but 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 a child without HIV includes information about ARV exposure, should unusual symptoms develop later in life, or if adverse late effects of HIV or ARV exposure in children without HIV are identified in the future.^{8,28,29}

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 malignancies, follow-up was limited to early childhood.^{1,2,25} Animal studies have reported potential transplacental genotoxicity of nucleoside analogue therapy in monkeys and micro-nucleated erythrocytes have been identified among infants with *in utero* nucleoside analogue exposure.^{30,31} 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 but 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.³² An updated report from the French Perinatal Cohort described 21 cancers in 15,163 children without HIV (median age 9.9 years) exposed *in utero* to HIV and at least one NRTI drug.³³ 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 ratio (95% CI, 2.1–14.4) of cancer with first trimester didanosine exposure. **In a study in the United States, there were 4 cancer diagnoses among 3,087 HIV-exposed children; cancer incidence in HIV-exposed children who were not exposed to ARV prophylaxis was not significantly different than incidence in children exposed to any ARV prophylaxis, and the number of cases did not differ significantly from cases expected based on national reference rates.**³⁴ Continued follow-up of HIV- and ARV-exposed but 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 infant without HIV is unclear. One study reported lower CD4 T lymphocyte (CD4) cell counts in HIV-exposed but uninfected infants born to mothers whose viral load at the time of delivery was >1,000 copies/mL compared to HIV-exposed but uninfected infants whose mothers had a viral load <50 copies/mL at the time of delivery.³⁵ 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.³⁶

Potential Increased Morbidity and Mortality

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 numbers near the time of delivery.³⁷

Data from Botswana also show higher rates of morbidity and mortality in HIV-exposed but uninfected infants and children than in HIV-unexposed infants.³⁸⁻⁴⁰ **A meta-analysis assessing all-cause mortality in HIV-exposed but uninfected infants and children consistently observed increased risk in this group compared to HIV-**

unexposed infants.⁴¹ Further study is needed regarding the reproducibility of these data, and whether there is an immunological basis for the increased susceptibility of HIV-exposed but uninfected infants and children to infectious diseases.⁴²

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 pregnant women with HIV currently receive ART regimens, it is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defect and cancer registries to identify potential adverse outcomes.

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Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed (Last updated March 27, 2018; last reviewed March 27, 2018)

Panel's Recommendations

- Breastfeeding **is not recommended** for women living with HIV in the United States (AII).
- Women who have questions about breastfeeding or who desire to breastfeed should receive patient-centered, evidence-based counseling on infant feeding options (AIII).
- When women with HIV choose to breastfeed despite intensive counseling, they should be counseled to use harm-reduction measures to minimize the risk of HIV transmission to their infants (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

Avoidance of breastfeeding is the standard, strong recommendation for women living with HIV in the United States, because

- Maternal antiretroviral therapy (ART) reduces but does not eliminate the risk of HIV transmission via breast milk;
- Safe and affordable infant feeding alternatives are readily accessible in the United States; and
- There is a paucity of safety data on most modern ART regimens during breastfeeding.

The recommendations in the United States differ from those in many low- and middle-income countries, where cost limits access to formula and where inadequate quantities of formula and/or unsafe water mixed into formula have been associated with high rates of infant mortality.¹ Women from areas in the United States without access to safe water may face similar challenges. Infant replacement feeding using formula, banked breast milk, or a properly screened HIV-negative wet nurse remains the only way to eliminate the risk of HIV transmission through infant feeding. However, women may face environmental, social, familial, and personal pressures to consider breastfeeding, despite the risk of HIV transmission via breast milk.²⁻⁴

A qualitative study of mothers living with HIV in Canada found that infant feeding is a social, cultural, and emotional issue, often underpinned by HIV-related stigma.⁴ Some women, especially those from a country or cultural background where breastfeeding is the norm, fear that not breastfeeding will lead to disclosure of their HIV status.² Multiple experts have called for a patient-centered, harm-reduction approach to counseling women living with HIV on infant feeding options in high-resource countries.^{2,5,6} This section of the guidelines is intended to provide tools to help providers counsel women living with HIV on the potential risks associated with breastfeeding and to provide a harm-reduction approach for women who choose to breastfeed despite intensive counseling. **This section is not intended to be an endorsement of breastfeeding, nor is it a recommendation to breastfeed for women living with HIV in the United States.**

Breastfeeding and Strategies to Reduce Risk of HIV Transmission

Both the evidence regarding the risks of HIV transmission via breastfeeding and the strategies to reduce this type of transmission come from studies conducted in low- and middle-income countries, where rates of infant mortality are high and many families do not have access to safe water and affordable formula. Without maternal ART and infant antiretroviral (ARV) prophylaxis, the risk of a woman with HIV transmitting the virus to a breastfeeding infant is 15% to 20% over 2 years.^{7,8}

Studies have shown that maternal ART throughout pregnancy and breastfeeding and infant ARV prophylaxis during breastfeeding can reduce, but not eliminate, the risk of HIV transmission through breast milk.^{9,13} However, most of these studies only provided ARV drugs to women or their infants through 6 months postpartum and collected limited data on maternal plasma HIV viral load during breastfeeding.

As ART has become more widely available for women during pregnancy and the postpartum period, studies have looked at women who started ART earlier in pregnancy and continued ART longer than in previous studies. A study of women with CD4 T lymphocyte cell counts ≥ 350 cells/mm³ compared extended infant nevirapine to maternal ART, with both treatments continued through cessation of breastfeeding or 18 months postpartum, whichever came first. This study estimated transmission rates of 0.3% at 6 months and 0.6% at 12 months in both arms.¹⁴ Importantly, cases of HIV transmission via breastfeeding have occurred despite undetectable maternal plasma viral loads.¹⁵

Prior to the current accessibility of ART in low-income countries, studies demonstrated that exclusive breastfeeding during the first 6 months of life is associated with lower HIV transmission than mixed feeding (a term used to describe infants fed breast milk plus other liquid or solid foods, including formula).^{16,17} After 6 months, when complementary foods are required for adequate infant nutrition, demand for breast milk decreases and gradual weaning can occur. Rapid weaning over several days is not recommended. Studies from low-income countries that were conducted before ART was widely accessible for breastfeeding women observed the potential for increased HIV shedding into breast milk and an increased risk of HIV transmission during rapid weaning.¹⁸⁻²⁰

Safety of Maternal and Infant Use of Antiretroviral Drugs during Breastfeeding

Studied NNRTIs (nevirapine, efavirenz, and etravirine) get into breast milk, but to a lower extent than the levels in maternal plasma. Studied PIs (lopinavir, nelfinavir, ritonavir, indinavir, atazanavir) reach very low concentrations in breast milk, with little to no drug detectable in the blood of the breastfed infant.²¹ NRTIs show more variability than PIs and NNRTIs. Tenofovir disoproxil fumarate has very little transfer into breast milk, with no detectable drug concentration in the blood of the breastfed infant.²¹⁻²³ Emtricitabine and lamivudine have more accumulation in breast milk and can sometimes be detected in the blood of the breastfed infant (in 19% and 36% of infants, respectively).²¹ For more details on ARV passage into breastmilk, see the individual [drug sections in Appendix B](#).

A review of studies of women with and without HIV taking TDF during pregnancy found generally normal infant growth.^{21,24} One reviewed study showed a decrease in bone mineral content among the babies of mothers on combination ART (whether the mothers received tenofovir diphosphate (DP)-based ART or zidovudine-based ART) compared to the babies of mothers receiving zidovudine alone. Another study showed a decrease in bone mineral content among breastfeeding mothers receiving tenofovir DP-based ART compared to mothers who received no ART, but whether these findings will persist after discontinuation of breastfeeding is not known.²⁴

Serious adverse infant events associated with ART in breastfeeding mothers appear to be relatively uncommon. In two studies that compared the efficacy of maternal ART (zidovudine-based ART in one study and TDF-based ART in the other) to infant nevirapine prophylaxis with no maternal ART during breastfeeding for prevention of postnatal HIV transmission, no significant differences in adverse events were observed between study arms.^{10,14} One study reported that anemia occurred more frequently among infants who were exposed to zidovudine-based ART during breastfeeding than among infants who were not exposed to ART.²⁵ An infant who acquires HIV while breastfeeding is at risk of developing ARV drug resistance due to subtherapeutic drug levels in breast milk, especially if the breastfeeding woman develops viremia.^{26,27}

As noted above, extended infant ARV prophylaxis during breastfeeding has similar rates of serious adverse events compared to maternal ART. In one study, the rate of adverse events in infants receiving 6 months of nevirapine was not significantly different from those receiving nevirapine placebo. A second study comparing

two infant ARV prophylaxis regimens (lopinavir/ritonavir vs. lamivudine) found no significant difference in the rates of adverse events in infants receiving the two regimens.^{10-12,14} Studies to date have only examined short-term adverse events, and there is little data on whether there might be long-term consequences of these drug exposures.

Approach to Counseling and Management

Formula, banked donor milk, and milk from an HIV-negative wet nurse who has been properly screened remain the only completely reliable methods of preventing HIV transmission during breastfeeding. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends that women living with HIV in the United States not breastfeed their infants. However, patient-centered counseling on infant feeding must balance maternal psychosocial concerns, infant health benefits of breastfeeding, and risks of HIV transmission. Providers can initiate counseling with a nonjudgmental inquiry about infant feeding early in pregnancy, and then engage the mother by offering joint problem solving and shared decision making. One approach is to say to all pregnant women living with HIV “In the United States, we recommend formula feeding to avoid the risk of HIV transmission to your baby through breast milk. Do you have any questions or concerns about this?” For women who are considering breastfeeding, we recommend engaging each woman privately in a nonjudgmental conversation about the motivation behind her desire to breastfeed, as well as consultation with the clinician(s) who will be managing the infant’s care.

If, despite extensive counseling, a woman decides to breastfeed, harm-reduction measures should be taken to reduce the risk of HIV transmission. These include:

- Demonstrating maternal ART adherence and engagement in care both during pregnancy and throughout breastfeeding.
- Documenting consistent viral suppression prior to delivery and throughout breastfeeding. This can be accomplished by monitoring maternal plasma viral loads every 1 to 2 months during breastfeeding. If maternal viral load becomes detectable, consult an expert immediately.
- Breastfeeding exclusively for up to 6 months postpartum, followed by breastfeeding in combination with the introduction of complementary foods.
- Developing a plan for weaning with input from the family and providers. Rapid weaning over a few days is not recommended.
- Infants should receive at least 6 weeks of infant ARV prophylaxis with zidovudine and/or nevirapine. In non-breastfeeding infants, there is high quality evidence that 4 weeks to 6 weeks of infant prophylaxis with zidovudine prevents HIV transmission (see Antiretroviral Management of Newborns with Perinatal HIV Exposure of Perinatal HIV). The most extensively studied infant prophylaxis in breastfeeding infants is daily infant nevirapine, which has been shown to be safe and effective when used for extended prophylaxis in infants whose mothers are not receiving ART.^{11,14} If the mother is receiving ART, infant ARV prophylaxis can be discontinued after 6 weeks. Some experts in the United States have felt more comfortable with continuing infant ARV prophylaxis through 1 month after cessation of weaning, even when the mother is receiving ART. However, during the HPTN 046 trial, in which the mothers received ART, there was no difference in postnatal transmission when the infant received nevirapine or placebo, suggesting no additive effect.¹¹
- Monitoring the infant for HIV acquisition during breastfeeding. A reasonable approach to infant monitoring would include virologic HIV testing at the standard time points (see [Maternal HIV Testing and Identification of Perinatal HIV Exposure](#)) and then every 3 months throughout breastfeeding, followed by monitoring at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding.

- In the unlikely case of HIV transmission via breastfeeding, it is important to promptly initiate a full combination ARV treatment regimen for the infant. Resistance testing should be done on the infant viral isolate. If resistance is identified, the treatment regimen can be adjusted appropriately.
- Maternal mastitis and infant thrush should be promptly identified and treated, as both conditions increase the risk of HIV transmission through breastfeeding. Milk from the affected breast should be pumped and discarded until mastitis resolves.

The immediate postpartum period poses unique challenges to adherence to medical care and ART. Close follow-up and enhanced support services should be considered for women planning to breastfeed (see [Postpartum Follow-Up of Women Living with HIV Infection](#)).

Clinicians caring for a woman with HIV who is considering breastfeeding should consult with an expert and, if necessary, the Perinatal HIV Hotline (888-448-8765).

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Appendix A: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission (Last updated November 14, 2017; last reviewed November 14, 2017)

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 that are more applicable in resource-constrained settings. In addition, multiple studies have examined optimal regimens to reduce postnatal transmission during breastfeeding. **More recently, in the context of recommendations for universal antiretroviral therapy (ART), studies have also explored the efficacy of universal ART during pregnancy and 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, 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. **Furthermore, these studies have provided critical information elucidating the risks, timing, and mechanisms of perinatal transmission.**

ART is more effective antenatally than a single-drug prophylactic regimen in reducing perinatal transmission.

The use of ARV drugs to prevent transmission is highly effective, even in women living with advanced HIV.^{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 ART over zidovudine-based prophylaxis for prevention of *in utero* transmission in women with CD4 T lymphocyte (CD4) cell counts >350 cells/mm³.¹⁸ 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 1 week of life was significantly lower among women receiving ART (0.5%, 9 infections among 1,710 infants) compared with those randomized to receive zidovudine plus single-dose nevirapine plus postpartum TDF/emtricitabine tail (1.8%, 25 infections among 1,386 infants).

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 at high risk for HIV acquisition.

Delayed maternal HIV diagnosis or delayed presentation for pregnancy care may result in missing the opportunity to provide maternal ARV drugs during pregnancy or labor. 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 (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 women with HIV infection is not recommended in the United States.

Breastfeeding by women living with HIV (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 **in resource-limited settings** have demonstrated that both infant prophylaxis (daily infant nevirapine, lamivudine, and lopinavir/ritonavir) 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 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 women living in the United States (including those receiving combination ARV drug regimens).²² Finally, both infant nevirapine prophylaxis and maternal ART during breastfeeding may be associated with the development of ARV drug resistance in infants who acquire HIV despite prophylaxis; multi-class drug resistance has been described in breastfeeding infants with HIV 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).

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 <u>Oral IP:</u> • 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 <u>Oral IP:</u> • 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	4 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). <i>In utero</i> 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 <u>Oral IP:</u> • 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 <i>in utero</i>).
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 <u>Oral IP:</u> • 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 ZDV/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 <u>Oral IP:</u> • 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) <u>Oral IP:</u> • 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%.

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 without HIV 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 <u>Oral IP:</u> • 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 without HIV 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	<u>Initial:</u> • Short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding <u>Revised:</u> • 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.	<u>First Randomization:</u> • ZDV from 34 weeks <u>Oral IP:</u> • ZDV plus either SD NVP or placebo	<u>Second Randomization:</u> • Breastfeeding plus ZDV (infant) 6 months plus SD NVP; infant only, vs. • Formula feeding plus ZDV (infant) 4 weeks plus SD NVP; infant only	<u>Initial Design:</u> • 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). <u>Revised Design:</u> • 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.

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 <u>Oral IP:</u> • SD NVP	Infant SD NVP vs. NVP for 6 weeks	<u>Postnatal Infection in Infants Without HIV at Birth:</u> • 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. 2 extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV <u>Oral IP:</u> • 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	<u>Postnatal Infection in Infants Without HIV at Birth:</u> • 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; 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.

