

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



Developed by the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

## How to Cite the Perinatal Guidelines:

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.

Accessed (insert date) [include page numbers, table number, etc. if applicable]

It is emphasized that concepts 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>).



access AIDSinfo  
mobile site

## What's New in the Guidelines (Last updated March 28, 2014; last reviewed March 28, 2014)

Key changes to the Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions to Reduce Perinatal HIV Transmission in the United States are summarized below. Some content has been reorganized and revised to enhance usability. Text, appendices, and references have been updated to include new data and publications where relevant. The terms “mother-to-child transmission (MTCT)” and “prevention of mother-to-child transmission (PMTCT)” have been replaced with “perinatal transmission” and “prevention of perinatal transmission,” respectively. All changes are highlighted throughout the guidelines.

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

- The Panel recommends that all HIV-infected women contemplating pregnancy be on a maximally suppressive antiretroviral (ARV) regimen (**AII**).
- HIV-infected women who do not desire pregnancy should be offered effective and appropriate contraceptive methods. They can use all available contraceptive methods, including hormonal contraception and emergency contraception, as appropriate.
- Further discussion about drug interactions between ARV agents and hormonal contraceptives has been added, including revised and updated [Table 3: Drug Interactions between Antiretroviral Agents and Hormonal Contraceptives](#).

### Reproductive Options for HIV-Concordant and Serodiscordant Couples

- The Panel recommends that HIV-infected partner(s) in HIV-seroconcordant and HIV-serodiscordant couples planning pregnancy attain maximum viral suppression before attempting conception (**AIII**).
- The Panel notes that periconception administration of ARV pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission (**CIII**). A new table has been added reviewing clinical trials of PrEP (see [Table 4: Clinical Trials of Pre-Exposure Prophylaxis](#)).
- The Panel also notes that no studies exist about the utility of PrEP in an uninfected individual whose infected partner is receiving combination antiretroviral therapy (cART) and has a suppressed viral load.
- Pregnancy is not a contraindication to PrEP.

### General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

- This section incorporates content previously included in separate, earlier sections (Mechanisms of Action of Antiretroviral Prophylaxis in Reducing Perinatal Transmission of HIV and Perinatal Transmission of HIV and Maternal HIV RNA Copy Number).

### Nevirapine and Hepatic/Rash Toxicity

- Language has been strengthened to indicate that in patients with pre-existing liver disease, use of ARV medications other than nevirapine should be considered.

### Recommendations for Use of Antiretroviral Drugs during Pregnancy

- A new table has been added indicating cART regimen choices for ARV-naive HIV-infected pregnant women and including the rationale for the choices (see [Table 6: What to Start: Initial Combination Regimens for Antiretroviral Naive-Pregnant Women](#)).

- [Table 7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy](#) has been redesigned, streamlined, and updated to summarize information about formulation, dosing, and recommendations for use of individual ARV drugs in pregnancy. More detailed information on individual drugs is found in [Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#).
- The Preferred dual nucleoside analogue reverse transcriptase inhibitors (NRTI) for ARV-naive pregnant women have been expanded to include abacavir plus lamivudine and tenofovir plus emtricitabine or lamivudine in addition to zidovudine plus lamivudine.
- The Preferred protease inhibitors (PIs) for ARV-naive pregnant women remain ritonavir-boosted atazanavir and ritonavir-boosted lopinavir. Alternative PIs include ritonavir-boosted darunavir and ritonavir-boosted saquinavir.
- The Preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) for ARV-naive pregnant women is now efavirenz, initiated after the first 8 weeks of pregnancy. Nevirapine is the alternative NNRTI for ARV-naive pregnant women.
- Raltegravir has been moved to the Alternative category for ARV-naive pregnant women, for consideration particularly when drug interactions with PI -based regimens are a concern.
- Drugs for which data are currently insufficient in pregnancy to recommend routine use in ARV-naive women include dolutegravir, elvitegravir/cobicistat/tenofovir/emtricitabine fixed drug combination, ritonavir-boosted fosamprenavir, maraviroc, and rilpivirine.

### **HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Treatment**

- The Panel discusses the use of raltegravir in late pregnancy in women with high viral load, but because the efficacy and safety of this approach have only been described in anecdotal reports, the Panel does not routinely recommend this approach.

### **HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment**

- The Panel discusses updated data related to virologic response to cART in women who previously received cART but subsequently stopped therapy and were on no ARV drugs prior to re-starting cART in the current pregnancy.

### **HIV/Hepatitis C Coinfection**

- The Panel discusses availability of new anti-hepatitis C drugs and the lack of data on these new agents in pregnancy. Interferon alfa and pegylated interferon are not recommended in pregnancy and ribavirin should not be used in pregnancy (**AII**). Because management of HIV/hepatitis C coinfection in pregnancy is complex, consultation with an expert in management of these conditions is recommended.

### **HIV-2 Infection and Pregnancy**

- The Panel discusses difficulties in diagnosis of HIV-2 and difficulties with the currently available tests in the United States; confirmatory testing for HIV-2 can be obtained from the Centers for Disease Control and Prevention.
- No validated HIV-2 genotype or phenotype resistance assays are available in the United States; European experts have developed a rule set and an automated tool for HIV-2 drug resistance analyses that is freely available on the Internet (see <http://www.hiv-grade.de>).

## Monitoring of the Woman and Fetus during Pregnancy

- While monitoring of CD4 T lymphocyte (CD4) cell count during pregnancy is generally recommended every 3 months, this can be reduced to 6-month intervals in patients on cART with consistently suppressed viral load who have immune reconstitution (CD4 cell count increase well above the threshold for risk of opportunistic infection) (CIII).

## Intrapartum Antiretroviral Therapy/Prophylaxis

- The HIV RNA threshold for requiring administration of intravenous (IV) zidovudine during labor (in addition to continuing antepartum cART) has been modified to be consistent with the threshold for scheduled cesarean delivery and based on additional data summarized in the section.
- IV zidovudine should be administered to HIV-infected women with HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery (AI), but it is not required for HIV-infected women receiving combination ARV regimens who have HIV RNA ≤1,000 copies/mL consistently during late pregnancy and near delivery and no concerns regarding adherence to the regimen.

## Postpartum Follow-Up of HIV-Infected Women

- The Panel's discussion about continuing cART postpartum has been revised to highlight collaborative decision-making between provider and patient, the importance of ensuring continuity of treatment from the antepartum to the postpartum period, and to reflect the current adult ARV treatment guidelines.
  - Decisions about continuing cART after delivery should be made in consultation with a woman and her HIV provider, ideally before delivery (AIII). cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission, although the strength and evidence for this recommendation vary by pretreatment CD4 cell count.

## Infant Antiretroviral Prophylaxis

- A 4-week neonatal zidovudine chemoprophylaxis regimen can be considered when the mother has received standard cART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence (BII).
- The Panel provides information on the case of a functional cure in an infant. The Panel notes that further investigation is ongoing and clinical trials are planned to address whether administration of a three-drug regimen in therapeutic doses to HIV-exposed high-risk infants could alter the establishment and long-term persistence of HIV infection. Investigation also is ongoing and clinical trials are planned to assess the safety of such an approach in infants, particularly in the setting of preterm delivery for which pharmacokinetic data on most drugs are lacking.
- The NICHD/HPTN 040/P1043 two-drug infant prophylaxis regimen of 6 weeks of zidovudine plus 3 doses of nevirapine in the first week of life continues to be the general recommendation for infant prophylaxis for infants born to mothers who did not receive antepartum ARV drugs or received only intrapartum drugs (AI); the regimen should be initiated as soon after delivery as possible. Decisions about use of alternative combination ARV prophylaxis regimens in infants should be made in consultation with a pediatric HIV specialist before delivery, if possible, and should be accompanied by a discussion with the mothers about potential risks and benefits of this approach.

## Appendix A. Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal Transmission of HIV

- Content about lessons from clinical trials and the table [Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal Transmission of HIV](#) has been moved from the beginning of the document to a new [Appendix](#).

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## Members of the Panel on Treatment of HIV-Infected Pregnant Woman and Prevention of Perinatal Transmission (Last updated March 28, 2014; last reviewed March 28, 2014)

Revisions to the July 31, 2012, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal Transmission in the United States have been made by the Department of Health and Human Services (HHS) Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (a Working Group of the Office of AIDS Research Advisory Council).

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## Financial Disclosure List for Members of the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (Last updated March 28, 2014; last reviewed March 28, 2014)

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

## Introduction (Last updated March 28, 2014; last reviewed March 28, 2014)

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Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal transmission of HIV have evolved considerably in the United States over the last 25 years, reflecting changes in the epidemic and the science of prevention.<sup>1</sup> With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral (ARV) prophylaxis, scheduled cesarean delivery, and avoidance of breastfeeding, the rate of perinatal transmission of HIV has dramatically diminished to less than 2% in the United States and Europe.<sup>2-4</sup>

These guidelines update the July 31, 2012, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. The Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel), a working group of the Office of AIDS Research Advisory Council (OARAC), develops these guidelines. The guidelines provide health care providers with information for discussion with HIV-infected pregnant women to enable the patient/provider team to make informed decisions regarding the use of ARV drugs during pregnancy and use of scheduled cesarean delivery to reduce perinatal transmission of HIV. The recommendations in the guidelines are accompanied by discussion of various circumstances that commonly occur in clinical practice and the factors influencing treatment considerations. The Panel recognizes that strategies to prevent perinatal transmission and concepts related to management of HIV in pregnant women are rapidly evolving and will consider new evidence and adjust recommendations accordingly. The updated guidelines are available from the AIDSinfo website (<http://aidsinfo.nih.gov>).