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	<u>Arm 1:</u> • ZDV/3TC/LPV/r <u>Arm 2:</u> • ZDV plus SD NVP From 28 weeks through labor	<u>Arm 1:</u> • Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP plus ZDV for 1 week <u>Arm 2:</u> • 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) (<i>P</i> = 0.029).
Mma Bana; Botswana;² Breastfeeding	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 counts >200 cells/mm ³	<u>Arm 1:</u> • ZDV/3TC/ABC <u>Arm 2:</u> • ZDV/3TC/LPV/r From 26 weeks through labor	<u>Arm 1:</u> • Maternal ZDV/3TC/ABC for 6 months, infant SD NVP plus ZDV for 4 weeks <u>Arm 2:</u> • 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 (<i>P</i> = 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 <u>IP Regimens</u> <u>Arm 1 (Control):</u> • ZDV/3TC plus SD NVP <u>Arm 2:</u> • ZDV/3TC plus SD NVP <u>Arm 3:</u> • ZDV/3TC plus SD NVP	<u>Arm 1 (Control):</u> • Maternal ZDV/3TC for 1 week; infant SD NVP plus ZDV/3TC for 1 week <u>Arm 2:</u> • Control as above, then maternal ZDV/3TC/LPV/r for 6 months <u>Arm 3:</u> • Control as above, then infant NVP for 6 months	<u>Postnatal Infection in Infants Without HIV at Age 2 Weeks:</u> • Perinatal transmission at age 28 weeks was 5.7% in control Arm 1, 2.9% in maternal triple-drug prophylaxis Arm 2 (<i>P</i> = 0.009 vs. control), and 1.7% in infant NVP Arm 3 (<i>P</i> < 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 (<i>P</i> = 0.0273 vs. control), and 4% in infant NVP Arm 3 (<i>P</i> = 0.0027 vs. control). No significant difference between maternal triple-drug prophylaxis (Arm 2) and infant NVP (Arm 3) (<i>P</i> = 0.12 at 28 weeks and <i>P</i> = 0.426 at 48 weeks).

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
<p>HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;^{37,43} Breastfeeding</p>	<p>Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP</p>	<p>AP drugs allowed if required for maternal health</p>	<p>All infants received daily NVP from birth through age 6 weeks.</p> <p><u>Arm 1:</u></p> <ul style="list-style-type: none"> Daily infant NVP from age 6 weeks through age 6 months <p><u>Arm 2:</u></p> <ul style="list-style-type: none"> Daily infant placebo from age 6 weeks through age 6 months 	<p>In infants without HIV 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 ($P = 0.048$).</p> <p>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.</p> <p>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.</p> <p>For mothers receiving triple-drug ARV regimens at the time of randomization, in infants without HIV 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%).</p> <p>For mothers with CD4 counts >350 cells/mm³ who were not receiving triple-drug ARV regimens, in infants without HIV 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 ($P = 0.014$).</p>
<p>NICHD-HPTN 040/PACTG 1043 Trial; Brazil, Argentina, South Africa, United States;⁴⁴ Formula feeding</p>	<p>Infant prophylaxis with 6 weeks ZDV vs.</p> <p>6 weeks infant ZDV plus 3 doses of NVP in first week of life vs.</p> <p>6 weeks infant ZDV plus 2 weeks 3TC/NFV</p>	<p>No AP drugs</p> <p>If mother presented early enough, IV ZDV during labor through delivery</p>	<p><u>Arm 1 (Control):</u></p> <ul style="list-style-type: none"> Infant ZDV for 6 weeks <p><u>Arm 2:</u></p> <ul style="list-style-type: none"> 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 <p><u>Arm 3:</u></p> <ul style="list-style-type: none"> Control as above, plus 3TC and NFV from birth through age 2 weeks 	<p>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).</p> <p>Overall HIV transmission rates, including <i>in utero</i> 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).</p> <p>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 ($P < 0.001$).</p>

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 Without HIV 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 (<i>P</i> = 0.83). • HIV-free survival was 96.5% (84.6–97.7) in Arm 1 and 96.3% (94.4–97.5) in Arm 2 (<i>P</i> = 0.85).
PROMOTE; Uganda; ⁴⁵ Breastfeeding	Compared 2 triple-ARV regimens; no CD4 restriction	Arm 1: • ZDV/3TC/LPV/r Arm 2: • ZDV/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 (<i>P</i> = 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 ZDV prophylaxis and 2 ART 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: • ART 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 ART arms vs. ZDV arm difference in perinatal transmission risk: -1.3% (95% CI, -2.1% to -0.4%)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; ART = antiretroviral therapy; 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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Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Table 9. Antiretroviral Drug Use in Pregnant Women with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 1 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
NRTIs				
NRTIs are recommended for use as part of combination regimens, usually including 2 NRTIs with either an NNRTI or 1 or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection. See text for discussion of potential maternal and infant mitochondrial toxicity.				
Abacavir (ABC) <i>Ziagen</i> (ABC/3TC) <i>Epzicom</i> (ABC/3TC/ZDV) <i>Trizivir</i> (ABC/3TC/DTG) <i>Triumeq</i>	ABC (Ziagen)^a <i>Tablet:</i> • 300 mg <i>Solution:</i> • 20 mg/mL Epzicom^a • ABC 600 mg plus 3TC 300 mg tablet Trizivir^a • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet Triumeq: • ABC 600 mg plus 3TC 300 mg plus DTG 50 mg tablet	Standard Adult Doses <i>ABC (Ziagen):</i> • 300 mg twice daily or 600 mg once daily, without regard to food <i>Epzicom:</i> • 1 tablet once daily without regard to food <i>Trizivir:</i> • 1 tablet twice daily without regard to food <i>Triumeq:</i> • 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 1.5-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.	November 14, 2017
Didanosine (ddl) <i>Videx</i> <i>Videx EC</i>	ddl (Videx) <i>Buffered Tablets (Non-EC):</i> • No longer available <i>Solution:</i> • 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 <i>Body Weight ≥60 kg:</i> • 400 mg once daily <i>With TDF:</i> • 250 mg once daily; take 1/2 hour before or 2 hours after a meal. <i>Body Weight <60kg:</i> • 250 mg once daily <i>With TDF:</i> • 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.	Low-moderate placental transfer to fetus. ^b In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddl 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. ddl should not be used with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together.	November 14, 2017

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 2 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
		<p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK not significantly altered in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 		
<p>Emtricitabine (FTC) <i>Emtriva</i></p> <p>(FTC/TDF) <i>Truvada</i></p> <p>(FTC/TDF/EFV) <i>Atripla</i></p> <p>(FTC/TDF/RPV) <i>Complera</i></p> <p>(FTC/TDF/EVG/ COBI) <i>Stribild</i></p> <p>(FTC/TAF) <i>Descovy</i></p> <p>(FTC/TAF/RPV) <i>Odefsey</i></p> <p>(FTC/TAF/EVG/ COBI) <i>Genvoya</i></p>	<p><u>Emtriva (FTC)</u> <i>Capsules:</i></p> <ul style="list-style-type: none"> • 200 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 10 mg/mL <p><u>Truvada:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TDF 300 mg tablet <p><u>Atripla:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TDF 300-mg plus EFV^c 600 mg tablet <p><u>Complera:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet <p><u>Stribild:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet <p><u>Descovy:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TAF 25 mg tablet <p><u>Odefsey:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TAF 25 mg plus RPV 25 mg tablet <p><u>Genvoya:</u></p> <ul style="list-style-type: none"> • FTC 200 mg plus TAF 10 mg plus EVG 150 mg plus COBI 150 mg tablet 	<p><u>Standard Adult Dose</u></p> <p><u>Emtriva (FTC)</u> <u>Capsule:</u></p> <ul style="list-style-type: none"> • 200 mg once daily without regard to food <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 240 mg (24 mL) once daily without regard to food <p><u>Truvada:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <p><u>Atripla:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. <p><u>Complera:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><u>Stribild:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><u>Descovy:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with or without food <p><u>Odefsey:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><u>Genvoya:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK of FTC not significantly altered in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in FTC dose indicated. <p>• For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., TDF, TAF, EFV, RPV, EVG/c)</p>	<p>High placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>If HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 3 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Lamivudine (3TC) <i>Epivir</i></p> <p>(3TC/ZDV) <i>Combivir</i></p> <p>(3TC/ABC) <i>Epzicom</i></p> <p>(3TC/ZDV/ABC) <i>Trizivir</i></p> <p>(3TC/ABC/DTG) <i>Triumeq</i></p>	<p><u>3TC (Epivir)</u></p> <p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 150 mg^g • 300 mg^g <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 10 mg/mL^g <p><u>Combivir:</u></p> <ul style="list-style-type: none"> • 3TC 150 mg plus ZDV 300 mg tablet^g <p><u>Epzicom:</u></p> <ul style="list-style-type: none"> • 3TC 300 mg plus ABC 600 mg tablet^g <p><u>Trizivir:</u></p> <ul style="list-style-type: none"> • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet^g <p><u>Triumeq:</u></p> <ul style="list-style-type: none"> • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg tablet 	<p><u>Standard Adult Dose</u></p> <p><u>3TC (Epivir):</u></p> <ul style="list-style-type: none"> • 150 mg twice daily or 300 mg once daily, without regard to food <p><u>Combivir:</u></p> <ul style="list-style-type: none"> • 1 tablet twice daily without regard to food <p><u>Epzicom:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <p><u>Trizivir:</u></p> <ul style="list-style-type: none"> • 1 tablet twice daily without regard to food <p><u>Triumeq:</u></p> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK not significantly altered in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>If HBV-coinfected, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.</p>	<p>November 14, 2017</p>
<p>Stavudine (d4T) <i>Zerit</i></p> <p>Note: Generic products available for all formulations.</p>	<p><u>d4T (Zerit)</u></p> <p><u>Capsules:</u></p> <ul style="list-style-type: none"> • 15 mg • 20 mg • 30 mg • 40 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 1 mg/mL following reconstitution 	<p><u>Standard Adult Dose^f</u></p> <p><u>Body Weight ≥60 kg:</u></p> <ul style="list-style-type: none"> • 40 mg twice daily without regard to meals <p><u>Body Weight <60 kg:</u></p> <ul style="list-style-type: none"> • 30 mg twice daily without regard to meals <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK not significantly altered in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer.^b</p> <p>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</p> <p>d4T is not recommended for pregnant women.</p> <p>Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 4 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Tenofovir Alafenamide (TAF) <i>Vemlidy^d</i> (TAF/FTC/EVG/COBI) <i>Genvoya</i> (TAF/FTC/RPV) <i>Odefsey</i> (TAF/FTC) <i>Descovy</i>	<u>Vemlidy</u> • TAF 25 mg tablet <u>Genvoya:</u> • TAF 10 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet <u>Odefsey:</u> • TAF 25 mg plus FTC 200 mg plus RPV 25 mg tablet <u>Descovy:</u> • TAF 25 mg plus FTC 200 mg tablet	<u>Standard Adult Dose</u> <u>Vemlidy:</u> • 1 tablet once daily with food <u>Genvoya, Odefsey:</u> • 1 tablet once daily with food <u>Descovy:</u> • 1 tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without pharmaco-enhancers <u>PK in Pregnancy:</u> • No PK studies in human pregnancy <u>Dosing in Pregnancy:</u> • Insufficient data to make dosing recommendation	No data are available on placental transfer of TAF. 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.	November 14, 2017
Tenofovir Disoproxil Fumarate (TDF) <i>Viread</i> (TDF/FTC) <i>Truvada</i> (TDF/FTC/EFV) <i>Atripla</i> (TDF/FTC/RPV) <i>Complera</i> (TDF/FTC/EVG/COBI) <i>Stribild</i>	<u>TDF (Viread)</u> <u>Tablet:</u> • 300 mg <u>Powder:</u> • 40 mg/1 g oral powder <u>Truvada:</u> • TDF 300 mg plus FTC 200 mg tablet <u>Atripla:</u> • TDF 300 mg plus FTC 200 mg plus EFV ^c 600 mg tablet <u>Complera:</u> • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet <u>Stribild:</u> • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet	<u>Standard Adult Dose</u> <u>TDF (Viread)</u> <u>Tablet:</u> • 300 mg once daily without regard to food <u>Powder:</u> • 8 mg/kg (up to maximum 300 mg), take with food <u>Truvada:</u> • 1 tablet once daily without regard to food <u>Atripla:</u> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. <u>Complera:</u> • 1 tablet once daily with food <u>Stribild:</u> • 1 tablet once daily with food <u>PK in Pregnancy:</u> • AUC lower in third trimester than postpartum but trough levels adequate <u>Dosing in Pregnancy:</u> • 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 consistent link to low birth weight , 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.	October 19, 2017

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 5 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Zidovudine (ZDV, AZT) <i>Retrovir</i></p> <p>(ZDV/3TC) <i>Combivir</i></p> <p>(ZDV/3TC/ABC) <i>Trizivir</i></p> <p>Note: Generics are approved for all formulations</p>	<p><u>ZDV (Retrovir)</u></p> <p><u>Capsule:</u></p> <ul style="list-style-type: none"> • 100 mg <p><u>Tablet:</u></p> <ul style="list-style-type: none"> • 300 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 10 mg/mL <p><u>Intravenous Solution:</u></p> <ul style="list-style-type: none"> • 10 mg/mL <p><u>Combivir:</u></p> <ul style="list-style-type: none"> • ZDV 300 mg plus 3TC 150 mg tablet <p><u>Trizivir:</u></p> <ul style="list-style-type: none"> • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet 	<p><u>Standard Adult Dose</u></p> <p><u>ZDV (Retrovir):</u></p> <ul style="list-style-type: none"> • 300 mg BID or 200 mg TID, without regard to food <p><u>Active Labor:</u></p> <ul style="list-style-type: none"> • 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery <p><u>Combivir:</u></p> <ul style="list-style-type: none"> • 1 tablet twice daily, without regard to food <p><u>Trizivir:</u></p> <ul style="list-style-type: none"> • 1 tablet twice daily, without regard to food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK not significantly altered in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 6 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>NNRTI NNRTIs are recommended for use in combination regimens with 2 NRTI drugs. Hypersensitivity reactions, including hepatic toxicity and rash, more common in women; unclear if increased in pregnancy.</p>				
<p>Efavirenz (EFV) <i>Sustiva</i> (EFV/TDF/FTC) <i>Atripla</i></p>	<p><u>EFV (Sustiva)^a</u> <i>Capsules:</i> • 50 mg • 200 mg <i>Tablet:</i> • 600 mg <u>Atripla:</u> • EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet</p>	<p><u>Standard Adult Dose</u> <i>EFV (Sustiva):</i> • 600 mg once daily at or before bedtime, on empty stomach to reduce side effects <i>Atripla:</i> • 1 tablet once daily at or before bedtime, on empty stomach to reduce side effects <u>PK in Pregnancy:</u> • AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester participants exceeded target exposure. <u>Dosing in Pregnancy:</u> • No change in dose indicated.</p>	<p>Moderate placental transfer to fetus.^b Potential fetal safety concern: The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administration in the first trimester of pregnancy as fetal harm may occur. Although the limited data on first-trimester EFV exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from a 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. As a result, the current Perinatal Guidelines do not include a restriction of use of EFV in pregnant women or in women planning to become pregnant, consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy. EFV should be continued in pregnant women receiving a virologically suppressive EFV-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission (see Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy).</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 7 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Etravirine (ETR) <i>Intelence</i></p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 25 mg • 100 mg • 200 mg <p>For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.</p>	<p><u>Standard Adult Dose(s):</u></p> <ul style="list-style-type: none"> • 200 mg twice daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK data in pregnancy (n = 26) suggest 1.2–1.6-fold increased etravirine exposure during pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 19 mother-infant pairs).^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p>	<p>November 14, 2017</p>
<p>Nevirapine (NVP) <i>Viramune</i> <i>Viramune XR</i> (Extended Release)</p> <p>Note: Generic available for all formulations</p>	<p><u>NVP (Viramune)</u></p> <p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 200 mg <p><u>Oral Suspension:</u></p> <ul style="list-style-type: none"> • 50 mg/5 mL <p><u>Viramune XR Tablets:</u></p> <ul style="list-style-type: none"> • 100 mg • 400 mg 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 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. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK of immediate release tablets not significantly altered in pregnancy. • No data are available on extended release (Viramune XR) formulations in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer to fetus.^b</p> <p>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).</p> <p>Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts ≥250/mm³ when first initiating therapy; pregnancy does not appear to increase risk.</p> <p>NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm³ 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.</p> <p>Women who become pregnant while taking NVP-containing regimens and are tolerating them well can continue therapy, regardless of CD4 cell count.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 8 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Rilpivirine (RPV) <i>Edurant</i></p> <p>(RPV/TDF/FTC) <i>Complera</i></p> <p>(RPV/TAF/FTC) <i>Odefsey</i></p>	<p>RPV (<i>Edurant</i>)</p> <p><i>Tablets:</i></p> <ul style="list-style-type: none"> • 25 mg <p><i>Complera:</i></p> <ul style="list-style-type: none"> • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet <p><i>Odefsey:</i></p> <ul style="list-style-type: none"> • RPV 25 mg plus TAF 25 mg plus FTC 200 mg tablet 	<p><u>Standard Adult Dose</u></p> <p><i>RPV (Edurant):</i></p> <ul style="list-style-type: none"> • 25 mg once daily with food <p><i>Complera:</i></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><i>Odefsey:</i></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 50% in pregnancy compared with postpartum. While most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • While RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently. 	<p>Moderate to high placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 9 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>PIs PIs are recommended for use in combination regimens with 2 NRTI drugs. Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see Combination Antiretroviral Drug Regimens and Pregnancy Outcomes).</p>				
<p>Atazanavir (ATV) <i>Reyataz</i></p> <p>Note: Must be combined with low-dose RTV boosting in pregnancy</p> <p>Atazanavir/Cobicistat (ATV/COBI) <i>Evotaz</i></p>	<p><u>Atazanavir (Reyataz)</u> <i>Capsules:</i></p> <ul style="list-style-type: none"> • 150 mg • 200 mg • 300 mg <p><i>Oral Powder:</i></p> <ul style="list-style-type: none"> • 50-mg packet <p><u>Evotaz:</u></p> <ul style="list-style-type: none"> • ATV 300 mg plus COBI 150 mg tablet 	<p>Standard Adult Dose</p> <p><u>Atazanavir (Reyataz)</u> <i>ARV-Naive Patients</i></p> <p><u>Without RTV Boosting:</u></p> <ul style="list-style-type: none"> • ATV 400 mg once daily with food; ATV without RTV boosting is not recommended when used with TDF, H₂-receptor antagonists, PPIs, or during pregnancy. <p><u>With RTV Boosting:</u></p> <ul style="list-style-type: none"> • 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 <p><i>ARV-Experienced Patients:</i></p> <ul style="list-style-type: none"> • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV. • If combined with an H₂-receptor antagonist: ATV 300 mg plus RTV 100 mg once daily with food • If combined with an H₂-receptor antagonist and TDF: ATV 400 mg plus RTV 100 mg once daily with food <p><u>Powder Formulation:</u></p> <ul style="list-style-type: none"> • Oral powder is taken once daily with food at the same recommended adult dosage as the capsules along with RTV. <p><u>Atazanavir/Cobicistat (Evotaz):</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food. <p><u>PK in Pregnancy</u></p> <p><i>Atazanavir (Reyataz):</i></p> <ul style="list-style-type: none"> • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H₂-receptor antagonist. <p><i>Atazanavir/Cobicistat (Evotaz):</i></p> <ul style="list-style-type: none"> • No PK studies in human pregnancy. 	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>Must be given as low-dose RTV-boosted regimen in pregnancy.</p> <p>Effect of <i>in utero</i> 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.</p> <p>Oral powder (but not capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 10 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
		<p><u>Dosing in Pregnancy</u> <i>Atazanavir [Reyataz]:</i></p> <ul style="list-style-type: none"> • Use of unboosted ATV is not recommended during pregnancy. • Use of ATV not recommended for treatment-experienced pregnant women taking TDF and an H₂-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 H₂-receptor antagonist. <p><i>Atazanavir/Cobicistat (Evotaz):</i></p> <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation in pregnancy (see Cobicistat section). 		November 14, 2017
<p>Darunavir (DRV) <i>Prezista</i></p> <p>Note: Must be combined with low-dose RTV or COBI boosting</p> <p>Darunavir/Cobicistat (DRV/COBI) <i>Prezcobix</i></p>	<p><u>DRV Tablets:</u></p> <ul style="list-style-type: none"> • 75 mg • 150 mg • 600 mg • 800 mg <p><u>DRV Oral Suspension:</u></p> <ul style="list-style-type: none"> • 100 mg/mL <p><u>Prezcobix Tablet (Co-Formulated):</u></p> <ul style="list-style-type: none"> • DRV 800 mg plus COBI 150 mg 	<p><u>Standard Adult Dose</u> <i>ARV-Naive Patients:</i></p> <ul style="list-style-type: none"> • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food <p><i>ARV-Experienced Patients:</i></p> <p><u>If No DRV Resistance Mutations:</u></p> <ul style="list-style-type: none"> • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food <p><u>If Any DRV Resistance Mutations:</u></p> <ul style="list-style-type: none"> • DRV 600 mg plus RTV 100 mg twice daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Decreased exposure in pregnancy with use of DRV/r. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • The Panel does not recommend once-daily dosing with DRV/r during pregnancy. • Twice-daily DRV/r 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/c co-formulation, so not recommended for use in pregnancy. 	<p>Low placental transfer to fetus.^b</p> <p>No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity.</p> <p>Must be boosted with low-dose RTV.</p>	November 14, 2017

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 11 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Fosamprenavir (FPV) <i>Lexiva (a prodrug of amprenavir)</i></p> <p>Note: Must be combined with low-dose RTV boosting in pregnancy</p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 700 mg <p><u>Oral Suspension:</u></p> <ul style="list-style-type: none"> • 50 mg/mL 	<p><u>Standard Adult Dose</u></p> <p><i>ARV-Naive Patients:</i></p> <ul style="list-style-type: none"> • 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 <p><i>PI-Experienced Patients</i></p> <ul style="list-style-type: none"> • Once-daily dosing not recommended • FPV 700 mg plus RTV 100 mg twice daily without food <p><i>Co-Administered with EFV:</i></p> <ul style="list-style-type: none"> • FPV 700 mg plus RTV 100 mg twice daily without food; or • FPV 1400 mg plus RTV 300 mg once daily without food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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). 	<p>Low placental transfer to fetus.^b</p> <p>Insufficient data to assess for teratogenicity in humans. Increased fetal loss in rabbits but no increase in defects in rats and rabbits.</p> <p>Must be given as low-dose RTV-boosted regimen in pregnancy.</p>	<p>November 14, 2017</p>
<p>Indinavir (IDV) <i>Crixivan</i></p> <p>Note: Must be combined with low-dose RTV boosting in pregnancy</p>	<p><u>Capsules:</u></p> <ul style="list-style-type: none"> • 200 mg • 400 mg 	<p><u>Standard Adult Dose</u></p> <p><i>Without RTV Boosting:</i></p> <ul style="list-style-type: none"> • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal. <p><i>With RTV Boosting:</i></p> <ul style="list-style-type: none"> • IDV 800 mg plus RTV 100 mg twice daily without regard to meals <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Use of unboosted IDV is not recommended during pregnancy. 	<p>Minimal placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity in cases reported to the Antiretroviral Pregnancy Registry (can rule out 2-fold increase in overall birth defects).</p> <p>Must be given as low-dose, RTV-boosted regimen in pregnancy.</p> <p>Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates. Minimal placental passage mitigates this concern.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 12 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Lopinavir/ Ritonavir (LPV/r) <i>Kaletra</i></p> <p>Note: Generic available for some formulations</p>	<p><u>Tablets (Co-Formulated):</u></p> <ul style="list-style-type: none"> • LPV 200 mg plus RTV 50 mg • LPV 100 mg plus RTV 25 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • LPV 400 mg plus RTV 100 mg/5 mL 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • LPV 400 mg plus RTV 100 mg twice daily, or • LPV 800 mg plus RTV 200 mg once daily <p><u>Tablets:</u></p> <ul style="list-style-type: none"> • Take without regard to food. <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • Take with food. <p><u>With EFV or NVP (PI-Naive or PI-Experienced Patients):</u></p> <ul style="list-style-type: none"> • 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 <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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 or LPV 500 mg plus RTV 125 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.. 	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>Oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy.</p> <p>Once-daily LPV/r dosing is not recommended during pregnancy</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 13 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Nelfinavir (NFV) <i>Viracept</i></p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 250 mg • 625 mg (tablets can be dissolved in small amount of water) <p><u>Powder for Oral Suspension:</u></p> <ul style="list-style-type: none"> • 50 mg/g 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 1250 mg twice daily or 750 mg three times daily with food <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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. 	<p>Minimal to low placental transfer to fetus.^b</p> <p>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.</p> <p>Contains aspartame; should not be used in individuals with phenylketonuria.</p>	<p>November 14, 2017</p>
<p>Saquinavir (SQV) <i>Invirase</i></p> <p>Note: Must be combined with low-dose RTV for PK boosting</p>	<p><u>Tablet:</u></p> <ul style="list-style-type: none"> • 500 mg <p><u>Capsule:</u></p> <ul style="list-style-type: none"> • 200 mg 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>Low placental transfer to fetus.^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p> <p>Must be boosted with low-dose RTV.</p> <p>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with preexisting cardiac conduction system disease.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 14 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Tipranavir (TPV) <i>Aptivus</i></p> <p>Note: Must be combined with RTV for PK boosting</p>	<p><u>Capsules:</u></p> <ul style="list-style-type: none"> • 250 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 100 mg/mL 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • TPV 500 mg plus RTV 200 mg twice daily <p><u>With RTV Tablets:</u></p> <ul style="list-style-type: none"> • Take with food. <p><u>With RTV Capsules or Solution:</u></p> <ul style="list-style-type: none"> • Take without regard to food; however, administering with food may help make the dose more tolerable. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Limited PK data in human pregnancy <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation 	<p>Moderate placental transfer to fetus reported in 1 patient.^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p> <p>Must be given as low-dose RTV-boosted regimen.</p>	<p>November 14, 2017</p>
Entry Inhibitors				
<p>Enfuvirtide (T-20) <i>Fuzeon</i></p>	<p><u>Injectable:</u></p> <ul style="list-style-type: none"> • 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. 	<p>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.</p> <p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 90 mg (1 mL) twice daily without regard to meals <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • No PK data in human pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation. 	<p>Minimal to low placental transfer to fetus.^b</p> <p>No data on human teratogenicity.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 15 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Maraviroc (MVC) <i>Selzentry</i></p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 150 mg • 300 mg 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 300 mg twice daily with or without food • Maraviroc should only be used for patients with CCR5-tropic virus (and no X4-tropic virus). <p><u>Dose Adjustments:</u></p> <ul style="list-style-type: none"> • 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, itraconazole. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • 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. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Standard adult dosing adjusted for concomitant ARV use appears appropriate. 	<p>No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans.</p> <p>MVC placental passage category should be moderate.^b</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 16 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Integrase Inhibitors				
<p>Dolutegravir (DTG) <i>Tivicay</i></p> <p>(DTG/ABC/3TC) <i>Triumeq</i></p>	<p><u>DTG Tablets:</u></p> <ul style="list-style-type: none"> • 50 mg <p><u>Triumeq:</u></p> <ul style="list-style-type: none"> • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet 	<p><u>Standard Adult Dose</u> <i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive Patients)</i></p> <p><u>DTG (Tivicay):</u></p> <ul style="list-style-type: none"> • 1 tablet once daily, without regard to food. <p><u>DTG/ABC/3TC (Triumeq):</u></p> <ul style="list-style-type: none"> • 1 tablet once daily, without regard to food. <p><i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced</i></p> <p><u>DTG (Tivicay):</u></p> <ul style="list-style-type: none"> • 1 tablet twice daily, without regard to food. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • AUC may be decreased during the third trimester compared with postpartum, but good viral suppression in third trimester recipients. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer to fetus.</p> <p>No evidence of teratogenicity in mice, rats, or rabbits. Preliminary data suggest no increased risk of teratogenicity in humans.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 17 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
<p>Elvitegravir (EVG) <i>Vitekta</i></p> <p>Note: As of October 2017, <i>Vitekta</i> (i.e., EVG as a single-entity formulation) is no longer available</p> <p>Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate (EVG/COBI/ FTC/TDF) <i>Stribild</i></p> <p>Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide (EVG/COBI/FTC/TAF) <i>Genvoya</i></p>	<p><u>Tablet (Stribild):</u></p> <ul style="list-style-type: none"> • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg <p><u>Tablet (Genvoya):</u></p> <ul style="list-style-type: none"> • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg 	<p><u>Standard Adult Dose (Stribild and Genvoya):</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation. 	<p>Evidence of high placental transfer of EVG and low transfer of COBI.</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p> <p>EVG/c is not recommended for initial use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/c regimen is continued, viral load should be monitored frequently, and TDM (if available) may be useful.</p>	<p>November 14, 2017</p>
<p>Raltegravir (RAL) <i>Isentress</i> <i>Isentress HD</i></p>	<p><u>Isentress</u></p> <p><u>Film-Coated Tablets:</u></p> <ul style="list-style-type: none"> • 400 mg <p><u>Chewable Tablets:</u></p> <ul style="list-style-type: none"> • 25 mg • 100 mg <p><u>Isentress HD</u></p> <p><u>Film-Coated Tablets:</u></p> <ul style="list-style-type: none"> • 600 mg 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 400-mg film-coated tablets twice daily without regard to food. • Two, 600-mg film-coated (1200 mg) once daily for treatment-naïve patients or patients already virologically suppressed on initial regimen of RAL 400 mg BID) without regard to food <p>Chewable and oral suspension doses are not interchangeable to either film-coated tablets or to each other.</p> <p><u>With Rifampin:</u></p> <ul style="list-style-type: none"> • Two, 400-mg film-coated tablets (800 mg) twice daily without regard to food. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Decreased levels in third trimester not of sufficient magnitude to warrant change in dosing. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. • Once-daily dosing (i.e., two 600-mg film-coated tablets) should not be used in pregnant women until more information is available. 	<p>High placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>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.</p> <p>Chewable tablets contain phenylalanine.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 18 of 19)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy	Last Reviewed
Pharmaco-Enhancers				
<p>Cobicistat (COBI) <i>Tybost</i></p> <p>Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/COBI/ TDF/FTC) <i>Stribild</i></p> <p>Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (EVG/COBI/TAF/FTC) <i>Genvoya</i></p> <p>Atazanavir/Cobicistat (ATV/COBI) <i>Evotaz</i></p> <p>Darunavir/Cobicistat (DRV/COBI) <i>Prezcobix</i></p>	<p><u>Tablet (Tybost):</u></p> <ul style="list-style-type: none"> • 150 mg <p><u>Tablet (Stribild):</u></p> <ul style="list-style-type: none"> • EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg <p><u>Tablet (Genvoya):</u></p> <ul style="list-style-type: none"> • EVG 150 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg <p><u>Tablet (Evotaz):</u></p> <ul style="list-style-type: none"> • ATV 300 mg plus COBI 150 mg <p><u>Tablet (Prezcobix):</u></p> <ul style="list-style-type: none"> • DRV 800 mg plus COBI 150 mg 	<p><u>Standard Adult Dose</u></p> <p><i>Tybost:</i></p> <ul style="list-style-type: none"> • As an alternative PK booster with ATV or DRV/r: 1 tablet (150 mg) once daily with food. <p><i>Stribild, Genvoya, Evotaz, Prezcobix:</i></p> <ul style="list-style-type: none"> • 1 tablet once daily with food. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Based on limited data, COBI exposure and pharmacoenhancing effect are markedly reduced in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • While COBI exposure is markedly reduced during pregnancy, higher than standard doses have not been studied. The Panel recommends the use of RTV as the preferred pharmaco-enhancer during pregnancy until more data are available on COBI activity during pregnancy. 	<p>Low placental transfer to fetus.^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p>	<p>November 14, 2017</p>
<p>Ritonavir (RTV) <i>Norvir</i></p>	<p><u>Capsules:</u></p> <ul style="list-style-type: none"> • 100 mg <p><u>Tablets:</u></p> <ul style="list-style-type: none"> • 100 mg <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> • 80 mg/mL <p>Powder:</p> <ul style="list-style-type: none"> • 100 mg/sachet 	<p><u>Standard Adult Dose as PK Booster for Other PIs:</u></p> <ul style="list-style-type: none"> • 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) <p><i>Tablet:</i></p> <ul style="list-style-type: none"> • Take with food. <p><i>Capsule or Oral Solution:</i></p> <ul style="list-style-type: none"> • To improve tolerability, recommended to take with food if possible. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Lower levels during pregnancy compared with postpartum. <p><u>Dosing in Pregnancy:</u></p> <p>No dosage adjustment necessary when used as booster.</p>	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>Should only be used as low-dose booster for other PIs.</p> <p>Oral solution contains 43% alcohol and is therefore not recommended during pregnancy, because there is no known safe level of alcohol exposure during pregnancy.</p>	<p>November 14, 2017</p>

Table 9. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy^a (page 19 of 19)

^a Individual ARV 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

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

^d Only indicated for use in chronic HBV virus infection in adults.