Health care providers considering the use of ARV agents for HIV-infected women during pregnancy must take into account two separate—but related—issues:

1. ARV treatment of maternal HIV infection; and
2. ARV chemoprophylaxis to reduce the risk of perinatal transmission of HIV.

The benefits of ARV drugs for a pregnant woman must be weighed against the risks of adverse events to the woman, fetus, and newborn. Combination drug regimens are considered the standard of care both for treatment of HIV infection and for prevention of perinatal transmission of HIV. After provider counselling and discussion about ARV drug use during pregnancy, a pregnant woman's informed choice on whether to take ARV drugs for her treatment, for prevention of perinatal transmission, and/or to follow other medical recommendations intended to reduce perinatal transmission of HIV should be respected. Coercive and punitive policies are potentially counterproductive; they may undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize fetal and neonatal well-being.

The current guidelines have been structured to reflect the management of an individual mother-child pair and are organized into a brief discussion of preconception care followed by principles for management of a woman and her infant during the antepartum, intrapartum, and postpartum periods. Although perinatal transmission of HIV occurs worldwide, these recommendations have been developed for use in the United States. Alternative strategies may be appropriate in other countries. Policies and practices in other countries regarding the use of ARV drugs for reduction of perinatal transmission of HIV may differ from the recommendations in these guidelines and will depend on local considerations, including availability and cost of ARV drugs, accessibility of facilities for safe intravenous infusions during labor, and local recommendations regarding breastfeeding by HIV-infected women.

## Guidelines Development Process

**Table 1. Outline of the Guidelines Development Process**

Topic	Comment
<b>Goal of the Guidelines</b>	Provide guidance to HIV care practitioners on the optimal use of ARV agents in pregnant women for treatment of HIV infection and for prevention of perinatal transmission of HIV in the United States.
<b>Panel Members</b>	The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (such as training in either obstetrics/gynecology or women's health) and interventions for prevention of perinatal transmission (such as specialized training in pediatric HIV infection) as well as community representatives with knowledge of HIV infection in pregnant women and interventions for prevention of perinatal transmission. The U.S. government representatives, appointed by their agencies, include at least 1 representative from each of the following Department of Health and Human Services agencies: the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. A list of all Panel members can be found on Page IV of the guidelines.
<b>Financial Disclosures</b>	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDSinfo website ( <a href="http://aidsinfo.nih.gov">http://aidsinfo.nih.gov</a> ).
<b>Users of the Guidelines</b>	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
<b>Developer</b>	Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—a working group of OARAC
<b>Funding Source</b>	Office of AIDS Research, NIH
<b>Evidence for Recommendations</b>	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.
<b>Recommendation Grading</b>	See <a href="#">Table 2</a> .
<b>Method of Synthesizing Data</b>	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. A structured literature search is conducted by staff from the HIV/AIDS National Resource Center at the Francois-Xavier Bagnoud Center (through funding from HRSA) and provided to the Panel working group. The members review and synthesize the available data and propose recommendations to the entire Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals receiving endorsement from a consensus of members are included in the guidelines as official Panel recommendations.
<b>Other Guidelines</b>	These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines outline the use of ARV agents in non-pregnant HIV-infected adults and adolescents, HIV-infected children, and people who experience occupational or non-occupational exposure to HIV. The guidelines described are also available on the AIDSinfo website ( <a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a> ). Preconception management for non-pregnant women of reproductive age is briefly discussed in this document. However, for more detailed discussion on issues of treatment of non-pregnant adults, the Working Group defers to the designated expertise offered by Panels that have developed those guidelines.
<b>Update Plan</b>	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, new dosing formulations, or changes in dosing frequency), significant new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and accompanying recommendations on the AIDSinfo website until the guidelines can be updated with appropriate changes. Updated guidelines are available on the AIDSinfo website ( <a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a> ).

## Guidelines Development Process

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

Topic	Comment
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 <a href="mailto:contactus@aidinfo.nih.gov">contactus@aidinfo.nih.gov</a> .

### *Basis for Recommendations*

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommended statement is rated with a letter of **A**, **B**, or **C** that represents the strength of the recommendation and with a numeral **I**, **II**, or **III**, according to the quality of evidence.

**Table 2. Rating Scheme for Recommendations**

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

## References

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# Preconception Counseling and Care for HIV-Infected Women of Childbearing Age (Last updated March 28, 2014; last reviewed March 28, 2014)

## Panel's Recommendations

- Discuss childbearing intentions with all women of childbearing age on an ongoing basis throughout the course of their care (AIII).
- Include 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, illicit drugs, and smoking, which are important for the health of all women as well as for fetal/infant health, should pregnancy occur (AII).
- All HIV-infected women contemplating pregnancy should be on a maximally suppressive antiretroviral regimen (AII).
- When selecting or evaluating combination antiretroviral therapy (cART) for HIV-infected women of childbearing age, consider a regimen's effectiveness, a woman's hepatitis B virus disease status, teratogenic potential of the drugs in the cART regimen, should pregnancy occur, and possible adverse outcomes for the mother and fetus (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, and other national organizations recommend offering all women of childbearing age comprehensive family planning and the opportunity to receive preconception counseling and care as a component of routine primary medical care. The purpose of preconception care is to improve the health of each woman before conception by identifying risk factors for adverse maternal or fetal outcome, providing education and counseling targeted to patients' individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes.<sup>1</sup> 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<sup>2-6</sup> 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.<sup>7-9</sup> HIV care providers who routinely care for women of reproductive age play an important role in promoting preconception health and informed reproductive decisions.

The fundamental principles of preconception counseling and care are outlined in the CDC Preconception Care Work Group's [Recommendations to Improve Preconception Health and Health Care](#). In addition to the general components of preconception counseling and care that are appropriate for all women of reproductive age, HIV-infected women have specific needs that should be addressed.<sup>10-12</sup> Because many HIV-infected women are aware of their HIV status before becoming pregnant, issues that impact pregnancy can be addressed before conception during their routine medical care for HIV disease. In addition to the principles outlined by the CDC Preconception Care Work Group,<sup>13</sup> the following components of preconception counseling and care are specifically recommended for HIV-infected women. Health care providers should:

- Discuss reproductive options; actively assess women's pregnancy intentions on an ongoing basis throughout the course of care; and, when appropriate, make referrals to experts in HIV and women's health, including experts in reproductive endocrinology and infertility when necessary.<sup>14,15</sup>
- Counsel on safe sexual practices that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted diseases, and reduce the potential to acquire more virulent or resistant

strains of HIV.

- Counsel on eliminating alcohol, illicit drug use, and cigarette smoking.
- Counsel women contemplating pregnancy to take a daily multivitamin that contains 400 ug of folic acid to help prevent certain birth defects.
- Educate and counsel women about risk factors for perinatal transmission of HIV, strategies to reduce those risks, potential effects of HIV or of antiretroviral (ARV) drugs given during pregnancy on pregnancy course and outcomes, and the recommendation that HIV-infected women in the United States not breastfeed because of the risk of transmission of HIV to their infant and the availability of safe and sustainable infant feeding alternatives.
- When prescribing combination antiretroviral therapy (cART) to women of childbearing age, consider the regimen's effectiveness, an individual's hepatitis B disease status, the drugs' potential for teratogenicity, should pregnancy occur, and possible adverse outcomes for mother and fetus.<sup>16-18</sup>
- Use the preconception period in women who are contemplating pregnancy to adjust cART to exclude efavirenz or other drugs with teratogenic potential.
- Make a primary treatment goal for women who are on cART and who **are planning a pregnancy** to attain a stable, maximally suppressed maternal viral load prior to conception to decrease the risk of perinatal transmission **and of HIV transmission to an uninfected partner**.
- Evaluate and appropriately manage therapy-associated side effects such as hyperglycemia, anemia, and hepatotoxicity that may adversely impact maternal-fetal health outcomes.
- Evaluate the need for appropriate prophylaxis or treatment for opportunistic infections, including safety, tolerability, and potential toxicity of specific agents when used in pregnancy.
- Administer medical immunizations for influenza, pneumococcal or hepatitis A and B vaccines, and other vaccines as indicated (see <http://www.cdc.gov/vaccines/acip/committee/guidance/rec-vac-preg.html>).
- Encourage sexual partners to receive counseling and HIV testing and, if infected, to seek appropriate HIV care.
- Offer all women who do not desire pregnancy effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. HIV-infected women can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs).<sup>19</sup> Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy (see [Table 3](#) below).
- Offer emergency contraception as appropriate, including emergency contraceptive pills and the copper IUD. Concerns about drug interactions between ARVs and emergency contraceptive pills containing estrogen and a progestin, or containing levonorgestrel only, may be similar to concerns when those formulations are used for regular contraception.<sup>20</sup> There are no data on potential interactions between ARVs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is predominantly metabolized by CYP3A4, so interactions can be expected.

Data on drug interactions between ARV agents and hormonal contraceptives primarily come from drug labels and limited studies,<sup>21-28</sup> and the clinical implications have not been well studied. The magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy or increase contraceptive-associated adverse effects is unknown. No studies have addressed differences in pregnancy rates in women using hormonal contraception and ARVs compared to those not using ARVs. Hormonal contraceptives can be used with cART in women without other contraindications. Additional or alternative methods of contraception may be recommended when drug interactions are known. For women using ritonavir-boosted protease inhibitors who are on combination hormonal contraceptives (e.g., pills, patches, rings) or progestin-only pills, use of an

alternative or additional method of contraception is recommended. Implants generally can be used, but providers may also consider use of an alternative method or recommend the additional use of a reliable barrier method. Depot medroxyprogesterone acetate (DMPA) can be used without restriction because of its relative higher dose and limited studies that have shown no significant interaction between DMPA and ARVs.<sup>22,24</sup>

Because no high-quality, definitive, evidence-based studies exist on pregnancy rates among women on different hormonal contraceptives and ARVs, the dosing recommendations in Table 3 are based on consensus expert opinion. Whenever possible, we based our recommendations on available data regarding pharmacokinetic (PK) interactions between ARVs and combined hormonal methods, DMPA and etonogestrel implants. The lowest decrease in PK for which we recommended use of an alternative method was 14% decrease in norethindrone (with ritonavir-boosted darunavir) and 19% decrease in ethinyl estradiol (ritonavir-boosted atazanavir). For women using atazanavir without ritonavir boosting (ethinyl estradiol increase 48%, norethindrone increase 110%), we recommend use of oral contraceptives containing  $\leq 30$  ug ethinyl estradiol. The panel did not recommend any ethinyl estradiol dose change for etravirine (ethinyl estradiol increase 22%), rilpivirine (ethinyl estradiol increase 14%), or indinavir (ethinyl estradiol increase 25%, norethindrone increase 26%).

All recommendations in the following table are based on consensus expert opinion.

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

ARV Drug	Effect on Contraceptive Drug Levels	Dosing Recommendation/ Clinical Comment for Combined Hormonal Methods and Progestin- Only Pills	Dosing Recommendation/ Clinical Comment for DMPA <sup>a</sup>	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants
<b>NNRTIs</b>				
<b>EFV</b>	<u>Oral Ethinyl Estradiol/ Norgestimate:</u> <ul style="list-style-type: none"> <li>• No effect on ethinyl estradiol concentrations</li> <li>• ↓ active metabolites of norgestimate (levonorgestrel AUC ↓ 83%; norelgestromin AUC ↓ 64%)</li> </ul> <u>Implant:</u> <ul style="list-style-type: none"> <li>• ↓ etonogestrel</li> </ul> Levonorgestrel (Emergency contraception) AUC ↓ 58%	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Use alternative or additional contraceptive method.
<b>ETR</b>	Ethinyl estradiol AUC ↑ 22% <u>Norethindrone:</u> <ul style="list-style-type: none"> <li>• No significant effect</li> </ul>	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.
<b>NVP</b>	Ethinyl estradiol AUC ↓ 20% Norethindrone AUC ↓ 19% <u>DMPA:</u> <ul style="list-style-type: none"> <li>• No significant change</li> </ul>	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.
<b>RPV</b>	Ethinyl estradiol AUC ↑ 14% <u>Norethindrone:</u> <ul style="list-style-type: none"> <li>• No significant change</li> </ul>	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.

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

ARV Drug	Effect on Contraceptive Drug Levels	Dosing Recommendation/ Clinical Comment for Combined Hormonal Methods and Progestin- Only Pills	Dosing Recommendation/ Clinical Comment for DMPA <sup>a</sup>	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants
<b>RTV-Boosted PIs</b>				
ATV/r	↓ Ethinyl estradiol AUC ↓ 19% ↑ Norgestimate ↑ 85%	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Can consider an alternative method or a reliable method of barrier contraception in addition to this method.
DRV/r	Ethinyl estradiol AUC ↓ 44% Norethindrone AUC ↓ 14%	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Can consider an alternative method or a reliable method of barrier contraception in addition to this method.
FPV/r	Ethinyl estradiol AUC ↓ 37% Norethindrone AUC ↓ 34%	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Can consider an alternative method or a reliable method of barrier contraception in addition to this method.
LPV/r	Ethinyl estradiol AUC ↓ 42% Norethindrone AUC ↓ 17%	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Can consider an alternative method or a reliable method of barrier contraception in addition to this method.
SQV/r	↓ Ethinyl estradiol	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Can consider an alternative method or a reliable method of barrier contraception in addition to this method.
TPV/r	Ethinyl estradiol AUC ↓ 48% <u>Norethindrone:</u> • No significant change	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Can consider an alternative method or a reliable method of barrier contraception in addition to this method.
<b>PIs without RTV</b>				
ATV	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	No additional contraceptive protection is needed.  Oral contraceptive should contain ≤30 ug of ethinyl estradiol or use alternative method.  Oral contraceptives containing <25 ug ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.

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

ARV Drug	Effect on Contraceptive Drug Levels	Dosing Recommendation/ Clinical Comment for Combined Hormonal Methods and Progestin- Only Pills	Dosing Recommendation/ Clinical Comment for DMPA <sup>a</sup>	Dosing Recommendation/ Clinical Comment for Etonogestrel Implants
<b>PIs without RTV, continued</b>				
FPV	<u>Amprenavir:</u> • ↑ Ethinyl estradiol • ↑ Norethindrone  <u>Fosamprenavir with Ethinyl Estradiol/Norethindrone:</u> • ↓ Amprenavir (AUC 22%, C <sub>min</sub> 20%)	Use alternative contraceptive method.  Use of fosamprenavir alone with ethinyl estradiol/norethindrone may lead to loss of virologic response.	No additional contraceptive protection is needed.	Use alternative or additional contraceptive method.
IDV	Ethinyl estradiol AUC ↑ 25% Norethindrone AUC ↑ 26%	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.
NFV	Ethinyl estradiol AUC ↓ 47% Norethindrone AUC ↓ 18%	Use alternative or additional contraceptive method.	No additional contraceptive protection is needed.	Use alternative or additional contraceptive method.
<b>CCR5 Antagonist</b>				
MVC	No significant effect on ethinyl estradiol or levonorgestrel	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.
<b>Integrase Inhibitor</b>				
RAL	No significant effect	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.
DTG	No significant effect on norgestimate or ethinyl estradiol	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.
EVG/ COBI	Norgestimate AUC ↑ 2.26 Ethinyl estradiol AUC ↓ 0.75	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.	No additional contraceptive protection is needed.

<sup>a</sup> Because the hormonal levels achieved with DMPA are substantially higher than are required for contraception, any small reduction in hormonal level due to ARVs is unlikely to reduce contraceptive effectiveness.

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; C<sub>min</sub> = minimum plasma concentration; COBI = cobicistat; DMPA = depot medroxyprogesterone acetate; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; IDV = indinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = ritonavir-boosted saquinavir; TPV/r = ritonavir-boosted tipranavir

Derived from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. Tables 15a, 15b, and 15d. Last accessed March 17, 2014.



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## Reproductive Options for HIV-Concordant and Serodiscordant Couples (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel's Recommendations
For Couples who Want to Conceive
<b>For Both Concordant (Both Partners are HIV-Infected)/Discordant Couples:</b>
<ul style="list-style-type: none"><li>• Expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple (<b>AIII</b>).</li><li>• Partners should be screened and treated for genital tract infections before attempting to conceive (<b>AII</b>).</li><li>• The HIV-infected partner should attain maximum viral suppression before attempting conception (<b>AIII</b>).</li></ul>
<b>For Discordant Couples:</b>
<ul style="list-style-type: none"><li>• Combination antiretroviral therapy (cART) for the infected partner may not be fully protective against sexual transmission of HIV.</li><li>• Periconception administration of antiretroviral pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission (<b>CIII</b>). The utility of PrEP of the uninfected partner when the infected partner is receiving cART and has a suppressed viral load has not been studied.</li></ul>
<b>Discordant Couples with HIV-Infected Female:</b>
<ul style="list-style-type: none"><li>• The safest conception option is artificial insemination, including the option of self-insemination with a partner's sperm during the peri-ovulatory period (<b>AIII</b>).</li></ul>
<b>Discordant Couples with HIV-Infected Male:</b>
<ul style="list-style-type: none"><li>• The use of donor sperm from an HIV-uninfected male with artificial insemination is the safest option.</li><li>• When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or <i>in vitro</i> fertilization should be considered (<b>AII</b>).</li><li>• Semen analysis is recommended for HIV-infected males before conception is attempted to prevent unnecessary exposure to infectious genital fluid when the likelihood of getting pregnant is low because of semen abnormalities (<b>AIII</b>).</li></ul>
<b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional
<b>Rating of Evidence:</b> 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 couples in which one or both are HIV-infected, optimal health should be attained before attempting conception. The infected partner should be on combination antiretroviral therapy (cART) and have achieved maximal suppression of HIV infection.