^e Generic formulation available

^f WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; AUC = area under the curve; AZT = zidovudine; BID = twice daily; CD4 = CD4 T lymphocyte; CI = confidence interval; CNS = central nervous system; COBI = cobicistat; d4T = stavudine; ddl = didanosine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EC = enteric coated; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPC = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HBV = hepatitis B virus; IDV = indinavir; IV = intravenous; LPV = lopinavir; 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; SQ = subcutaneous; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TID = three times a day; TPV = tipranavir; TPV/r = tipranavir/ritonavir; WHO = World Health Organization; ZDV = zidovudine

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 November 14, 2017; last reviewed November 14, 2017)

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).

Teratogenicity/Adverse Pregnancy Outcomes

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

Human Studies in Pregnancy

Pharmacokinetics

In pregnant women, pharmacokinetic (PK) studies of 300 mg twice daily and² 600 mg daily concluded³ that the PK during pregnancy is equivalent to postpartum. A population 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.^{2,5} In the Mma Bana study,⁶ 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/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to abacavir in humans 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 abacavir. Among cases of first-trimester abacavir exposure reported to the APR, the prevalence of birth defects was 2.98% (30 of 1007 births; 95% CI, 2.01% to 4.23%) compared with 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁷ There was no association of birth defects with first-trimester exposure to abacavir in the SMARTT study (aOR 0.94 [0.53–1.65]),⁸ in the French Perinatal Study (aOR 1.01, [0.73–1.41]),⁹ or in a series of 897 births to women with HIV in Spain between 2000 and 2009 (aOR 0.99, [0.34–2.87]).¹⁰

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 and should not receive abacavir; HLA screening should be done before initiation of abacavir. Two meta-analyses have confirmed the association of this genotype and the hypersensitivity reaction.^{11,12}

In the PHACS/SMARTT cohort (median follow-up: 2.4 years), after adjusting for birth cohort and other factors, use of abacavir by the mother during pregnancy led to no increase in the likelihood of adverse events for the infant in the following domains: metabolic, growth and development, cardiac, neurological, neurodevelopmental.¹³

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Abacavir (ABC) <i>Ziagen</i> (ABC/3TC) <i>Epzicom</i> (ABC/3TC/ZDV) <i>Trizivir</i> (ABC/3TC/DTG) <i>Triumeq</i>	ABC (Ziagen):^e <i>Tablet:</i> • 300 mg <i>Solution:</i> • 20 mg/mL Epzicom:^e • ABC 600 mg plus 3TC 300 mg tablet Trizivir:^e • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet Triumeq: • ABC 600 mg plus 3TC 300 mg plus DTG 50 mg tablet	Standard Adult Doses: <i>ABC (Ziagen):</i> • 300 mg twice daily or 600 mg once daily, without regard to food <i>Epzicom:</i> • 1 tablet once daily without regard to food <i>Trizivir:</i> • 1 tablet twice daily without regard to food <i>Triumeq:</i> • 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 1.5-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 ARV 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

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

^d Only indicated for use in chronic hepatitis B virus infection in adults.

^e Generic formulation available.

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

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Didanosine (Videx, ddI)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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.

Adverse Pregnancy Outcomes

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 pregnant women with HIV 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 pregnant women with HIV 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.

Adverse Pregnancy Outcomes

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% CI, 1.1–10.4), *P* = 0.04).⁴ Though the PHACS/SMARTT cohort found no association between any individual NRTIs and birth defects, after adjusting for birth cohort and other factors, didanosine in combination with stavudine was associated with an overall increase in congenital abnormalities;⁵ it should be noted that the combination of didanosine and stavudine **should no longer be used** in pregnant women with HIV (or anyone with HIV) because of higher risk of toxicity. Among 897 births to women with HIV 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 In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to didanosine in humans have been monitored to be able to detect at least a 2-fold increase in the risk of overall birth defects.⁷ Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.74% (20 of 422 births; 95% CI, 2.91% to 7.23%) compared with

2.73% 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 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.

The PHACS/SMARTT cohort found that after adjusting for birth cohort and other factors, didanosine in combination with stavudine was associated with occurrence of neurodevelopmental disability. However there was no increase in the likelihood of adverse events in the following domains with didanosine alone: metabolic, growth and development, cardiac, neurological, neurodevelopmental, behavior, language, and hearing.^{11,12} As noted above, the combination of didanosine and stavudine should no longer be used in pregnant women with HIV (or anyone with HIV) because of higher risk of toxicity.

In a multivariate analysis of the association of *in utero* ARV exposure and risk of cancer in HIV-exposed uninfected infants, the French Perinatal Study reported a 5.5-fold (95% CI, 2.1–14.4) increase in cancer incidence with first-trimester didanosine exposure.¹³

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
Didanosine (ddl) Videx Videx EC	<u>ddl (Videx)</u> <u>Buffered Tablets (Non-EC):</u> • No longer available <u>Solution:</u> • 10 mg/mL oral solution <u>Videx EC (EC Beadlets) Capsules:</u> • 125 mg • 200 mg • 250 mg • 400 mg <u>Generic Delayed-Release Capsules:</u> • 200 mg • 250 mg • 400 mg	<u>Standard Adult Doses</u> <u>Body Weight ≥60 kg:</u> • 400 mg once daily <u>With TDF:</u> • 250 mg once daily; take 1/2 hour before or 2 hours after a meal. <u>Body Weight <60kg:</u> • 250 mg once daily <u>With TDF:</u> • 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. <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> • No change in dose indicated.	Low-moderate placental transfer to fetus. ^b In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddl 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. ddl should not be used with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together

^a Individual ARV 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: APR = Antiretroviral Pregnancy Registry; CI = confidence interval; d4T = stavudine; ddl = didanosine; EC = enteric coated; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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Emtricitabine (Emtriva, FTC)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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

In the IMPAACT P1026s study, emtricitabine exposure was modestly lower during the third trimester (geometric mean 8.0 mcg*h/mL [90% CI, 7.1–8.9]) compared with the postpartum period (9.7 mcg*h/mL [90% CI, 8.6–10.9]). Fifty-eight percent (15 of 26) of pregnant women versus 95% (21 of 22) of postpartum women met the AUC target (≤30% reduction from typical exposure for nonpregnant historical controls). Trough emtricitabine levels were also lower during pregnancy (C24 geometric mean concentration 58 ng/mL [90% CI, 37–63]) compared with the postpartum period (85 ng/mL [90% CI, 70–100]).³ Similar differences in pharmacokinetic parameters of emtricitabine among women during pregnancy or after delivery were found in the PACTG 394 study⁴ and in a European study.^{5,6} The increase in emtricitabine clearance in pregnancy correlated with the normal pregnancy-related increase in glomerular filtration rate.⁶ 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 a study of 15 women who received emtricitabine during pregnancy, the mean cord-to-maternal-blood ratio was 1.2 (90% CI, 1.0–1.5).³ 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).⁴

Emtricitabine is excreted into human milk. In a study in the Ivory Coast, 5 women with HIV who exclusively breastfed their newborn infants were given 400 mg emtricitabine, 600 mg TDF, and 200 mg 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 IC₅₀ for HIV-1.⁷ In a study of 50 women without HIV who received 200 mg emtricitabine and 300 mg TDF orally daily as pre-exposure prophylaxis (PrEP), median peak and trough breastmilk concentrations of emtricitabine were 212.5 ng/mL (IQR 140.0–405.0) and 183.0 ng/mL (113.0–250.0), respectively. Emtricitabine was detectable in 47/49 infants at a median (IQR) concentration of 13.2 ng/mL (9.3–16.7), corresponding to estimated daily infant ingestion of 31.9 mcg/kg (IQR 21.0–60.8) dose of emtricitabine, or 0.5% of the daily dose for treating infants.⁸

Teratogenicity/Adverse Pregnancy Outcomes

In a study of pregnancies occurring during an HIV PrEP trial in which participants (who did not have HIV infection) 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 the U.S. PHACS SMARTT cohort study, emtricitabine exposure was not associated with an increase in specific or overall birth defect risk.¹⁰ In a large French cohort, emtricitabine exposure in the first trimester was associated with lower risk of birth defects.¹¹ In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 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 2.24% (48 of 2,145 births; 95% CI, 1.65% to 2.96%), compared with a 2.72% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.¹²

Other Safety Information

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of emtricitabine led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.¹³

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Emtricitabine (FTC) <i>Emtriva</i>	<u>Emtriva (FTC)</u> <u>Capsules:</u> • 200 mg	<u>Standard Adult Dose</u> <u>Emtriva (FTC)</u> <u>Capsule:</u> • 200 mg once daily without regard to food	High placental transfer to fetus. ^b
(FTC/TDF) <i>Truvada</i>	<u>Oral Solution:</u> • 10 mg/mL	<u>Oral Solution:</u> • 240 mg (24 mL) once daily without regard to food	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).
(FTC/TDF/EFV) <i>Atripla</i>	<u>Truvada:</u> • FTC 200 mg plus TDF 300 mg tablet	<u>Truvada:</u> • 1 tablet once daily without regard to food	If HBV-coinfected, it is possible that a HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection .
(FTC/TDF/RPV) <i>Complera</i>	<u>Atripla:</u> • FTC 200 mg plus TDF 300-mg plus EFV ^c 600 mg tablet	<u>Atripla:</u> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.	
(FTC/TDF/EVG/COBI) <i>Stribild</i>	<u>Complera:</u> • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet	<u>Complera:</u> • 1 tablet once daily with food	
(FTC/TAF) Descovy	<u>Stribild:</u> • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet	<u>Stribild:</u> • 1 tablet once daily with food	
(FTC/TAF/RPV) <i>Odefsey</i>	Descovy: • FTC 200 mg plus TAF 25 mg	Descovy: • 1 tablet once daily with or without food	
(FTC/TAF/EVG/COBI) <i>Genvoya</i>	<u>Odefsey:</u> • FTC 200 mg plus TAF 25 mg plus RPV 25 mg tablet <u>Genvoya:</u> • FTC 200 mg plus TAF 10 mg plus EVG 150 mg plus COBI 150 mg tablet	<u>Odefsey:</u> • 1 tablet once daily with food <u>Genvoya:</u> • 1 tablet once daily with food <u>PK in Pregnancy:</u> • PK of FTC not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> • No change in FTC dose indicated. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., TDF, TAF, EFV, RPV, EVG/c)	

^a Individual ARV 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

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

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

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Lamivudine (Epivir, 3TC)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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

Placental and Breast Milk Passage

In studies of pregnant rats, lamivudine is transferred to the fetus through the placenta.¹

Human Studies in Pregnancy

Pharmacokinetics

Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in 2 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 subtherapeutic 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 nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1,214 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 (IC₅₀ of lamivudine against wild-type HIV = 0.6–21 ng/mL). **In a separate study of breastfeeding women in Malawi who were receiving lamivudine (in combination with tenofovir and efavirenz), concentrations of lamivudine in breast milk were higher than those in maternal plasma at 1 month (3.29-fold higher) and 12 months (2.35-fold higher) after delivery; infant plasma levels at ages 6 and 12 months, on the other hand, revealed median (IQR) lamivudine concentrations of only 2.5 (2.5–7.6) and 0 (0–2.5) ng/mL, respectively.⁶**

Teratogenicity/Adverse Pregnancy Outcomes

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% CI, 1.06–1.73) but there was no organ system or specific birth defect that predominated.⁷ However, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in cardiovascular and 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 Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (145 of 4,763 births; 95% CI, 2.6% to 3.6%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁸

An analysis of Antiretroviral Pregnancy Registry data demonstrated lower risk of spontaneous abortions, induced abortions, and preterm births for lamivudine-containing regimens compared with non-lamivudine antiretroviral regimens.⁹

Other Safety Information

In a large, U.S. cohort study of uninfected infants born to women living with HIV, lamivudine exposure during pregnancy was not associated with increased risk of adverse infant outcomes in any of the growth, hearing, language, neurology, neurodevelopment, metabolic, hematologic/clinical chemistry, and blood lactate domains assessed.¹⁰

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Lamivudine (3TC) <i>EpiVir</i> (3TC/ZDV) <i>Combivir</i> (3TC/ABC) <i>Epzicom</i> (3TC/ZDV/ABC) <i>Trizivir</i> (3TC/ABC/DTG) <i>Triumeq</i>	<u>3TC (EpiVir)</u> <u>Tablets:</u> <ul style="list-style-type: none"> • 150 mg^e • 300 mg^e <u>Oral Solution:</u> <ul style="list-style-type: none"> • 10 mg/mL^e <u>Combivir:</u> <ul style="list-style-type: none"> • 3TC 150 mg plus ZDV 300 mg tablet^e <u>Epzicom:</u> <ul style="list-style-type: none"> • 3TC 300 mg plus ABC 600 mg tablet^e <u>Trizivir:</u> <ul style="list-style-type: none"> • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet^e <u>Triumeq:</u> <ul style="list-style-type: none"> • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg tablet 	<u>Standard Adult Dose</u> <u>3TC (EpiVir):</u> <ul style="list-style-type: none"> • 150 mg twice daily or 300 mg once daily, without regard to food <u>Combivir:</u> <ul style="list-style-type: none"> • 1 tablet twice daily without regard to food <u>Epzicom:</u> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <u>Trizivir:</u> <ul style="list-style-type: none"> • 1 tablet twice daily without regard to food <u>Triumeq:</u> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> • PK not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> • 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 ARV 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

^e Generic formulation available

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 November 14, 2017; last reviewed November 14, 2017)

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

Stavudine is not recommended for use in pregnant women with HIV due to its toxicity.

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 no demonstrated 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 μ M and of post-blastocyst development at 10 μ M.²

Teratogenicity/Adverse Pregnancy Outcomes

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 women living with HIV 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/Adverse Pregnancy Outcomes

No association was found between first-trimester exposure to stavudine and birth defects in a large French cohort study that had 70% power to detect an increased adjusted odds ratio of 1.5.⁸ In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to stavudine in humans have been

monitored to be able to detect at least a two-fold increased risk of overall birth defects. No such increase in birth defects has been observed with stavudine. Among cases of first-trimester stavudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.6% (21 of 811 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 (ARV) agents.¹⁰⁻¹² The FDA and Bristol-Myers Squibb 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](#)). **Didanosine and stavudine** should not be prescribed together for pregnant women.