For concordant or serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple.

Before attempting to conceive, both partners should be screened for genital tract infections. If any such infections are identified, they should be treated because genital tract inflammation is associated with genital tract shedding of HIV.<sup>1-5</sup>

### Serodiscordant Couples

Before conception is attempted, maximal viral suppression is recommended for individuals who are on combination antiretroviral therapy (cART). Observational studies have demonstrated a decreased rate of transmission of HIV in heterosexual serodiscordant couples among whom the index partners were on cART compared with those not on therapy.<sup>6-8</sup> HPTN 052 was a randomized clinical trial designed to evaluate whether immediate versus delayed initiation of ART by HIV-infected individuals with CD4 T lymphocyte (CD4) cell counts of 350 to 550 cells/mm<sup>3</sup> could prevent sexual transmission of HIV among serodiscordant couples. Most of the participants were from Africa (54%), with 30% from Asia and 16% from North and South America. Data from this study showed that earlier initiation of cART led to a significant reduction in

transmission of HIV to the uninfected partner. Of 28 cases of HIV infection documented to be genetically linked to the infected partner, 27 occurred in the 877 couples in which the HIV-infected partner delayed initiation of ART until the CD4 cell count fell below 250 cells/mm<sup>3</sup>, whereas only 1 case of HIV infection occurred in the 886 couples with an HIV-infected partner who began immediate cART; 17 of the 27 transmissions in the delayed-therapy group occurred in individuals with CD4 cell counts >350 cells/mm<sup>3</sup>. The majority of transmissions (82%) were observed in participants from Africa. These are the first data from a randomized trial to demonstrate that provision of treatment to infected individuals can reduce the risk of transmission to their uninfected sexual partners.<sup>9</sup> Based on the results from HPTN 052, initiation of cART would be recommended for the infected partner in a serodiscordant couple who has a CD4 cell count of ≤550 cells/mm<sup>3</sup> if the couple wishes to conceive. Initiation of cART is also recommended for HIV-infected individuals with CD4 cell counts >550 cells/mm<sup>3</sup>, although the benefit of cART in reducing sexual transmission from individuals with higher CD4 cell counts has not been determined.

It is important to recognize that no single method (including treatment of the infected partner) is fully protective against transmission of HIV. Effective cART that decreases plasma viral load to undetectable levels is also associated with decreased concentration of virus in genital secretions. In a prospective study of 2,521 African HIV-infected serodiscordant couples, higher genital HIV RNA concentrations were associated with greater risk of heterosexual HIV-1 transmission and this effect was independent of plasma HIV concentrations.<sup>10</sup> Each log<sub>10</sub> increase in genital HIV-1 RNA levels increased the risk of female-to-male or male-to-female HIV transmission by 1.7-fold.<sup>10</sup> Discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus.<sup>11-13</sup> In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.<sup>14</sup> Thus, maximal plasma viral suppression may not completely eliminate risk of heterosexual transmission. Although use of cART may not eliminate all risk of sexual transmission, it may contribute to lowering risk in couples who have decided to conceive through unprotected intercourse despite known risks.

Reducing the risk of perinatal transmission is another potential rationale for starting cART before conception in HIV-infected women. Data suggest that early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission,<sup>15,16</sup> but that does not completely eliminate the risk of perinatal transmission.<sup>16</sup> In addition, reports are mixed on the possible effects of cART on prematurity and low birthweight, with some but not all data suggesting that such outcomes may be more frequent in women on ARV drugs at conception.<sup>17,18</sup>

The implications of initiating therapy before conception solely for prevention of sexual and/or perinatal transmission should be discussed with **the couple**. These issues include willingness and ability **of the HIV-infected partner** to commit to potential lifelong therapy, the potential risks versus benefits of stopping or continuing the regimen after conception in the male or postpartum in the female, and the need for strict adherence to achieve maximal viral suppression. Consultation with an expert in HIV care is strongly recommended.

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

For HIV-discordant couples in which the male is the HIV-infected partner, **the use of donor sperm from an HIV-uninfected male with artificial insemination is the safest option**. When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization has been reported to be effective in avoiding seroconversion in uninfected women and offspring in several studies.<sup>19-21</sup> Sperm preparation should utilize optimal methods that can detect the presence of HIV. Couples should also consider the cost and other possible complications of *in vitro* fertilization. More data are needed to demonstrate the complete efficacy of these techniques, and couples should be cautioned about the potential risk of transmission of HIV to the uninfected partner and to their offspring.<sup>20</sup> Semen analysis is recommended for HIV-infected males before conception is attempted because

HIV, and possibly cART, may be associated with a higher prevalence of semen abnormalities such as low sperm count, low motility, higher rate of abnormal forms, and low semen volume. If such abnormalities are present, the uninfected female partner may be exposed unnecessarily and for prolonged periods to her partner's infectious genital fluids when the likelihood of getting pregnant naturally is low or nonexistent.<sup>22-25</sup>

Discordant couples who do not have access to assisted reproduction services and who still want to try to conceive after comprehensive counseling should be advised that timed, peri-ovulatory unprotected intercourse after the infected partner has achieved maximal viral suppression (with use of condoms at all other times) may reduce but not completely eliminate the risk of sexual transmission.<sup>20</sup> HIV-uninfected women who become pregnant should be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV and the possible risk of perinatal transmission (see [Monitoring of HIV Uninfected Pregnant Women with a Partner Known to be HIV Infected](#)).

Periconception pre-exposure prophylaxis (PrEP) may offer an additional option to minimize risk of transmission of HIV within discordant couples. PrEP is use of ARV medications by an HIV-uninfected individual to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. **Many studies have demonstrated that PrEP reduces the risk of HIV acquisition in both men and women, with minimal risk of incident ARV resistance. Others did not show benefit, which is likely related to adherence issues.**<sup>9,26-31</sup> Table 4 summarizes clinical trials of PrEP.<sup>32</sup>

**Table 4. Clinical Trials of Pre-Exposure Prophylaxis (page 1 of 2)**

<b>Trial</b>	<b>Study Population</b>	<b>Location</b>	<b>Intervention</b>	<b>Outcome</b>	<b>Comments</b>
<b>TDF2</b>	1,219 sexually active adults; 55% male, 45% female; 94 % unmarried; approximately 90% aged 21–29 years	Botswana	Daily oral TDF/FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately.
<b>PIP</b>	4,758 heterosexual serodiscordant couples; 38% negative-female, 68% negative-male partner; 98% married; median age 33 years	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	67% protection with TDF alone; 75% protection with TDF/FTC	Discordant couples may be a distinct, unique population.
<b>FEM-PrEP</b>	1,951 heterosexual women aged 18–35 years 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.
<b>VOICE MTN-003</b>	5,029 heterosexual women aged 18–45 years 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: HIV incidence was 5.7 per 100 person years. Effectiveness was -48.8% for TDF; -4.2% for TDF/FTC; and 14.7% for TDF gel.	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.

**Table 4. Clinical Trials of Pre-Exposure Prophylaxis (page 2 of 2)**

Trial	Study Population	Location	Intervention	Outcome	Comments
HPTN 052	1,763 heterosexual serodiscordant couples; 50% negative-female, 50% negative-male partner; 94% married; 61% aged 26–40 years	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand	Immediate or delayed cART in HIV-infected partner	96% protection	Suppression of viraemia on therapy assured by routine monitoring.

**Key to Acronyms:** cART = combination antiretroviral therapy; TDF = tenofovir disoproxil fumarate; TFV=tenofovir; FTC=emtricitabine

**Source:** Adapted from Kashuba et al., Antiretroviral-based HIV prevention studies: *Lancet* 379(9835): 2409-2411

PrEP may offer an additional strategy for safer conception. Couples should be advised to use condoms at all times except during periovulatory intercourse. Several studies evaluating the efficacy of PrEP in heterosexual discordant couples planning pregnancy are ongoing but complete data are not yet available. One study evaluated timed intercourse with PrEP in 46 heterosexual HIV-discordant couples with an HIV-uninfected female partner. The male HIV-infected partners were receiving cART and had undetectable plasma HIV RNA levels. One dose of oral tenofovir was taken by the women at luteinizing hormone peak and a second oral dose was taken 24 hours later. None of the women became HIV infected and pregnancy rates were high, reaching a plateau of 75% after 12 attempts.<sup>33</sup>

Only combination tenofovir/emtricitabine is being evaluated currently in ongoing heterosexual PrEP trials. Adherence is critical. The use of continued PrEP is recommended for anyone who is at ongoing risk of HIV acquisition.