In a U.S. cohort study evaluation of safety of ARV drugs used during pregnancy, children without HIV born to women with HIV who received didanosine plus stavudine during the pregnancy had an increased risk of both adverse neurodevelopmental (relative risk [RR] of 12.40, 95% CI, 5.29–29.08) and language (RR of 4.84, 95% CI, 1.14–20.51) outcomes compared to children whose mothers did not receive these drugs during pregnancy.¹³

Stavudine is not recommended for use in pregnant women with HIV due to its toxicity.

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Stavudine (d4T) Zerit Note: Generic products available for all formulations.	d4T (Zerit) <i>Capsules:</i> • 15 mg • 20 mg • 30 mg • 40 mg <i>Oral Solution:</i> • 1 mg/mL following reconstitution	<u>Standard Adult Dose^f</u> <i>Body Weight ≥60 kg:</i> • 40 mg twice daily without regard to meals <i>Body Weight <60 kg:</i> • 30 mg twice daily without regard to meals <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> • 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 is not recommended for pregnant women. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together.

^a Individual ARV 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

^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; ddl = didanosine; PK = pharmacokinetic; WHO = World Health Organization

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Tenofovir Alafenamide (Genvoya, Odefsey, Descovy, TAF)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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 TAF administration.¹⁻³

Teratogenicity/Adverse Pregnancy Outcomes

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/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, **only 3 cases of** exposures to TAF have been reported **so far;** **therefore, no conclusions can be made about risk of birth defects.**⁴

Excerpt from Table 9^a

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

^a Individual ARV 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

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

^d Only indicated for use in chronic hepatitis B virus infection in adults.

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

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Tenofovir Disoproxil Fumarate (Viread, TDF)

(Last updated October 19, 2017; last reviewed October 19, 2017)

Tenofovir disoproxil fumarate (TDF), an orally bioavailable form of tenofovir, is classified as Food and Drug Administration Pregnancy Category B.¹ For information about tenofovir alafenamide (TAF), see the [TAF section](#).

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/Adverse Pregnancy Outcomes

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 TDF, 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 the 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 of TDF during pregnancy continues to be recommended.

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 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; infant plasma levels were not directly measured in this study.¹¹ In a study of 50 breastfeeding women without HIV infection who received TDF/emtricitabine (under directly observed therapy for 10 days) as pre-exposure prophylaxis (PrEP), median (IQR) peak and trough time-averaged tenofovir breastmilk concentrations were similar at 3.2 ng/mL (2.3-4.7) and 3.3 ng/mL (2.3-4.4), respectively. The infant plasma tenofovir concentration was unquantifiable (<0.31 ng/mL) in 94% (46/49) of infants; in the 3 infants with detectable tenofovir, the level was 0.9 ng/mL in two and 17.4 ng/mL in one. Based on this study's results, the median tenofovir dose ingested through breastmilk was estimated at 0.47 mcg/kg or <0.01% of the proposed 6 mg/kg pediatric daily TDF dose.¹²

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.¹³

Teratogenicity/Adverse Pregnancy Outcomes

In a study of 431 pregnancies occurring during an HIV pre-exposure prophylaxis trial in which women who did not have HIV infection 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.¹⁴ No association was seen between maternal TDF and offspring birth defects in three large U.S. cohorts of children born to women living with HIV: PACTG 219/219C (n = 2,202 with 214 first-trimester TDF exposures), P1025 (n = 1,112 with 138 first-trimester TDF exposures),^{15,16} and PHACS (n = 2,580 with 431 first-trimester TDF exposures).¹⁷ 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).¹⁸ 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 birth defects.¹⁹ 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% (75 of 3,229 births; 95% confidence interval [CI], 1.8% to 2.9%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²⁰

In the PHACS study from the United States, 449 (21%) of the 2,029 infants exposed to HIV who were uninfected 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 (LBW), small-for-gestational-age (SGA), and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively).²¹ In a different U.S. cohort study, P1025, maternal TDF use was similarly not associated with differences in body size parameters at birth.²² A fetal ultrasound study in South Africa demonstrated no association between duration of maternal TDF use and long-bone (femur and humerus) growth.²³ However, in a Dutch study of 74 HIV-exposed infants (including 9 with *in utero* TDF exposure), maternal TDF use was linked to an increased risk of LBW <2500g.²⁴

In the largely Africa-based PROMISE trial, in which pregnant women living with HIV but without advanced disease or immunosuppression (CD4 counts ≥ 350) were randomized at ≥ 14 weeks' (median 26 weeks') gestation to receive zidovudine alone, zidovudine/lamivudine/lopinavir/ritonavir (zidovudine-based ART), or TDF/emtricitabine/lopinavir/ritonavir (tenofovir-based ART), there was no significant difference between tenofovir-based ART and zidovudine-based ART arms in LBW $< 2,500$ g (16.9% vs. 20.4%, $P = 0.3$) or preterm delivery < 37 weeks (18.5% vs 19.7%, $P = 0.77$) but tenofovir-based ART was associated with higher rates than zidovudine-based ART of very preterm delivery before 34 weeks (6.0% vs. 2.6%, $P = 0.04$) and early infant death (4.4% vs. 0.6%, $P = 0.001$).²⁵ The greater number of early infant deaths were likely attributable to poor outcomes of very preterm infants in settings where the trial took place, but the higher rate of very preterm delivery in the tenofovir-based ART arm remains unexplained. Potential explanations include a lower than expected severe preterm delivery rate in the zidovudine-based ART arm or increased tenofovir exposure due to coadministration with lopinavir/ritonavir (lopinavir/ritonavir doses were increased in trial participants in late pregnancy).

In contrast to the PROMISE trial results, in a large observational study in Botswana of more than 11,000 births among women with HIV who received ART during pregnancy and gave birth between August 2014 and August 2016, the risk of any adverse birth outcome was lower in those who received TDF/emtricitabine/efavirenz than in those who received any other regimen (TDF/emtricitabine/nevirapine, adjusted relative risk [ARR], 1.15; TDF/emtricitabine/lopinavir/ritonavir, ARR, 1.31; zidovudine/lamivudine/nevirapine, ARR, 1.30; zidovudine-lamivudine-lopinavir-ritonavir, ARR, 1.21) Furthermore, TDF/emtricitabine/efavirenz was associated with a lower risk of SGA compared with all other regimens, and zidovudine/lamivudine/lopinavir/ritonavir was associated with higher risk of preterm birth, very preterm birth and neonatal death compared with TDF/emtricitabine/efavirenz. Finally, among infants exposed to ART from conception, tenofovir/emtricitabine/efavirenz was associated with lower risk for adverse birth outcomes than other ART regimens.²⁶

Additionally, the placebo-controlled trial of 300 mg TDF initiated at 28 weeks' gestation in Thai women with hepatitis B (but not HIV infection) permits an assessment of potential TDF impact on birth outcomes when TDF is used in pregnancy without other antiviral drugs and outside the context of maternal HIV infection. In this study, 322 deliveries resulted in 323 live births (including 2 twin pairs and 1 stillbirth in the TDF arm) and no difference in birthweight (median birth weight 3,028 g in TDF arm and 3,061 g in placebo arm) or preterm delivery (8/162 [5%] in TDF arm including none < 35 weeks and 13/160 [8%] in the placebo arm including 3/160 [2%] at 32–34 weeks) between TDF and placebo arms.²⁷

In all, there remains some concern for a link between maternal TDF use and preterm birth or LBW but the evidence is mixed and the role of potential cofactors and/or confounders needs better definition.

Other Safety Data

Maternal Safety Outcomes

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 (1 woman's postpartum eGFR was 60 mL/min).²⁸

Infant Safety Outcomes

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of TDF led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.²⁹

In the DART trial (described above), there were no differences noted in infant mortality or growth.¹⁹ In the U.S. PHACS Study, while there was no difference at birth between those exposed to combination drug regimens with or without TDF in **LBW, SGA or newborn LAZ and HCAZ**, 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

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 the U.S. P1025 study, 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 A Kenyan cohort study also found an association between maternal TDF-ART use (compared to ART without TDF) and lower 6-week WAZ despite no difference in weight at birth; however, TDF exposure was not associated with WAZ differences at age 9 months, and there were no associations with all other anthropometric measures at the 6-week or 9-month time points.³⁰ In the Dutch study of 74 HIV-exposed infants, maternal TDF use was linked to lower 6-month HAZ and WAZ, adjusted for differences in birthweight and adjusted for prematurity.²⁴ Finally, in the placebo-controlled trial of TDF initiated at 28 weeks' gestation in Thai women with hepatitis B (but not HIV) infection, there was no difference in growth outcomes at age 6 months between infants in the maternal TDF and placebo arms.²⁷

In all, there is inconsistent evidence that maternal TDF use during pregnancy may be associated with transient, small growth delays in the first year of life that are of uncertain clinical significance.³¹

In a cross-sectional study of 68 children ages 1 to 6 years who were exposed to but not infected with HIV and 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.³² In contrast, a study evaluating whole body dual-energy X-ray absorptiometry (DXA) 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.³³

A study of 136 infants in Malawi whose mothers received TDF/emtricitabine/efavirenz in pregnancy (and no control group for comparison) documented low-grade, transient abnormalities of serum phosphate and serum creatinine at ages 6 and 12 months.³⁴

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Tenofovir Disoproxil Fumarate (TDF) <i>Viread</i> (TDF/FTC) <i>Truvada</i> (TDF/FTC/EFV) <i>Atripla</i> (TDF/FTC/RPV) <i>Complera</i> (TDF/FTC/EVG/COBI) <i>Stribild</i>	<u>TDF (Viread)</u> <u>Tablet:</u> • 300 mg <u>Powder:</u> • 40 mg/1 g oral powder <u>Truvada:</u> • TDF 300 mg plus FTC 200-mg tablet <u>Atripla:</u> • TDF 300 mg plus FTC 200 mg plus EFV ^c 600-mg tablet <u>Complera:</u> • TDF 300 mg plus FTC 200 mg plus RPV 25-mg tablet <u>Stribild:</u> • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150-mg tablet	<u>Standard Adult Dose</u> <u>TDF (Viread)</u> <u>Tablet:</u> • 300 mg once daily without regard to food <u>Powder:</u> • 8 mg/kg (up to maximum 300 mg), take with food <u>Truvada:</u> • 1 tablet once daily without regard to food <u>Atripla:</u> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. <u>Complera:</u> • 1 tablet once daily with food <u>Stribild:</u> • 1 tablet once daily with food <u>PK in Pregnancy:</u> • AUC lower in third trimester than postpartum but trough levels adequate <u>Dosing in Pregnancy:</u> • 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 consistent link to low birth weight , 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 ARV 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 November 14, 2017; last reviewed November 14, 2017)

Available evidence does not suggest that zidovudine use by pregnant women is associated with an increased risk of adverse fetal or pregnancy outcomes.¹

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.² 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.¹

Two trans-placental carcinogenicity studies were conducted in mice.^{3,4} In 1 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.⁴ 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.³ 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.⁵

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, administration of oral zidovudine to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposure (expressed as “area under the curve”, AUC) approximately 33 times higher than human exposures at the recommended clinical dose. However, no embryotoxicity was observed after administration to pregnant rats during organogenesis at doses that produced AUC approximately 117 times higher than clinical exposures. Administration of oral zidovudine to pregnant rabbits during organogenesis resulted in embryotoxicity at doses that produced exposures approximately 108 times higher than the clinical exposure. No embryotoxicity was observed at doses that produced exposures approximately 23 times higher than the clinical exposure.¹

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 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.^{6,7} 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.⁸ However, standard dosing of IV zidovudine during labor continues to be recommended. **In pregnant women, as with nonpregnant adults, intracellular zidovudine triphosphate concentrations do not vary with plasma concentrations, over a wide range of plasma zidovudine concentrations.**⁹

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 1.5.¹⁰ 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 nursing infants who received zidovudine only via breast milk.¹¹⁻¹³

Teratogenicity/Adverse Pregnancy Outcomes

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.^{6,14} Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.^{15,16} 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.^{17,18} In the PHACS/SMARTT cohort, there was no association between first-trimester exposure and congenital anomalies.¹⁹ 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 **cardiovascular and** genitourinary systems. 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 4161 births; 95% CI, 2.7% to 3.8%),** compared with a total prevalence in the US population of 2.72%, based on Centers for Disease Control and Prevention surveillance.²⁰ Similarly, a series of 897 infants exposed to HIV 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]).²¹

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]). 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).²²

In the PRIMEVA trial, mothers were randomized to antepartum treatment with zidovudine/lamivudine/lopinavir/ritonavir or lopinavir/ritonavir. Female infants of women in the first group 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.²³ In a study that performed fetal echocardiography of 42 HIV fetuses exposed to HIV who were not infected and 84 fetuses without HIV exposure, multivariate analysis revealed that maternal zidovudine treatment was associated with thicker myocardial walls and smaller left ventricular cavities among infants exposed to zidovudine compared to other infants with or without HIV exposure, and maternal zidovudine treatment was

the only factor significantly associated with fetal cardiac changes.²⁴

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,²⁵ in prospective cohort studies,²⁶ and in matches between HIV surveillance and cancer registries.^{27,28}

Other Safety Information

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.²⁹

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.^{14,25}

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.

The PHACS/SMARTT cohort used a “trigger-based design” in which a number of domains (e.g., metabolic) had predetermined “triggers;” children meeting the definition of a trigger were further investigated to determine if they had met the definition of a “case” in that domain. The study found that after adjusting for birth cohort and other factors, zidovudine was associated with increased risk of meeting the study’s definition of a metabolic case (RR=1.69, 95% CI, 1.08–2.64).^{30,31}

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Zidovudine (ZDV, AZT) <i>Retrovir</i> (ZDV/3TC) <i>Combivir</i> (ZDV/3TC/ABC) <i>Trizivir</i> Note: Generics are approved for all formulations	<u>ZDV (Retrovir)</u> <i>Capsule:</i> • 100 mg <i>Tablet:</i> • 300 mg <i>Oral Solution:</i> • 10 mg/mL <i>Intravenous Solution:</i> • 10 mg/mL <i>Combivir:</i> • ZDV 300 mg plus 3TC 150 mg tablet <i>Trizivir:</i> • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	<u>Standard Adult Dose</u> <i>ZDV (Retrovir):</i> • 300 mg BID or 200 mg TID, without regard to food <u>Active Labor:</u> • 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery <i>Combivir:</i> • 1 tablet twice daily, without regard to food <i>Trizivir:</i> • 1 tablet twice daily, without regard to food <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> • 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 ARV 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 Acronyms: 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 U.S. Food and Drug Administration (FDA) approved: delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Delavirdine is no longer available in the United States.

Efavirenz (Sustiva, EFV)

(Last updated November 14, 2017; last reviewed November 14, 2017)

The Food and Drug Administration (FDA) cautions that efavirenz should not be used in the first trimester of pregnancy because of the potential risk of neural tube defects, which have been observed among children exposed to efavirenz *in utero* and in animal studies.¹

However, the current Perinatal Guidelines, based on review of updated evidence, do not include a restriction on use of efavirenz in pregnant women or in women planning to become pregnant, consistent with both the British HIV Association and World Health Organization (WHO) guidelines for use of antiretroviral (ARV) drugs in pregnancy.

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/Adverse Pregnancy Outcomes

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 \leq 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 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, 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 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

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.⁷ 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 1,000 ng/mL recommended for treatment of adults with HIV. In a study of 51 women in 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.⁸ 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).⁹ 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/Adverse Pregnancy Outcomes

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through **January 2017** birth defects were observed in **22** of **978** live births with first-trimester exposure (**2.2%**, 95% CI, **1.4%** to **3.4%**).¹⁰ 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.¹⁰ Among retrospective cases, there are six reports of CNS defects, including three cases of meningocele 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 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%).¹¹ 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 remains insufficient to rule out a significant increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02% to 0.2%).

A French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester efavirenz exposure.¹² 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 (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.¹³ 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,¹⁴ or an analysis of a national cohort in Italy that included 1,257 pregnancies, 80 after first-trimester efavirenz exposure.¹⁵

Although two small studies (PACTG protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to efavirenz compared with those without exposure, the number of exposures was small (35 exposures in PACTG 219/219C and 42 in P1025) and there is overlap in defect cases between the two studies.¹⁶⁻¹⁸ 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. As a result, the current Perinatal Guidelines do not include the restriction of use **of efavirenz in pregnancy or in women planning pregnancy**, consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy (which note that efavirenz can be used throughout pregnancy).^{19,20} **Efavirenz should be continued in pregnant women receiving a virologically suppressive, efavirenz-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission.**²¹

Additional Information

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.²²⁻²⁵ A retrospective chart review study suggests that efavirenz may decrease the efficacy of levonorgestrel implants (e.g., Jadelle).²⁶ 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 levonorgestrel and efavirenz-based antiretroviral therapy (ART) regimen. In comparison to the ART-naïve women, the women on efavirenz-based regimens had lower levonorgestrel PK.²⁷

Interaction between the etonogestrel-releasing implant and three ARV drug regimens (atazanavir/ritonavir, lopinavir/ritonavir, efavirenz) in postpartum women who chose an etonogestrel implant for contraception were evaluated in P1026s. There was no significant change in the concentration levels of the ARV drugs after insertion of the etonogestrel implant. However, of the three ARV drug regimens, efavirenz use was associated with greatly decreased etonogestrel concentrations to levels that could impair contraceptive efficacy.²⁸ Thus, women receiving efavirenz and using combined oral contraceptive pills, progestin-only pills, or progestin implants should be informed of the possible decreased effectiveness of these contraceptive methods and strongly advised to also use barrier contraception.

Alternative contraceptive regimens for which efficacy is not reduced by concomitant efavirenz 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.²⁹ 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.

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name)	Formulation	Dosing Recommendations	Use in Pregnancy
Efavirenz (EFV) <i>Sustiva</i> (EFV/TDF/FTC) <i>Atripla</i>	EFV (Sustiva)^e <i>Capsules:</i> • 50 mg • 200 mg <i>Tablet:</i> • 600 mg Atripla: • EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet	Standard Adult Dose <i>EFV (Sustiva):</i> • 600 mg once daily at or before bedtime, on empty stomach to reduce side effects <i>Atripla:</i> • 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: The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administration in the first trimester of pregnancy as fetal harm may occur. Although the limited data on first-trimester EFV exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from a 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. As a result, the current Perinatal Guidelines do not include a restriction of use of EFV in pregnant women or in women planning to become pregnant , consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy. EFV should be continued in pregnant women receiving a virologically suppressive EFV-based regimen, because ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission (see Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy).

^a Individual ARV 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

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

^d Only indicated for use in chronic hepatitis B virus infection in adults.

^e Generic formulation available

Key to Abbreviations: ARV = antiretroviral; AUC = area under the curve; EFV = efavirenz; FDA = Food and Drug Administration; FTC = emtricitabine; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization

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Etravirine (Intelence, ETR)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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 in mice and rats for up to approximately 104 weeks. Areas under the concentration-time curve (AUC) were 0.6-fold (mice) and 0.2-fold to 0.7-fold (rats) compared to human AUC due to intolerance of the formulation. In rats and male mice, no significant findings were noted. In female mice, increased incidences of hepatocellular carcinoma and of hepatocellular adenomas or carcinomas combined were seen. The relevance to humans of these liver tumor findings in mice is unknown.¹

Reproduction/Fertility

Etravirine had no effect on fertility and early embryonic development when tested in rats at maternal doses resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).¹

Teratogenicity/Adverse Pregnancy Outcomes

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.¹

Human Studies in Pregnancy

Pharmacokinetics

Etravirine pharmacokinetics (PK) in pregnant women have been reported in two studies. Ramgopal et al. found that total etravirine AUC, C_{\min} , and C_{\max} were increased approximately 1.1-fold to 1.4-fold in the second trimester (n = 13) and third trimester (n = 10) compared with levels in the same women postpartum (n = 10). Differences in unbound etravirine concentrations were less pronounced, with least-squares mean ratios of approximately 0.9 to 1.2.² Similarly, Mulligan et al. found increases by 1.3-fold to 1.9-fold in total etravirine AUC, C_{\min} , and C_{\max} during the third trimester (n = 13) compared with levels in the same women postpartum (n = 8).³ Etravirine was well tolerated in both of these studies.

Placental and Breast Milk Passage

The median (range) ratio of etravirine concentrations in cord blood-to-maternal-plasma at delivery in 7 mother-infant pairs was 0.52 (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 Placental passage of etravirine was described in a report of the use of etravirine, darunavir/ritonavir, 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 14.⁵ 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 AUC₀₋₁₂ 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/**Adverse Pregnancy Outcomes**

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 **Among cases of first-trimester etravirine exposure reported to the Antiretroviral Pregnancy Registry, 1 defect has been noted in 60 live births; due to this low number of cases to date, no conclusions can be made about risk of birth defects.⁷**

Excerpt from **Table 9^a**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Etravirine (ETR) <i>Intence</i>	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 19 mother-infant pairs). ^b Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

^a Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see the [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: ETR= etravirine; PK = pharmacokinetic

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Nevirapine (Viramune, NVP)

(Last updated November 14, 2017; last reviewed November 14, 2017)

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for nevirapine compared with the background rate for major birth defects in a U.S. reference population. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to nevirapine 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 has been observed.

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/Adverse Pregnancy Outcomes

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 An intensive PK study of 59 women with genotype information found that women who had one or two mutations in CYP 2B6 had higher clearance in pregnancy compared to a different group of postpartum women with mutations.⁵ In fast metabolizers (no mutations), no differences in exposure were seen in pregnant women versus postpartum women. 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 0.60–1.02).^{6,7} 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).⁸ 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 0.27.⁹ 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.¹⁰ An additional study in 122 Nigerian mother/infant pairs found that the median (range) milk-to-plasma nevirapine AUC ratio was 0.95 (0.56–1.5). Infant plasma concentrations from exposure through breast milk were 660 ng/mL (104–3,090).⁵

Teratogenicity/Adverse Pregnancy Outcomes

In the **Antiretroviral Pregnancy Registry**, 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 **Antiretroviral Pregnancy Registry**, the prevalence of birth defects was 2.82% (32 of 1,134 births; 95% CI, 1.93% to 3.97%) compared with a total prevalence of 2.76% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.¹¹ Similarly, the French Perinatal Cohort reported no association between nevirapine and birth defects with 71% power to detect a 1.5-fold increase.¹²

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—has been reported in patients with HIV infection 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.¹³ 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 (range 0.04% to 0.40%).^{1,14} 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 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/mm³ 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 U.S. studies have been seen in international cohorts of non-pregnant women, although not all have reported an association with CD4 cell counts >250 cells/mm³.¹⁸ 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/mm³ 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 adverse events and that the relationship between genetic variants and adverse events may vary by race.²⁰⁻²³ Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.¹

Although deaths as a result of hepatic failure have been reported in pregnant women with HIV infection

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 adverse event (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 adverse events associated with nevirapine during pregnancy is not higher than reported for nevirapine in the general population, consistent with data from two multicenter prospective cohorts in which pregnancy was not associated with an increased risk of nevirapine-associated hepatic toxicity.^{26,27} In contrast, an 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

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/mm³ (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/mm³.²⁹ A small case-control study (6 cases, 30 controls) in South Africa reported that pregnancy increased the chance of developing Stevens-Johnson syndrome (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/mm³ only if the benefit clearly outweighs the risk. Women with CD4 cell counts < 250 cells/mm³ can receive nevirapine-based regimens, and women who become pregnant while taking nevirapine and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity (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 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<p>Nevirapine (NVP) <i>Viramune</i> <i>Viramune XR</i> (Extended Release)</p> <p>Note: Generic available for all formulations</p>	<p><u>NVP (Viramune)</u> <i>Tablets:</i> • 200 mg</p> <p><i>Oral Suspension:</i> • 50 mg/5 mL</p> <p><u>Viramune XR</u> <i>Tablets:</i> • 100 mg • 400 mg</p>	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 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. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • PK of immediate release tablets not significantly altered in pregnancy. • No data are available on extended release formulations in pregnancy. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer to fetus.^b</p> <p>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).</p> <p>Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts ≥250/mm³ when first initiating therapy; pregnancy does not appear to increase risk.</p> <p>NVP should be initiated in pregnant women with CD4 cell counts ≥250 cells/mm³ 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.</p> <p>Women who become pregnant while taking NVP-containing regimens and are tolerating them well can continue therapy, regardless of CD4 cell count.</p>

^a Individual ARV 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: CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic

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Rilpivirine (Edurant, RPV)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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. Exposures were 15 and 70 times higher **in pregnancy and lactation**, 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 study presenting pharmacokinetic (PK) and safety data from 32 pregnant women with HIV found median rilpivirine area under the curve (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 EC₉₀ for rilpivirine. PK exposure was highly variable in this study.² **Another study in 16 pregnant women with HIV found similarly decreased exposure by approximately 50% in the third trimester compared to postpartum.**³ These authors recommended therapeutic drug monitoring in the third trimester, and also ensuring that rilpivirine doses are taken with meals. Cervicovaginal fluid rilpivirine concentrations were described in a study of 24 women taking rilpivirine daily during pregnancy and postpartum, which showed **cervicovaginal rilpivirine steady-state concentrations similar to those seen in plasma in the same women.** **Rilpivirine cervicovaginal fluid AUC compared to plasma AUC was higher during pregnancy than postpartum.**⁴

Placental and Breast Milk Passage

One of the PK and safety studies described above included rilpivirine delivery concentration data from **21** mother-infant pairs, with median (range) cord blood rilpivirine plasma concentration of **29.2** ng/mL (<10.0 to **101.5** ng/mL), maternal delivery plasma rilpivirine concentration of **55.2** ng/mL (<10.0 to **233.8** ng/mL) and cord blood/maternal plasma ratio of 0.55 (**0.3 to 0.8**).² Similarly, Colbers et al. found a median (range) cord **blood-to-maternal plasma ratio of 0.5 (0.35–0.81) in 5 women.**³ 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/Adverse Pregnancy Outcomes

Among cases of first-trimester exposures to rilpivirine reported to the Antiretroviral Pregnancy Registry, **the prevalence of birth defects was 0.5% (1 of 202 births; 95% CI, 0.0% to 2.7%) compared with a**

total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁷

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Rilpivirine (RPV) Edurant (RPV/TDF/FTC) Complera (RPV/TAF/FTC) Odefsey	RPV (Edurant) Tablets: • 25 mg Complera: • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet Odefsey: • RPV 25 mg plus TAF 25 mg plus FTC 200 mg tablet	Standard Adult Dose RPV (Edurant): • 25 mg once daily with food Complera: • 1 tablet once daily with food Odefsey: • 1 tablet once daily with food PK in Pregnancy: • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 50% in pregnancy compared with postpartum. While most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. Dosing in Pregnancy: • While RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently.	Moderate to high placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).

^a Individual ARV 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: AUC = area under the curve; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; 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 protease inhibitor (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 November 14, 2017; last reviewed November 14, 2017)

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 Studies

Carcinogenicity

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/Adverse Pregnancy Outcomes

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.^{2,3}

Placental and Breast Milk Passage

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

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 2 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 non-pregnant adults with HIV infection.^{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 historic controls with HIV infection.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}

Atazanavir/ritonavir combined with tenofovir disoproxil fumarate (TDF) and emtricitabine provides a complete once-a-day antiretroviral therapy (ART) 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-naïve patients) in pregnant women in their third trimester.¹³ In a therapeutic drug monitoring (TDM) study of 103 women (mostly African) 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 controls with HIV infection 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 patients with HIV infection 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 in the second and third trimesters only for antiretroviral-experienced pregnant women who are 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 [Adult and Adolescent Guidelines](#).

Placental and Breast Milk Passage

In studies of women receiving atazanavir/ritonavir 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 3 women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.¹⁵

Teratogenicity/Adverse Pregnancy Outcomes

In a multicenter, U.S. cohort of children exposed to HIV who were uninfected, 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. Although 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 defects with first-trimester atazanavir exposure was 2.1% (26 of 1,227 births; 95% CI, 1.4% to 3.1%) 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 In a different study, PI-based ART regimens were associated with elevated levels of estradiol in maternal and cord blood of pregnant women living with HIV and these levels correlated with lower birth weight percentile.¹⁹

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.²⁰ 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.^{1,5,7,8,10,21-23} 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.^{21,22} Elevated neonatal bilirubin in neonates exposed to atazanavir is not associated with UGT-1 genotypes associated with decreased UGT function.²³

In an evaluation of neurodevelopmental outcomes in 374 infants aged 9 to 15 months who were exposed to HIV but were uninfected, the adjusted mean score on the language and social-emotional domains of the Bayley-III test was significantly lower for infants with perinatal exposure to atazanavir compared to those with exposure to other drugs.^{24,25} In a study of language assessments among 792 children (aged 1 and 2 years) who were exposed to HIV but were uninfected, children with atazanavir exposure 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 children without atazanavir exposure but the association was not significant at 24 months.²⁶

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 2 (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life.²⁷

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<p>Atazanavir (ATV) <i>Reyataz</i></p> <p>Note: Must be combined with low-dose RTV boosting in pregnancy</p> <p>Atazanavir/ Cobicistat (ATV/COBI) <i>Evotaz</i></p>	<p><u>Atazanavir (Reyataz)</u></p> <p><u>Capsules:</u></p> <ul style="list-style-type: none"> • 150 mg • 200 mg • 300 mg <p><u>Oral Powder:</u></p> <ul style="list-style-type: none"> • 50 mg packet <p><u>Evotaz:</u></p> <ul style="list-style-type: none"> • ATV 300 mg plus COBI 150 mg tablet 	<p>Standard Adult Dose</p> <p><u>Atazanavir (Reyataz)</u> <i>ARV-Naive Patients</i></p> <p><u>Without RTV Boosting:</u></p> <ul style="list-style-type: none"> • ATV 400 mg once daily with food; ATV without RTV boosting is not recommended when used with TDF, H₂-receptor antagonists, or PPIs, or during pregnancy. <p><u>With RTV Boosting:</u></p> <ul style="list-style-type: none"> • 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 <p><i>ARV-Experienced Patients:</i></p> <ul style="list-style-type: none"> • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV. • If combined with an H₂-receptor antagonist: ATV 300 mg plus RTV 100 mg once daily with food • If combined with an H₂-receptor antagonist and TDF: ATV 400 mg plus RTV 100 mg once daily with food <p><u>Powder Formulation:</u></p> <ul style="list-style-type: none"> • Oral powder is taken once daily with food at the same recommended adult dosage as the capsules along with RTV. <p><u>Atazanavir/Cobicistat (Evotaz):</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food. <p><u>PK in Pregnancy</u></p> <p><u>Atazanavir (Reyataz):</u></p> <ul style="list-style-type: none"> • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H₂-receptor antagonist. <p><u>Atazanavir/Cobicistat (Evotaz):</u></p> <ul style="list-style-type: none"> • No PK studies in human pregnancy. <p><u>Dosing in Pregnancy</u></p> <p><u>Atazanavir (Reyataz):</u></p> <ul style="list-style-type: none"> • Use of unboosted ATV is not recommended during pregnancy. • Use of ATV not recommended for treatment-experienced pregnant women taking TDF and an H₂-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 H₂-receptor antagonist. <p><u>Atazanavir/Cobicistat (Evotaz):</u></p> <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation in pregnancy (see Cobicistat section). 	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>Must be given as low-dose RTV-boosted regimen in pregnancy.</p> <p>Effect of <i>in utero</i> 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.</p> <p>Oral powder (but not capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria.</p>

^a Individual ARV 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; 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 November 14, 2017; last updated November 14, 2017)

Available reports to the Antiretroviral Pregnancy Registry indicate no increase in the rate of overall birth defects with first trimester darunavir exposure compared to control populations and are of sufficient number to rule out a more than 2-fold increase in the rate of birth defects.