Pregnancy is not a contraindication to PrEP. However, the use of daily oral PrEP during pregnancy and lactation has not been well studied in HIV-uninfected women with HIV-infected partners. Condom use should be encouraged in pregnancy because several studies have reported increased incidence of HIV acquisition during pregnancy which may also lead to increased perinatal transmission. Continuation of PrEP during pregnancy can be considered.<sup>34-38</sup> Currently, there is no reported increase in congenital anomalies among children born to women exposed to tenofovir (2.4%) or to emtricitabine (2.5%) during pregnancy, including in the first trimester.<sup>39</sup>

It will be important to have outcome studies that examine adverse events, including risk of congenital abnormalities. In addition, the utility of daily oral PrEP when the HIV-infected partner is receiving cART has not been studied. If clinicians elect to use PrEP for HIV-uninfected women or men in serodiscordant couples, the couples should be educated about the potential risks and benefits and all available alternatives for safer conception. Laboratory testing for HIV infection, baseline renal function, and chronic hepatitis B virus (HBV) infection should be performed before initiating PrEP. Hepatitis B-uninfected individuals should be vaccinated. Individuals receiving PrEP should be monitored for potential side effects such as renal dysfunction and clinical toxicities. They should be educated about symptoms associated with acute HIV infection and advised to contact their providers immediately for further evaluation, should symptoms occur. HIV-uninfected partners should undergo frequent HIV testing to detect HIV infection quickly. If HIV infection is documented, the PrEP ARV agents should be discontinued to minimize selection of drug-resistant virus and measures should be instituted to prevent perinatal transmission if pregnancy has occurred and attempts at conception stopped if it has not. Refer patient to HIV specialist immediately. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.<sup>40</sup> Clinicians are strongly encouraged to register HIV-uninfected women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

### Concordant Couples

Both partners should be on cART with maximum viral suppression before attempting conception. Periovulatory unprotected intercourse (with use of condoms at all other times) is a reasonable option. The



risk of HIV superinfection or infection with a resistant virus is negligible when both partners are on cART and have fully suppressed plasma viral loads.<sup>41</sup>

The National Perinatal HIV Hotline (1-888-448-8765) is a resource for a list of institutions offering reproductive services for HIV concordant/serodiscordant couples.

The Centers for Disease Control and Prevention has issued guidelines for the use of PrEP in sexually active heterosexual adults.<sup>42</sup>

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

Clinicians may increasingly be seeing HIV-uninfected women who present during pregnancy and indicate that their partners are HIV-infected. They, like all pregnant women, should be notified that HIV screening is recommended and they will receive an HIV test as part of the routine panel of prenatal tests unless they decline. These women also should receive a second HIV test during the third trimester, preferably before 36 weeks' gestation, as is recommended for high-risk women. Furthermore, pregnant women who present in labor without results of third-trimester testing should be screened with a rapid HIV test on the labor and delivery unit. If at any time during pregnancy a clinician suspects that a pregnant woman may be in the "window" period of seroconversion (i.e., she has signs or symptoms consistent with acute HIV infection), then a plasma HIV RNA test should be used in conjunction with an HIV antibody test. If the plasma HIV RNA is negative, it should be repeated in 2 weeks. All HIV-uninfected pregnant women with HIV-infected partners should always use condoms during sexual intercourse to prevent acquisition of HIV. Women should be counseled regarding the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash, myalgia, arthralgia, diarrhea, headache) and the importance of seeking medical care and testing if they experience such symptoms.

Pregnancy is not a contraindication to PrEP and should be considered in HIV-seronegative pregnant women who are at ongoing risk of HIV acquisition. However, the use of daily oral PrEP during pregnancy and lactation has not been well studied (see section on [Serodiscordant Couples](#)).

Women who test HIV seropositive on either conventional or rapid HIV tests should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate cART and consideration of elective cesarean delivery according to established guidelines (see [Transmission and Mode of Delivery](#)). In cases where confirmatory test results are not readily available, such as with rapid testing during labor, it is still appropriate to initiate interventions to reduce perinatal transmission (see [Infant Antiretroviral Prophylaxis](#)).

Women with HIV-infected partners who test HIVseronegative should continue to be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV. Women with primary HIV infection during pregnancy or lactation are at high risk of transmitting HIV to their infants.<sup>43,44</sup>

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# Antepartum Care (Last updated March 28, 2014; last reviewed March 28, 2014)

## General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

Panel's Recommendations
<ul style="list-style-type: none"><li>Initial evaluation of HIV-infected pregnant women should include assessment of HIV disease status and recommendations regarding initiation of combination antiretroviral therapy (cART) or the need for any modification if currently receiving cART (<b>AIII</b>). The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.</li><li>All pregnant HIV-infected women should receive cART to prevent perinatal transmission regardless of plasma HIV RNA copy number or CD4 T lymphocyte count (<b>AI</b>).</li><li>Combined antepartum, intrapartum, and infant antiretroviral (ARV) prophylaxis is recommended because ARV drugs reduce perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and providing infant pre- and post-exposure prophylaxis (<b>AI</b>).</li><li>The known benefits and potential risks of ARV use during pregnancy should be discussed with all <b>HIV-infected</b> women (<b>AIII</b>).</li><li>In counseling patients, the importance of adherence to their ARV regimens should be emphasized (<b>AI</b>).</li><li>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., &gt;500 to 1,000 copies/mL) (see <a href="#">Antiretroviral Drug Resistance and Resistance Testing in Pregnancy</a>) (<b>AIII</b>). When HIV is diagnosed later in pregnancy, cART should be initiated promptly without waiting for results of resistance testing (<b>BIII</b>).</li><li>Coordination of services among prenatal care providers, primary care and HIV specialty care providers, <b>and when appropriate</b>, mental health and drug abuse treatment services, and public assistance programs, is essential to ensure that infected women adhere to their ARV drug regimens (<b>AIII</b>).</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> 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 those who are HIV infected should include assessment of HIV disease status and recommendations for HIV-related medical care. This initial assessment should include the following:

- Review of prior HIV-related illnesses and past CD4 T lymphocyte (CD4) cell counts and plasma HIV RNA levels;
- Current CD4 cell count;
- Current plasma HIV RNA copy number;
- Assessment of the need for prophylaxis against opportunistic infections such as *Pneumocystis jirovecii* pneumonia and *Mycobacterium avium* complex (see [Adult and Adolescent Opportunistic Infections Guidelines](#));
- Screening for hepatitis C virus and tuberculosis in addition to standard screening for hepatitis B virus (HBV) infection;
- Assessment of the need for immunizations per** guidelines from the American College of Obstetricians and Gynecologists, with particular attention to hepatitis A, HBV, influenza, pneumococcus, and Tdap immunizations;<sup>1,2</sup>
- Complete blood cell count and renal and liver function testing;
- HLA-B\*5701 testing if abacavir use is anticipated (see [Table 7](#));
- History of prior and current antiretroviral (ARV) drug use, including prior ARV use for prevention of perinatal transmission or treatment of HIV and history of adherence problems;

- Results of prior and current HIV ARV drug-resistance studies;
- History of **adverse** effects or toxicities from prior ARV regimens; and
- Assessment of supportive care needs **such as mental health services, substance abuse treatment, and smoking cessation**.

### ***The National Perinatal HIV Hotline***

The National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service providing free clinical consultation to providers caring for HIV-infected women and their infants.

### ***HIV RNA and Transmission***

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of CD4 cell counts and HIV RNA levels. Although the risk of perinatal transmission in women with undetectable plasma HIV RNA levels appears to be extremely low, transmission has been reported even in women with very low or undetectable levels of maternal HIV RNA on combination antiretroviral therapy (cART).<sup>3-5</sup> Although there is a general correlation between viral loads in plasma and in the genital tract, discordance between blood and genital tract virus has also been reported; low-level cervico-vaginal HIV RNA and DNA shedding has been detected even in women treated with cART who have undetectable plasma viral load, particularly in the presence of genital tract coinfections.<sup>6-8</sup> Penetration of ARV drugs into the female genital tract has been shown to vary between drugs.<sup>9-11</sup> If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV RNA levels may not always be an accurate indicator of risk.

### ***Mechanism of Action of Antiretrovirals in Prevention of Perinatal Transmission***

ARV drugs can reduce perinatal transmission through a number of mechanisms. Antenatal drug administration decreases maternal viral load in blood and genital secretions. Another mechanism of protection is infant pre-exposure prophylaxis achieved by administering ARV drugs that cross the placenta from mothers to infants and produce adequate systemic drug levels in the infants. Infant post-exposure prophylaxis is achieved by administering drugs to infants after birth, providing protection from cell-free or cell-associated virus that may have entered the fetal/infant systemic circulation during labor and delivery. The importance of the pre- and post-exposure components of prophylaxis in reducing perinatal transmission is demonstrated by the efficacy of interventions that involve administration of ARVs only during labor and/or to the newborns.<sup>12-18</sup> Therefore, combined antepartum, intrapartum, and infant ARV prophylaxis is recommended to prevent perinatal transmission of HIV.

### ***General Principles of Drug Selection***

In general, guidelines for the use of combination antiretroviral therapy (cART) for the benefit of maternal health during pregnancy are the same as for women who are not pregnant, with some modifications based on concerns about specific drugs and limited experience during pregnancy with newer drugs.

The known benefits and known and unknown risks of ARV drug use during pregnancy should be considered and discussed with women. Results from preclinical and animal studies and available clinical information about use of the various agents during pregnancy also should be discussed (see [Table 7](#) and [Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)). Potential risks of these drugs should be placed into perspective by reviewing the substantial benefits of ARV drugs for maternal health and in reducing the risk of transmission of HIV to infants. Counseling of pregnant women about ARV use should be noncoercive, and providers should help them make informed decisions regarding use of ARV drugs.