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/Adverse Pregnancy Outcomes

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

Several studies of the pharmacokinetics (PK) of darunavir/ritonavir during pregnancy have been completed.²⁻⁶ Darunavir plasma area under the curve (AUC) during the third trimester compared with postpartum was reduced by 17% to 26% with 600 mg/100 mg twice a day dosing and by 33% to 39% with 800 mg/100 mg once a day dosing.²⁻⁵ Darunavir trough concentration during the third trimester compared with postpartum was reduced by 8% to 12% with 600 mg/100 mg twice a day dosing and by 42% to 58% with 800 mg/100 mg once a day dosing.³⁻⁵ Three studies measured darunavir protein binding during pregnancy. One study found no change in darunavir protein binding during the third trimester. The other two studies reported decreased unbound darunavir concentrations during pregnancy that were not felt to be clinically significant.^{2,4,5} Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, especially for antiretroviral-experienced patients.

The FDA guidance indicates that once-daily darunavir/ritonavir 800 mg/100 mg could be considered in pregnant women who are already on a stable once-daily darunavir/ritonavir regimen prior to pregnancy, are virologically suppressed, and in whom a change to a twice daily darunavir/ritonavir regimen may compromise tolerability or adherence;¹ however, based on review of available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission continues not to recommend once-daily dosing of darunavir in pregnancy. 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.⁶ 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%.⁷ In 4 studies reporting data from between 8 and 14 subjects each, the median ratio of darunavir concentration in cord blood to that in maternal delivery plasma ranged from 13% to 24%.^{2-4,8} No data are available describing breast milk passage of darunavir in humans.

Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester darunavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.5% (10 of 407 births; 95% CI, 1.2% to 4.5%), which is a sufficient number of first-trimester exposures to conclude that there is not a two fold increase in the risk of overall birth defects compared to control populations.⁹

Other Safety Issues

No safety issues have been observed in case reports and PK studies of darunavir in pregnancy.^{2-6,8,10-14}

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Darunavir (DRV) <i>Prezista</i> Note: Must be combined with low-dose RTV or COBI boosting Darunavir/ Cobicistat (DRV/COBI) <i>Prezcobix</i>	<u>DRV Tablets:</u> <ul style="list-style-type: none"> • 75 mg • 150 mg • 600 mg • 800 mg <u>DRV Oral Suspension:</u> <ul style="list-style-type: none"> • 100 mg/mL <u>Prezcobix Tablet (Co- Formulated):</u> <ul style="list-style-type: none"> • DRV 800 mg plus COBI 150 mg 	<u>Standard Adult Dose</u> <i>ARV-Naive Patients:</i> <ul style="list-style-type: none"> • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food <i>ARV-Experienced Patients:</i> <u>If No DRV Resistance Mutations:</u> <ul style="list-style-type: none"> • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food <u>If Any DRV Resistance Mutations:</u> <ul style="list-style-type: none"> • DRV 600 mg plus RTV 100 mg twice daily with food <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> • Decreased exposure in pregnancy with use of DRV/r. <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> • The Panel does not recommend once-daily dosing with DRV/r during pregnancy. • Twice-daily DRV/r 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/c 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 boosted with low-dose RTV.

^a Individual ARV 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; **DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir;** PK = pharmacokinetic; RTV = ritonavir

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Fosamprenavir (Lexiva, FPV)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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](#)).

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/**Adverse Pregnancy Outcomes**

Two birth defects out of **110** live births with first-trimester exposure and 2 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 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Fosamprenavir (FPV) <i>Lexiva (a prodrug of amprenavir)</i> Note: Must be combined with low-dose RTV boosting in pregnancy	<u>Tablets:</u> • 700 mg <u>Oral Suspension:</u> • 50 mg/mL	<u>Standard Adult Dose</u> <i>ARV-Naive Patients:</i> • FPV 1400 mg twice daily without food, <i>or</i> • FPV 1400 mg plus RTV 100 or 200 mg once daily without food, <i>or</i> • FPV 700 mg plus RTV 100 mg twice daily without food <i>PI-Experienced Patients</i> • Once-daily dosing not recommended • FPV 700 mg plus RTV 100 mg twice daily without food <i>Co-Administered with EFV:</i> • FPV 700 mg plus RTV 100 mg twice daily without food; <i>or</i> • FPV 1400 mg plus RTV 300 mg once daily without food <u>PK in Pregnancy:</u> • 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. <u>Dosing in Pregnancy:</u> • 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 ARV 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; EFV = efavirenz; FPV = fosamprenavir; PI = protease inhibitor; PK = pharmacokinetic; RTV= ritonavir

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Indinavir (Crixivan, IDV)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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 pregnant patients with HIV 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 2 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 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/**Adverse Pregnancy Outcomes**

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 has not observed an increase in birth defects with indinavir.^{9,10} Among cases of first-trimester indinavir exposure reported to the Antiretroviral Pregnancy Registry, 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 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Indinavir (IDV) <i>Crixivan</i> Note: Must be combined with low-dose RTV boosting in pregnancy	Capsules: • 200 mg • 400 mg	Standard Adult Dose <i>Without RTV Boosting:</i> • IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal. <i>With RTV Boosting:</i> • 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 Antiretroviral Pregnancy Registry (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 ARV 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: APR = Antiretroviral Pregnancy Registry; IDV = indinavir; PK = pharmacokinetic; RTV = ritonavir

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Lopinavir/Ritonavir (Kaletra, LPV/r)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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} 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 (ARV)-naïve 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; larger women (>100 kg) or women who missed a dose were 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 C₁₂ did not differ throughout pregnancy, even with an increased dose of 500/125 mg. **Modeling of these data concluded that standard dosing should be effective with susceptible virus.**^{15,16} 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.¹⁷ 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 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.¹⁸

These studies have led some experts to support use of an increased dose of LPV/r in pregnant women with HIV during the second and third trimesters, especially in women who are PI-experienced 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.¹⁹ 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.¹⁹⁻²³

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and lopinavir or ritonavir with 85% power to detect a 1.5-fold increase.²⁴ The Pediatric HIV/AIDS Cohort Study found no association between lopinavir and congenital anomalies.²⁵ 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 populations without HIV.²⁶ 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 2.1% (30 of 1,400; 95% CI, 1.5% to 3.1%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²⁷ For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to the [Combination Antiretroviral Drug Regimens and Pregnancy Outcome](#) section.

In the PROMISE study, LPV/r with zidovudine plus lamivudine or with tenofovir disoproxil fumarate plus lamivudine resulted in decreased transmission rates compared to zidovudine alone, but also increased incidence of low birth weight (<2,500 g).²⁸ Compared to zidovudine alone, zidovudine plus lamivudine/ritonavir was associated with increased rates of preterm delivery (<37 weeks). PHACS SMARTT also found an increased rate of preterm birth with PI-based ARV therapy, although not with specific individual drugs.²⁹ Similarly, a study in China found that PI-based regimens had higher rates of preterm birth than did non-nucleoside-reverse-transcriptase-inhibitor-based regimens.³⁰

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 adverse events (e.g., 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), 9 of whom were born prematurely, who received LPV/r and experienced life-threatening events.³¹ In a separate report comparing 50 newborns exposed to HIV treated with LPV/r after birth to 108 neonates exposed to HIV treated with zidovudine alone, elevated concentrations of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21 α -hydroxylase activity, were seen only in the infants exposed to lopinavir. All term infants were asymptomatic but 3 of 8 preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.³² 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 9^a

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
Lopinavir/ Ritonavir (LPV/r) <i>Kaletra</i> Note: Generic available for some formulations	<u>Tablets (Co-Formulated):</u> <ul style="list-style-type: none"> • LPV 200 mg plus RTV 50 mg • LPV 100 mg plus RTV 25 mg <u>Oral Solution:</u> <ul style="list-style-type: none"> • LPV 400 mg plus RTV 100 mg/5 mL 	<u>Standard Adult Dose:</u> <ul style="list-style-type: none"> • LPV 400 mg plus RTV 100 mg twice daily, or • LPV 800 mg plus RTV 200 mg once daily <u>Tablets:</u> <ul style="list-style-type: none"> • Take without regard to food. <u>Oral Solution:</u> <ul style="list-style-type: none"> • Take with food. <u>With EFV or NVP (PI-Naive or PI-Experienced Patients):</u> <ul style="list-style-type: none"> • 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 <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> • 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. <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> • 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 or LPV 500 mg plus RTV 125 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 ARV 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: 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 November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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 women with HIV and their infants.² In the first 9 pregnant 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 2 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 currently marketed nelfinavir 625-mg tablet formulation (given as 1250 mg twice daily) in 25 women at 30 to 36 weeks' gestation (and 12 women 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

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 through 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/*Adverse Pregnancy Outcomes*

In the Antiretroviral Pregnancy Registry, 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 Antiretroviral Pregnancy Registry, prevalence of birth defects was 3.9% (47 of 1,212 births; 95% CI, 2.9% 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

Infant Safety Outcomes

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of nelfinavir led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.¹⁰

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Nelfinavir (NFV) <i>Viracept</i>	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 ARV 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: NFV = nelfinavir; PK = pharmacokinetic

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Saquinavir (Invirase, SQV)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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 800 to 1200 mg of the original hard-gel capsule formulation and 100 mg ritonavir demonstrated reduced saquinavir exposures compared with nonpregnant adults, but adequate C_{\min} in the majority of subjects.²⁻⁴ 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 have been studied in pregnant women in two studies.^{5,6} One study performed intensive sampling on pregnant women with HIV 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.⁵ 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.⁷ 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 pregnant women with HIV 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.⁶

Placental and Breast Milk Passage

In a Phase 1 study in pregnant women and their infants (PACTG 386), transplacental passage of saquinavir was minimal.⁸ 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.⁹ It is not known whether saquinavir is excreted in human milk.

Teratogenicity/**Adverse Pregnancy Outcomes**

The 182 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.¹⁰

Other Safety Information

One study of 42 pregnant women receiving antiretroviral therapy that included saquinavir/ritonavir 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).¹¹ In a study of 62 pregnant women on a regimen that included saquinavir/ritonavir, one severe adverse event occurred (maternal Grade 3 hepatotoxicity).⁶

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of saquinavir led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological outcomes. Late language emergence was more likely among saquinavir-exposed infants at 1 year (OR 2.72, 95% CI, 1.09, 6.91, $P = 0.03$), but not at 2 years. No significant differences were observed for other neurodevelopmental outcomes.¹²

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Saquinavir (SQV) <i>Invirase</i> Note: Must be combined with low-dose RTV for PK boosting	<u>Tablet:</u> • 500 mg <u>Capsule:</u> • 200 mg	<u>Standard Adult Dose:</u> • SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal <u>PK in Pregnancy:</u> • Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change. <u>Dosing in Pregnancy:</u> • 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 ARV 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: ECG = electrocardiogram; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir

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Tipranavir (Aptivus, TPV)

(Last reviewed November 14, 2017; last updated November 14, 2017)

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 doses ranging from 30 to 300 mg/kg/day tipranavir, with or without 40 mg/kg/day ritonavir; all doses resulted in systemic exposures below those in humans receiving the recommended dose. Incidence of benign hepatocellular adenomas, combined adenomas/carcinomas, and hepatocellular carcinoma was increased in both sexes with tipranavir/ritonavir. The clinical relevance of the carcinogenic findings in mice is unknown. Rats were administered doses ranging from 30 to 300 mg/kg/day tipranavir, with or without ritonavir. No drug-related findings were observed in male rats. At the highest dose of tipranavir (approximately equivalent to exposure in humans at the recommended therapeutic dose), an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. 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 tipranavir/ritonavir administered twice daily).¹

Teratogenicity/Adverse Pregnancy Outcomes

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/Adverse Pregnancy Outcomes

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

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Tipranavir (TPV) <i>Aptivus</i> Note: Must be combined with RTV for PK boosting	<u>Capsules:</u> • 250 mg <u>Oral Solution:</u> • 100 mg/mL	<u>Standard Adult Dose:</u> • TPV 500 mg plus RTV 200 mg twice daily <u>With RTV Tablets:</u> • Take with food. <u>With RTV Capsules or Solution:</u> • Take without regard to food; however, administering with food may help make the dose more tolerable. <u>PK in Pregnancy:</u> • Limited PK data in human pregnancy <u>Dosing in Pregnancy:</u> • Insufficient data to make dosing recommendation	Moderate placental transfer to fetus reported in 1 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 ARV 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: 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 2 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. Maraviroc is a CCR5 co-receptor antagonist that interferes with viral entry at the chemokine co-receptor level.

Enfuvirtide (Fuzeon, T-20)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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/Adverse Pregnancy Outcomes

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.¹

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/**Adverse Pregnancy Outcomes**

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 9^a

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
Enfuvirtide (T-20) Fuzeon	Injectable: <ul style="list-style-type: none">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: <ul style="list-style-type: none">90 mg (1 mL) twice daily without regard to meals PK in Pregnancy: <ul style="list-style-type: none">No PK data in human pregnancy. Dosing in Pregnancy: <ul style="list-style-type: none">Insufficient data to make dosing recommendation.	Minimal to low placental transfer to fetus. ^b No data on human teratogenicity.

^a Individual ARV 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; PK = pharmacokinetic; SQ = subcutaneous; T-20 = enfuvirtide

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Maraviroc (Selzentry, MVC)

(Last updated November 14, 2017; last reviewed November 14, 2017)

The limited data available on the use of maraviroc during pregnancy are not sufficient to assess any potential drug-associated risk of birth defects.

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 **in rats** showed no drug-related increases in tumor incidence **at exposures approximately 11 times those observed in humans at the therapeutic dose.**

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/Adverse Pregnancy Outcomes

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with maraviroc. During organogenesis in the rat and rabbit, systemic exposures (area under the curve [AUC]) to maraviroc were approximately 20 times (in rats) and 5 times (in rabbits) the exposure in humans at the recommended 300-mg, twice-daily dose. In the rat prenatal and postnatal development study, maternal maraviroc AUC was approximately 14 times the exposure in humans at the recommended 300-mg, twice-daily dose.¹

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 postpartum. 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

Placental and Breast Milk Passage

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.⁵ 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).^{3,6} Whether maraviroc is secreted into human milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

The 26 cases of first-trimester exposure that have been monitored to date in the Antiretroviral Pregnancy Registry and other available first-trimester exposure data are insufficient to make a risk determination regarding birth defects.^{7,8}

Other Safety Information

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.⁹ 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.¹⁰

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Maraviroc (MVC) Selzentry	Tablets: • 150 mg • 300 mg	<p>Standard Adult Dose:</p> <ul style="list-style-type: none"> • 300 mg twice daily with or without food • Maraviroc should only be used for patients with CCR5-tropic virus (and no X4-tropic virus). <p>Dose Adjustments:</p> <ul style="list-style-type: none"> • 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, itraconazole. <p>PK in Pregnancy:</p> <ul style="list-style-type: none"> • 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. <p>Dosing in Pregnancy:</p> <ul style="list-style-type: none"> • Standard adult dosing adjusted for concomitant ARV use appears appropriate. 	<p>No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans.</p> <p>MVC placental passage category should be moderate.^b</p>

^a Individual ARV 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:

Key to Acronyms: 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 November 14, 2017; last reviewed November 14, 2017)

Preliminary human data suggest that use of dolutegravir during pregnancy is not associated with an increased risk of birth defects and miscarriage.