Discussions with women about initiation of cART drug regimens should include information about:

- Maternal risk of disease progression and the benefits and risks of initiation of therapy for maternal health;



- Benefit of cART for preventing perinatal transmission of HIV;<sup>19</sup>
- Benefits of therapy for reducing sexual transmission to discordant partners when viral suppression is maintained;<sup>20</sup>
- The need for strict adherence to the prescribed drug regimen to avoid resistance;
- Potential adverse effects of ARV drugs for mothers, fetuses, and infants, including potential interactions with other medications the women may already be receiving; and
- The limited long-term outcome data for both women who use cART during pregnancy for prophylaxis of transmission and stop the regimen postpartum and for infants with *in utero* drug exposure.

**Transplacental passage of ARVs is an important mechanism of infant pre-exposure prophylaxis.** Thus, when selecting an ARV regimen for a pregnant woman, at least one nucleoside/nucleotide reverse transcriptase inhibitor agent with high placental transfer should be included as a component of the **cART regimen** (see [Table 7](#)).<sup>21-24</sup>

In women with plasma HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL), ARV drug-resistance studies should be performed before starting cART. When HIV is diagnosed later in pregnancy, however, cART should be initiated promptly without waiting for results of resistance testing (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)). **Counseling should emphasize the importance of adherence to the ARV drug regimen to minimize the development of resistance.**

Support services, mental health services, **smoking cessation**, and drug abuse treatment may be required, depending on a woman's individual circumstances. Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure that infected women adhere to their ARV drug regimens.

**All HIV-infected pregnant women should be started on cART during pregnancy to minimize the risk of transmission.** Providers should work with women to develop long-range plans regarding continuity of medical care. Considerations regarding postpartum continuation of cART for maternal therapeutic indications are the same as for nonpregnant individuals.

Medical care of HIV-infected pregnant women requires coordination and communication between HIV specialists and obstetrical providers. General counseling should include current knowledge about risk factors for perinatal transmission. Risk of perinatal transmission of HIV has been associated with potentially modifiable factors, including cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy.<sup>25-29</sup> Besides improving maternal health, cessation of cigarette smoking and drug use, treatment of genital tract infections, and use of condoms with sexual intercourse during pregnancy may reduce risk of perinatal transmission. In addition, the Centers for Disease Control and Prevention **and American Academy of Pediatrics** recommends that HIV-infected women in the United States (including those receiving cART) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk<sup>30,31</sup> and avoid pre-mastication of food for their infants, a potential risk factor for transmission.<sup>32</sup>

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### Panel's Recommendations

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see <http://www.APRegistry.com>) (AIII).
- Nonpregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens (AIII).
  - Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health (BIII).
- Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz can be continued in pregnant women receiving an efavirenz-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression (see [HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment](#)) (CIII).

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

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

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself but also on the dose ingested; the gestational age of the fetus at exposure; the duration of exposure; the interaction with other agents to which the fetus is exposed; and, to an unknown extent, the genetic makeup of mother and fetus.

Information regarding the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Data are limited for antiretroviral (ARV) drugs, particularly when used in combination antiretroviral therapy (cART). Drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of *in vitro* and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans.<sup>1</sup> Limited data exist regarding placental passage, pharmacokinetics and safety in pregnancy, and long-term safety for exposed infants for the Food and Drug Administration (FDA)-approved ARV drugs (see [Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)). In general, reports of birth defects in fetuses/infants of women enrolled in observational studies who receive ARV regimens during pregnancy are reassuring and find no difference in rates of birth defects for first-trimester compared with later exposures.<sup>2-4</sup> However, concerns have been raised about the risk of several ARV agents.

Most studies evaluating a possible association between ARV exposure and birth defects do not evaluate folate levels. Folate antagonists (e.g., trimethoprim-sulfamethoxazole), which may be associated with an increased risk of birth defects with first trimester use, may be prescribed to women with advanced HIV disease. Therefore, it may be important to consider the role of folate antagonists as well as folic acid supplementation when evaluating any potential association between ARV drugs and birth defects.<sup>5</sup>

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.<sup>6</sup> The malformations included anencephaly and unilateral anophthalmia in one, microphthalmia in another, and cleft palate in the third. Among pregnancies prospectively reported to

the Antiretroviral Pregnancy Registry through July 2013 that had exposure to efavirenz-based regimens, a 2.3% incidence of overall birth defects was seen with first-trimester exposure, a proportion not significantly different from that observed among U.S. births in the general population.<sup>7</sup> Defects reported prospectively included one report of myelomeningocele and a separate report of anophthalmia. The case of anophthalmia included severe oblique facial clefts and amniotic banding that is known to be associated with anophthalmia.<sup>7</sup> In addition, six cases of central nervous system defects, including myelomeningocele, have been retrospectively reported in infants born to mothers receiving efavirenz during the first trimester.<sup>6</sup> However, retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

A meta-analysis including data from 21 studies reporting on 1,437 first-trimester exposures found no increased risk of overall birth defects in infants born to women on efavirenz during the first trimester compared with those on other ARV drugs during the first trimester (relative risk [RR] 0.85; 95% confidence interval [CI], 0.61–1.20). One neural tube defect was observed, giving an incidence of 0.07% (95% CI, 0.002–0.39).<sup>8</sup> However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a two- to three-fold increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02%–0.2%).<sup>9</sup>

In contrast to the meta-analysis, the Pediatric AIDS Clinical Trials Protocols (PACTG) 219 and 219C studies reported a higher defect rate in infants with first-trimester exposure to efavirenz compared with those without first-trimester efavirenz exposure (adjusted odds ratio 4.31; 95% CI, 1.56–11.86). However, only 32 infants had efavirenz exposure.<sup>10</sup> 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,<sup>3</sup> there is overlap in the defect cases between the 2 studies and only 41 infants are included in this analysis. Thus, additional data are needed on first-trimester efavirenz exposures to be able to more conclusively determine if risk of neural tube defects or other malformations is elevated.

Although a causal relationship has not been established between these events and the use of efavirenz, in light of similar findings in primates, efavirenz has been classified as FDA Pregnancy Category D. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first 8 weeks of pregnancy (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens. Alternate cART regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health. However, the Panel now recommends that efavirenz can be continued in women who present for care in the first trimester and are receiving efavirenz-based cART that is effective in suppressing viral replication. This is because the neural tube closes at 36 to 39 days after the last menstrual period; hence the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (and pregnancy is rarely recognized before 5–6 weeks), and unnecessary changes in ARV drugs during pregnancy may be associated with a loss of virologic control and, thus, increased risk of transmission to the infant.<sup>11</sup> For more details, see [HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment](#).

Tenofovir has not demonstrated teratogenicity in rodents or monkeys. In infant monkeys with *in utero* exposure to tenofovir at maternal doses resulting in levels approximately 25 times those used in humans, low birth weights and reductions in fetal bone porosity were seen. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose-, exposure-, age-, and species-specific. Data from the Antiretroviral Pregnancy Registry show a birth defect incidence of 2.4% in 1,612 women with first-trimester tenofovir exposure, similar to that in the general

population.<sup>7</sup> An Italian study assessed growth patterns, bone health, and markers of bone metabolism in 33 infants with *in utero* exposure to tenofovir and found no difference compared with infants born to HIV-infected women who had not been exposed to tenofovir.<sup>12</sup> A larger study from the United States included 2,029 HIV-exposed but uninfected infants, 449 (21%) of whom had *in utero* exposure to tenofovir.<sup>13</sup> Although there were no differences in anthropomorphic parameters at birth, at age 1 year, infants exposed to tenofovir-based regimens had slight but significantly lower adjusted mean length and head circumference for age z-score than those without exposure to tenofovir.

A modest (but statistically significant) increase in overall birth defect rates for didanosine and nelfinavir is observed when compared with the U.S. population-based Metropolitan Atlanta Congenital Defects Program (MACDP).<sup>7</sup> The lower bounds of the CIs for didanosine and nelfinavir (3.0%, 2.9%, respectively) are slightly above the higher bound (2.76%) for the MACDP rate. No specific pattern of defects has been detected with either didanosine or nelfinavir, and the clinical relevance of this statistical finding is unclear. The Registry will continue to monitor didanosine and nelfinavir for any signal or pattern of birth defects.

See [Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy](#) to obtain detailed information on individual drugs.

Health care providers who are caring for HIV-infected pregnant women and their newborns are strongly advised to report instances of prenatal exposure to ARV drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. This registry is an epidemiologic project to collect observational, non-experimental data regarding ARV exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting physician.