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.¹

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.¹

Animal Teratogenicity/Developmental Toxicity

Studies in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity or effect on reproductive function with dolutegravir.¹

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.¹

Human Studies in Pregnancy

Pharmacokinetics

Reports of dolutegravir pharmacokinetics (PK) in human pregnancy are limited to **two studies and a series of case reports**.²⁻⁷ In a safety and PK study of 21 pregnant women, dolutegravir plasma concentrations were lower during 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

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pregnant women.⁴ In a study of five European pregnant women, dolutegravir was well tolerated and plasma exposures during pregnancy were similar to that postpartum.⁷ In the case reports, dolutegravir was used safely and effectively in pregnancy and plasma exposures were adequate.^{2,3,5,6}

Placental and Breast Milk Passage

Placental transfer of dolutegravir in an *ex vivo* perfusion model was high, with a fetal-to-maternal ratio of 60%.⁸ High placental transfer of dolutegravir has been confirmed in several of the case reports.^{2,5,6} In a report from one breast feeding mother receiving dolutegravir and her infant, the dolutegravir breast milk-to-maternal-plasma-concentration ratio was 0.02 and the plasma dolutegravir concentration in the infant was 0.10 mg/L, equal to the dolutegravir target trough plasma concentration in treatment-naive patients.⁹

Teratogenicity Data

As of January 31, 2017, the overall birth defect rate was 3.0% (4 infants) in 133 live births from 142 pregnancies with exposure to dolutegravir reported to the Antiretroviral Pregnancy Registry.¹⁰ In the larger PK study in pregnant women, discussed above, birth abnormalities were reported in 4 of 18 infants: total anomalous pulmonary venous return; cystic fibrosis and polycystic right kidney; congenital chin tremor; sacral dimple with filum terminale fibrolipoma.¹¹ In 2 reviews of clinical experience with pregnant women receiving dolutegravir, birth defects were noted in 3 infants born to 42 European women and in no infants born to 116 women from Botswana receiving dolutegravir during the first trimester.^{12,13}

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Dolutegravir (DTG) <i>Tivicay</i>	DTG Tablets: • 50 mg	Standard Adult Dose <i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive Patients)</i>	High placental transfer to fetus.
(DTG/ABC/3TC) <i>Triumeq</i>	Triumeq: • DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet	DTG (Tivicay): • 1 tablet once daily, without regard to food. DTG/ABC/3TC (Triumeq): • 1 tablet once daily, without regard to food. <i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced</i> DTG (Tivicay): • 1 tablet twice daily, without regard to food. PK in Pregnancy: • AUC may be decreased during the third trimester compared with postpartum, but good viral suppression in third trimester recipients. Dosing in Pregnancy: • No change in dose indicated.	No evidence of teratogenicity in mice, rats, or rabbits. Preliminary data suggest no increased risk of teratogenicity in humans.

^a Individual ARV 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 Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; EFV = efavirenz; FPV/r = fosamprenavir/ritonavir; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

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Elvitegravir (Vitekta, EVG)

(Last updated November 14, 2017; last reviewed November 14, 2017)

There are insufficient human data on the use of elvitegravir in pregnancy to inform a drug-associated risk determination for birth defects and miscarriage.

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/Adverse Pregnancy Outcomes

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.¹

Human Studies in Pregnancy

Pharmacokinetics

A study with pharmacokinetic (PK) and safety data from 29 pregnant women with HIV receiving a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (TDF) has been presented. Elvitegravir area under the curve (AUC) was 43% to 50% lower and C₂₄ was 86% to 87% lower in the second and third trimesters compared to levels in the same women postpartum. Cobicistat AUC was 54% to 57% lower and C₂₄ was 72% to 76% lower in the second and third trimesters compared to levels in the same women postpartum. Elvitegravir AUC was below 23 mcg*hr/mL (the 10th percentile for nonpregnant adults) in 50% of women during the second trimester, 55% during the third trimester and 12% postpartum. Plasma HIV RNA at delivery was less than 50 copies/mL for 14 of the 19 women (74%) for whom data were available.² A case report of elvitegravir and cobicistat PK, safety, and efficacy in a single pregnant woman found similar reductions in elvitegravir and cobicistat exposure during pregnancy, including elvitegravir C_{min} below the suggested target concentration of 0.13 mg/L. Despite the low elvitegravir exposure in this woman, viral load remained undetectable throughout the pregnancy.³

Placental and Breast Milk Passage

A large study of elvitegravir PK and safety observed that elvitegravir crossed the placenta well and had an elimination half-life in neonates similar to that in non-pregnant adults. Cobicistat was not detected in the plasma of any neonates.² In the single case report cited above, maternal delivery and cord blood plasma elvitegravir concentrations were both 0.30 mg/L, while cobicistat was not detectable in maternal delivery and cord blood samples.³ No data are available on human breast milk transfer of elvitegravir.

Teratogenicity/Adverse Pregnancy Outcomes

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.⁴ In the PK and safety study described above, congenital anomalies were reported in two of 26 infants: one infant with amniotic band syndrome, microcephaly, and intrauterine growth restriction and one infant with ulnar postaxial polydactyly.

(supernumerary digit).² In a study of the safety and efficacy of the elvitegravir, cobicistat, emtricitabine and TDF combination product in adult women with HIV, there were 10 infants born to study women and none had birth defects.⁵

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Elvitegravir (EVG) <i>Vitekta</i> Note: As of October 2017, <i>Vitekta</i> (i.e., EVG as a single-entity formulation) is no longer available Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate (EVG/COBI/ FTC/TDF) <i>Stribild</i> Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide (EVG/COBI/FTC/TAF) <i>Genvoya</i>	Tablet (Stribild): <ul style="list-style-type: none"> • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg Tablet (Genvoya): <ul style="list-style-type: none"> • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg 	Standard Adult Dose (Stribild and Genvoya): <ul style="list-style-type: none"> • 1 tablet once daily with food. PK in Pregnancy: <ul style="list-style-type: none"> • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy. Dosing in Pregnancy: <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation. 	Evidence of high placental transfer of EVG and low transfer of COBI. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. . EVG/c is not recommended for initial use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/c regimen is continued, viral load should be monitored frequently, and TDM (if available) may be useful.

^a Individual ARV 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 Acronyms: COBI = cobicistat; EVG = elvitegravir; **EVG/c = elvitegravir/cobicistat**; FTC = emtricitabine PK = pharmacokinetic; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; **TDM = therapeutic drug monitoring**

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Raltegravir (Isentress, RAL)

(Last updated November 14, 2017; last reviewed November 14, 2017)

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

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/Adverse Pregnancy Outcomes

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_{0-12hr} 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 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 PKs 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).³ In a case report of an infant born at 30 weeks' gestation after the mother had received 3 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

Caution is advised when raltegravir is co-administered with atazanavir, a UGT1A1 inhibitor, because the combination results in elevated levels of raltegravir, based on a study in healthy, adult non-pregnant women.⁷

Placental and Breast Milk Passage

High bidirectional transfer of raltegravir across the placenta was demonstrated in an *ex vivo* study of term placentas from normal pregnancies and established that raltegravir crosses the placenta.⁸

***In vivo* human studies have confirmed** that raltegravir readily crosses 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.^{3,9} Other case reports have shown cord blood/maternal blood drug level ratios of 1.00 to 1.06.^{10,11,12} In a series of 3 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 1.88.¹³

Whether raltegravir is secreted in human breast milk is unknown.

Teratogenicity/Adverse Birth Outcomes

As of **January 31, 2017, seven** cases with defects have been reported among **263** infants with first-trimester exposure to raltegravir included in the Antiretroviral Pregnancy Registry. The prevalence of birth defects in exposed cases was **2.7 (95% CI, 1.1–5.4) compared with a 2.8 % total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.**¹⁴

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 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.¹⁵⁻²¹

However, in 1 case report, 10- to 23-fold increases in maternal liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.²² Drug levels were not measured.

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.²³ In a study of 155 **non-pregnant** adults with HIV, mean age 49.2 years, who 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.²⁴

Because raltegravir is highly protein bound to albumin, there is concern about displacement of bilirubin from albumin in the neonate, potentially increasing the risk of neonatal hyperbilirubinemia. In an *in vitro* study of the effect of raltegravir on bilirubin-albumin binding, raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5 µM and 10 µM, caused a small but statistically significant increase in unbound bilirubin at 100 µM, and caused potentially harmful increases at 500 and 1000 µM.²⁵ 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).²⁵ In the P1097 study, one (4.6%) infant received phototherapy for treatment of hyperbilirubinemia, but this was judged not related to maternal raltegravir use.⁹ Raltegravir should not be used in neonates until PK and toxicity studies have been completed.^{9,25} In the P1097 study, no infant AEs were determined to be related to maternal raltegravir use.⁹

In a retrospective study of 31 pregnant women receiving raltegravir at a standard dose as part of a standard antiretroviral therapy regimen or as part of an intensification regimen late in pregnancy (median gestational age 34 weeks), mild elevation of transaminases in 35% of neonates was reported.²⁶

Chewable tablets contain phenylalanine.

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Raltegravir (RAL) <i>Isentress</i> Isentress HD	<u>Isentress</u> <i>Film-Coated Tablets:</i> • 400 mg <i>Chewable Tablets:</i> • 25 mg • 100 mg Isentress HD <i>Film-Coated Tablets:</i> • 600 mg	<u>Standard Adult Dose:</u> • 400-mg film-coated tablets twice daily without regard to food. • Two 600-mg film-coated (1200 mg) once daily for treatment-naïve patients or patients already virologically suppressed on initial regimen of RAL 400 mg BID without regard to food • Chewable and oral suspension doses are not interchangeable to either film-coated tablets or to each other. <u>With Rifampin:</u> • Two 400-mg film-coated tablets (800 mg) twice daily without regard to food. <u>PK in Pregnancy:</u> • Decreased levels in third trimester not of sufficient magnitude to warrant change in dosing. <u>Dosing in Pregnancy:</u> • No change in dose indicated. • Once-daily dosing (i.e., two 600-mg film-coated tablets) should not be used in pregnant women until more information is available.	High placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). 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 ARV 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 Acronyms: PK = pharmacokinetic; RAL = raltegravir

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Pharmaco-Enhancers

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 November 14, 2017, last reviewed November 14, 2017)

Cobicistat has insufficient data on human use in pregnancy to inform a drug-associated risk determination for birth defects or miscarriage.

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/Adverse Pregnancy Outcomes

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

A single case report found that cobicistat area under the curve (AUC) was reduced by 44% during the third trimester of pregnancy.³ **A recent abstract described cobicistat pharmacokinetics (PK) in paired third-trimester and postpartum evaluations from 15 pregnant women taking concomitant elvitegravir. Cobicistat AUC was significantly reduced by 57% in the third trimester. Post-dose concentrations (at 24 hours) were reduced by at least 76%; cobicistat was below detection (<10 ng/mL) in most trough samples in pregnancy. Oral clearance of cobicistat was more than doubled during pregnancy.⁴ The pharmaco-enhancing effect of cobicistat on elvitegravir was impacted during pregnancy; elvitegravir AUC was reduced by 42% and trough concentrations were reduced by 87% in the third trimester compared to postpartum. No data are available on the impact of pregnancy on the pharmaco-enhancing activity of cobicistat for other coadministered antiretroviral drugs during pregnancy, such as darunavir or atazanavir.**

Placental and Breast Milk Passage

No data are available on breast milk passage of cobicistat in humans. A study in 10 women found a median cord/maternal plasma concentration ratio of 0.09. This study also found measurable concentrations of cobicistat in placental tissue and cord blood peripheral blood mononuclear cells (PBMC), with a cord/maternal PBMC ratio of 0.49.⁵ In 16 neonates, cobicistat was below detection in all washout PK samples taken between 2 hours and 9 days post-delivery.⁴

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, 1 birth defect has been reported in 83 live births with first-trimester exposure. The number of first-trimester exposures to cobicistat in humans is insufficient to be able to make a risk determination.²

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
Cobicistat (COBI) <i>Tyboost</i>	<u>Tablet (Tyboost):</u> • 150 mg	<u>Standard Adult Dose</u> <i>Tyboost:</i> • As an alternative PK booster with ATV or DRV/r: 1 tablet (150 mg) once daily with food.	Low placental transfer to fetus.^b
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/COBI/ TDF/FTC) <i>Stribild</i>	<u>Tablet (Stribild):</u> • EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg	<i>Stribild, Genvoya, Evotaz, Prezcobix:</i> • 1 tablet once daily with food.	Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (EVG/COBI/TAF/FTC) <i>Genvoya</i>	<u>Tablet (Genvoya):</u> • EVG 150 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg	<u>PK in Pregnancy:</u> • Based on limited data, COBI exposure and pharmaco-enhancing effect are markedly reduced in pregnancy.	
Atazanavir/Cobicistat (ATV/COBI) <i>Evotaz</i>	<u>Tablet (Evotaz):</u> • ATV 300 mg plus COBI 150 mg	<u>Dosing in Pregnancy:</u> • While COBI exposure is markedly reduced during pregnancy, higher than standard doses have not been studied. The Panel recommends the use of RTV as the preferred pharmaco-enhancer during pregnancy until more data are available on COBI activity during pregnancy.	
Darunavir/Cobicistat (DRV/COBI) <i>Prezcobix</i>	<u>Tablet (Prezcobix):</u> • DRV 800 mg plus COBI 150 mg		

^a Individual ARV 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 Acronyms: ATV = atazanavir; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; EVG = elvitegravir; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate

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Ritonavir (Norvir, RTV)

(Last updated November 14, 2017; last reviewed November 14, 2017)

Available data from the Antiretroviral Pregnancy Registry show no difference between the rate of overall birth defects in infants born to mothers who are taking ritonavir and the background rate of birth defects in a U.S. reference population. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to be able to detect at least a 1.5-fold increase in risk of overall birth defects; however, no such increase has been observed. Ritonavir oral solution is not recommended during pregnancy, because this formulation contains alcohol and there is no known safe level of alcohol exposure during pregnancy.

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/Adverse Pregnancy Outcomes

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 1/2 safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in combination with zidovudine and lamivudine in pregnant women living with HIV 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 1 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 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/**Adverse Pregnancy Outcomes**

In the Antiretroviral Pregnancy Registry, 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 **Antiretroviral Pregnancy Registry**, the prevalence of birth defects was **2.2% (67 of 3056** births; 95% CI, **1.7% to 2.8%**) 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 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Ritonavir (RTV) Norvir	<p>Capsules:</p> <ul style="list-style-type: none"> • 100 mg <p>Tablets:</p> <ul style="list-style-type: none"> • 100 mg <p>Oral Solution:</p> <ul style="list-style-type: none"> • 80 mg/mL <p>Powder:</p> <ul style="list-style-type: none"> • 100 mg/sachet 	<p><u>Standard Adult Dose as PK Booster for Other PIs:</u></p> <ul style="list-style-type: none"> • 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) <p><u>Tablet:</u></p> <ul style="list-style-type: none"> • Take with food. <p><u>Capsule or Oral Solution:</u></p> <ul style="list-style-type: none"> • To improve tolerability, recommended to take with food if possible. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Lower levels during pregnancy compared with postpartum. <p><u>Dosing in Pregnancy:</u></p> <p>No dosage adjustment necessary when used as booster.</p>	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>Should only be used as low-dose booster for other PIs.</p> <p>Oral solution contains 43% alcohol and is therefore not recommended during pregnancy, because there is no known safe level of alcohol exposure during pregnancy.</p>

^a Individual ARV 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: 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>

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	anteartum
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

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	<i>Mycobacterium avium</i> complex
mtDNA	mitochondrial DNA
MVC	maraviroc

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	<i>Pneumocystis jirovecii</i> 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

UGT	uridine diphosphate glucuronosyltransferase
WHO	World Health Organization
ZDV	zidovudine