Referrals should be directed to:

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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## *Nevirapine and Hepatic/Rash Toxicity* (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- Nevirapine-based regimens should be initiated in women with CD4 T lymphocyte (CD4) cell counts >250 cells/mm<sup>3</sup> only if the benefits clearly outweigh the risks because of the drug's potential for causing hepatic toxicity/hypersensitivity reaction (**All**).
- Women who become pregnant while receiving nevirapine-containing regimens and who are tolerating the regimen well can continue on the therapy regardless of CD4 cell count (**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

Increases in hepatic transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. Signs and symptoms of systemic toxicity may be nonspecific and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, or hepatomegaly with or without initially abnormal hepatic transaminases.<sup>1</sup> Development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women.<sup>2,3</sup> Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than in men.<sup>4,5</sup> The degree of risk of rash and hepatic toxicity also appears to vary with CD4 T lymphocyte (CD4) cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts >250 cells/mm<sup>3</sup> were 9.8 times more likely than women with lower CD4 cell counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity;<sup>4</sup> a single-center study also found higher CD4 cell counts to be associated with increased risk of severe nevirapine-associated skin rash.<sup>2</sup> CD4 cell counts >250 cells/mm<sup>3</sup> predicted rash illness, but not liver enzyme elevation, among pregnant and non-pregnant women initiating nevirapine-based combination antiretroviral therapy (cART) in 3 U.S. university clinics.<sup>6</sup> Other international cohorts of non-pregnant women have experienced hepatotoxicity and rash at similar rates as in U.S. studies, but not in association with CD4 cell counts >250 cells/mm<sup>3</sup>.<sup>7</sup> In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine; severe or life-threatening rash has occurred in approximately 2% of patients receiving nevirapine.<sup>8</sup>

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of cART raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared with other antiretroviral (ARV) drugs.<sup>9,10</sup> **However, more recent** data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy.<sup>11-13</sup> **A meta-analysis of data from 3,582 pregnant women included in 20 studies did not find any evidence of increased risk of nevirapine-related adverse events in pregnant women compared with non-pregnant adults.** Nevertheless, if nevirapine is used in pregnancy, health care providers should be aware of potential hepatotoxicity with or without rash and should conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of nevirapine use. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through Month 4, and every 1 to 3 months thereafter (see the Hepatotoxicity section of the table on Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects in the [Adult and Adolescent Antiretroviral Guidelines](#)). In patients with pre-existing liver disease, **ARV medications other than nevirapine should be considered. If nevirapine is selected,** monitoring should be performed more frequently when initiating nevirapine and monthly thereafter.<sup>1</sup> Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe



transaminase elevations (i.e., more than 5 times the upper limit of normal) should stop nevirapine and not receive nevirapine again in the future.

Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV.<sup>14</sup> Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well can continue therapy, regardless of CD4 cell count.

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## ***Nucleoside Reverse Transcriptase Inhibitor Drugs and Mitochondrial Toxicity***

(Last updated March 28, 2014; last reviewed March 28, 2014)

### **Panel's Recommendations**

- The combination of stavudine and didanosine should not be prescribed during pregnancy because of reports of lactic acidosis and maternal/neonatal mortality with prolonged use in pregnancy (**All**).
- Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to antiretroviral (ARV) drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings (**All**).
- Long-term clinical follow-up is recommended for any child with *in utero* exposure to ARV drugs (**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

Nucleoside reverse transcriptase inhibitor (NRTI) drugs are known to induce mitochondrial dysfunction because the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction.<sup>1</sup> The relative potency of the NRTI drugs in inhibiting mitochondrial gamma DNA polymerase *in vitro* is highest for zalcitabine, followed by didanosine, stavudine, zidovudine, lamivudine, abacavir, and tenofovir.<sup>2</sup> In one study, didanosine and didanosine-containing regimens were associated with the greatest degree of mitochondrial suppression.<sup>3</sup> Toxicity related to mitochondrial dysfunction has been reported to occur in infected patients receiving long-term treatment with NRTI drugs and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested.<sup>1</sup> These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to NRTI drugs.

Lactic acidosis with microvesicular hepatic steatosis is a toxicity related to NRTI drugs that is thought to be related to mitochondrial toxicity; it has been reported to occur in infected individuals treated with NRTI drugs for longer than 6 months. In a report from the Food and Drug Administration Spontaneous Adverse Event Program, typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness.<sup>4</sup> Metabolic acidosis with elevated serum lactate levels and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight.

### **During Pregnancy**

Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance.<sup>5,6</sup> These syndromes have similarities to rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: acute fatty liver and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in development of acute fatty liver of pregnancy and HELLP syndrome<sup>7-10</sup> and possibly contribute to susceptibility to antiretroviral (ARV)-associated mitochondrial toxicity. HELLP syndrome also can occur postpartum in women with severe preeclampsia.<sup>11</sup>

The frequency of this syndrome in pregnant HIV-infected women receiving NRTI drugs is unknown but a number of case reports of severe (1) or fatal (3) outcomes have been reported including several cases with didanosine/stavudine used in combination during pregnancy. Nonfatal cases of lactic acidosis also have been reported in pregnant women receiving combination stavudine/didanosine.<sup>12</sup> Because of these reports of maternal mortality secondary to lactic acidosis with prolonged use of the combination of stavudine and didanosine by HIV-infected pregnant women, clinicians should not prescribe this ARV combination during

pregnancy. Likewise, combination stavudine/didanosine also is not recommended for non-pregnant adults.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for non-pregnant individuals receiving NRTI drugs. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving NRTI drugs to be alert for early signs of this syndrome.

In addition to low platelets and elevated liver enzymes, other laboratory findings reported in HIV-infected pregnant women on ARV drugs include depletion of mtDNA in the placenta but without evidence of ultrastructural damage to placental cells. The clinical significance of reduced mtDNA in placentas exposed to ARV drugs remains unknown.<sup>13</sup> A recent report by Hernandez et al. assessed mitochondrial and apoptotic parameters in mononuclear cells from maternal peripheral blood and infant cord blood from 27 HIV-infected, ARV-treated pregnant women and their infants and 35 uninfected controls and their infants.<sup>14</sup> Reduced newborn mtDNA levels, decreased maternal and fetal mitochondrial protein synthesis, and reduced maternal glycerol-3-phosphate and complex III function were observed in HIV- and ARV-exposed mothers and infants compared with uninfected controls. Maternal mtDNA depletion was particularly seen in HIV-infected pregnant women who had cumulative exposure to NRTIs of more than 100 months, suggesting NRTI-mediated injury. Also, Jitratkosol et al. reported increased prevalence of AG/TG mtDNA mutations among HIV-infected pregnant women receiving combination antiretroviral therapy (cART).<sup>15</sup> However, no clinical adverse outcomes were linked to these findings in either pregnant women or their infants.

### ***In Utero Exposure***

It has been suggested that mitochondrial dysfunction may develop in infants with *in utero* exposure to NRTI drugs. Data from a French cohort of 1,754 uninfected infants born to HIV-infected women who received ARV drugs during pregnancy identified 8 infants with *in utero* or neonatal exposure to either zidovudine/lamivudine (4) or zidovudine alone (4) who developed indications of mitochondrial dysfunction after the first few months of life.<sup>16</sup> Two of these infants (both exposed to zidovudine/lamivudine) contracted severe neurologic disease and died; 3 had mild-to-moderate symptoms; and 3 had no symptoms but had transient laboratory abnormalities.

In a larger cohort of 4,392 uninfected children (including the children in the previous study) followed within the French Pediatric Cohort or identified within a French National Register, the 18-month incidence of clinical symptoms of mitochondrial dysfunction was 0.26% and 0.07% for mortality.<sup>17</sup> All children had perinatal exposure to ARV drugs; risk was higher among infants exposed to cART (primarily zidovudine/lamivudine) than to zidovudine alone. The children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or episodes of significant hyperlactatemia, and deficits in mitochondrial respiratory chain complex enzyme function on biopsy of muscle. The same group also has reported an increased risk of simple febrile seizures in the first 18 months of life and persistently lower (but clinically insignificant) neutrophil, lymphocyte, and platelet counts in infants with *in utero* exposure to NRTIs.<sup>18,19</sup> More recently, in continued follow-up of the French Perinatal Cohort, researchers reported severe neurologic symptoms in the first 2 years of life as a rare event (0.3% to 0.5%).<sup>20</sup>

Other clinical studies from the United States and Europe generally have not duplicated the French reports.<sup>21-27</sup> The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring in children born to HIV-infected women and followed from 1986 to 1999 in 5 large, prospective U.S. perinatal cohorts. No deaths similar to those reported from France or with clinical findings attributable to mitochondrial dysfunction were identified in a database of more than 16,000 uninfected children born to HIV-infected women with and without exposure to ARV drugs.<sup>22</sup> However, most of the infants with exposure to ARVs had been exposed to zidovudine alone and only a relatively small proportion (approximately 6%) had been exposed to zidovudine/lamivudine.

The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort

with median follow-up of 2.2 years (maximum 16 years); 1,008 had perinatal exposure to ARV drugs.<sup>24</sup> No association was found between clinical manifestations suggestive of mitochondrial abnormalities and perinatal exposure to ARV drugs. Of the 4 children with seizures in this cohort, none had perinatal exposure to ARV drugs. In a report from a long-term follow-up study in the United States (PACTG 219/219C), 20 children with possible symptoms of mitochondrial dysfunction were identified in a cohort of 1,037 uninfected infants born to HIV-infected mothers.<sup>26</sup> Definitive diagnosis was not available because none of the children had biopsies for mitochondrial function. Three of the 20 children had no exposure to ARV drugs. In the 17 remaining children, although overall exposure to NRTIs was not associated with symptoms, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester. Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were found in stored specimens from these children, but the clinical significance of these observations remains unknown.<sup>28,29</sup>

Laboratory abnormalities without clinical symptoms have been reported in infants with perinatal exposure to ARV drugs compared with unexposed infants in a number of studies, most of which are limited by small numbers of subjects. In one study, mtDNA quantity was lower in cord and peripheral white blood cells at ages 1 and 2 years in 20 infants born to HIV-infected women compared with 30 infants born to uninfected women and was lowest in 10 HIV-exposed infants with zidovudine exposure compared with 10 without zidovudine exposure.<sup>30</sup> In a subsequent study, mitochondrial changes were evaluated in umbilical cord endothelial cells and cord blood from human infants and monkeys with *in utero* exposure to various NRTI-containing regimens.<sup>31</sup> Similar morphologic changes and mtDNA depletion were seen in the human and monkey infants. In the monkey study, mitochondrial damage demonstrated a gradient, with greatest damage with stavudine/lamivudine > zidovudine/didanosine > zidovudine/lamivudine > lamivudine. In a Canadian study of 73 ARV-exposed infants and 81 controls with blood samples during the first 8 months of life, investigators found that in the first weeks of life, blood mtDNA levels were higher and blood mitochondrial RNA levels were lower in the HIV- and ARV-exposed infants compared with infants without HIV and ARV exposure.<sup>32</sup>

Aldrovandi et al. reported that peripheral blood mononuclear cell mtDNA levels were lower at birth in HIV-exposed, ARV-exposed infants compared with infants without HIV and ARV exposure.<sup>33</sup> However, among the HIV-exposed infants, those with combination ARV drug exposure *in utero* had higher mtDNA levels than those exposed only to zidovudine *in utero*. Umbilical cord mtDNA sequence variants were 3-fold higher among HIV- and zidovudine-exposed infants compared with infants born to HIV-uninfected mothers.<sup>34</sup> Most recently, Jitratkosol et al. reported blood mtDNA mutations in HIV-exposed infants and Hernandez et al. reported subclinical mitochondrial dysfunction with decreased mtDNA levels and mtDNA protein synthesis.<sup>14,15</sup>

Transient hyperlactatemia during the first few weeks of life was reported in 17 HIV-exposed infants with perinatal exposure to ARV drugs; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up.<sup>35</sup> Similarly, the French Perinatal Cohort Study has reported asymptomatic hyperlactatemia in one-third of zidovudine-exposed newborns, which resolved following perinatal exposure to the drug.<sup>20</sup> Clinically asymptomatic hematologic findings have been reported by several investigators in uninfected infants with *in utero* exposure to ARV regimens in the United States and Europe,<sup>36-38</sup> and infants with exposure to triple-combination ARV regimens were found to be at increased risk of lowered hemoglobin compared with those with perinatal exposure to zidovudine or zidovudine/lamivudine.<sup>39</sup> Similar hematologic findings of anemia have also been reported in a Botswana study. Dryden-Peterson et al. reported that 12.5% of breastfed infants of mothers on ARV drugs during pregnancy and during breastfeeding in Botswana experienced at least 1 episode of Grade 3 or Grade 4 reduced hemoglobin by age 6 months compared with 5.3% of breastfed infants exposed to zidovudine *in utero* followed by daily infant zidovudine for 6 months and 2.5% of infants who were exposed to the drug *in utero* and for 1 month post-birth and were formula fed.<sup>40</sup> The Botswana study group has also reported decreased birth weight and decreased weight for age and length for age in the first several months of life in infants exposed to ARV drugs.

Echocardiographic abnormalities have been reported among 136 ARV drug- and HIV-exposed uninfected infants compared with 216 HIV-exposed, uninfected infants without ARV drug exposure in the NHLBI



CHAART-1 study.<sup>41</sup> In infants up to age 2 years, prenatal ARV exposure was associated with reduced left ventricular mass, dimension, and septal wall thickness z-scores and increased left ventricular fractional shortening and contractility compared with lack of ARV drug exposure. These findings were more prominent in female than in male infants.

The clinical significance of these differences in mtDNA, lactate levels, and hematologic and cardiac laboratory findings remains unclear. **Furthermore, not all studies have reported similar findings.**<sup>42</sup> Additional long-term studies are needed to validate the findings and assess whether they affect long-term growth and development of infants exposed to ARV drugs. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and must be balanced against the proven benefit of ARV prophylaxis in significantly reducing perinatal transmission.<sup>24,43,44</sup>

Development of new diagnostic techniques, including use of flow cytometry assays to screen for mitochondrial function, may lead to more accurate assessment of mitochondrial toxicity.<sup>45</sup> Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings. Current recommendations emphasize the need for long-term clinical follow-up for any child with *in utero*, peripartum, or postnatal exposure to ARV drugs used for prevention of perinatal transmission.

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## Combination Antiretroviral Drug Regimens and Pregnancy Outcome

(Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- Clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving protease-inhibitor (PI)-based combination antiretroviral therapy; however, given the clear benefits of such regimens for both a woman's health and prevention of perinatal transmission, PIs should not be withheld for fear of altering pregnancy outcome (**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

Early data were conflicting as to whether receipt of combination antiretroviral therapy (cART) during pregnancy is associated with adverse pregnancy outcomes and, in particular, preterm delivery. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study investigated the effects of cART in a population of 3,920 pregnant women who delivered between 1986 and 2000. Adjusting for CD4 T lymphocyte (CD4) cell count and intravenous drug use, they found a roughly twofold increase in the odds of preterm delivery for infants exposed to combination regimens with or without protease inhibitors (PIs) compared with no drugs; women receiving combination regimens that had been initiated before pregnancy were twice as likely to deliver prematurely as those who started drugs during the third trimester.<sup>1</sup> However, PI-based combination regimens were received by only 108 (3%) of the women studied; confounding by severity or indication may have biased the results (i.e., sicker women may have received PIs more often, but their advanced HIV infection may have actually caused the preterm births). Exposure to nucleoside reverse transcriptase inhibitor (NRTI) single-drug prophylaxis (primarily zidovudine) was not associated with prematurity.

An updated report from the European Collaborative Study, based on an adjusted analysis that included 2,279 pregnant women who delivered between 1986 and 2004, found a 1.9-fold increased risk of delivery at less than 37 weeks with cART started during pregnancy and a 2.1-fold increased risk with cART started prior to pregnancy compared with mono- or dual-NRTI prophylaxis.<sup>2</sup> In this report, 767 women received cART during pregnancy, although the proportion receiving PIs was not specified. The risk of delivery before 34 weeks' gestation was increased by 2.5-fold for those starting cART during pregnancy and 4.4-fold for those entering pregnancy on cART.

In contrast, in an analysis of 7 prospective clinical studies that included 2,123 HIV-infected pregnant women who delivered infants between 1990 and 1998 and had received antenatal antiretroviral (ARV) regimens and 1,143 women who did not receive antenatal ARV drugs, the use of multiple ARV drugs compared with no drugs or treatment with 1 drug was not associated with increased rates of preterm birth, low birth weight, low Apgar scores, or stillbirth.<sup>3</sup> Nor were any significant associations between adverse pregnancy outcome and use of ARV drugs by class or by category (including cART) found in an analysis from the Women and Infants Transmission Study, including 2,543 HIV-infected women (some of whom were included in the previous meta-analysis).<sup>4</sup>

More recent data have continued to be conflicting as to whether preterm delivery is increased with cART. Table 5 reviews results from studies that have evaluated the association of ARV drug use during pregnancy and preterm delivery. Multiple studies have detected small but significant increases (odds ratio [OR] 1.2–1.8 in the largest studies) in preterm birth with PI- or non-PI-based cART as well.<sup>5–8</sup> However, other recent studies that have controlled for maternal and pregnancy characteristics as well as factors related to HIV infection have shown no increase in adverse outcomes including preterm delivery and low birth weight in association with PI-containing drug regimens.<sup>9–11</sup> A meta-analysis of 14 European and American clinical studies found no increase in risk of preterm birth with either exposure to any ARV drug compared to no

drugs or to cART including PIs compared with no drugs.<sup>12</sup> However, a significant but modest increased risk of preterm birth (OR 1.35; 95% confidence interval [CI], 1.08–1.70) was found in women who received combination regimens with PIs compared with cART without PIs. Other reports have found increased rates of preterm birth when cART is compared with dual regimens<sup>13</sup> and when cART regimens containing non-nucleoside reverse transcriptase inhibitors were compared with other forms of cART.<sup>14</sup>

Other variables may confound these observational studies. Some studies have found increased rates of preterm birth if cART is begun before conception or earlier in pregnancy compared with later in pregnancy, which itself may reflect confounding by severity or indication.<sup>14,15</sup> Recent studies have assessed spontaneous preterm birth only, excluding delivery that was initiated at a preterm gestation because of medical or obstetrical reasons, and found no association between ARV and preterm birth.<sup>16,17</sup> However, a recent U.S. study found an increased risk of spontaneous and overall preterm birth with exposure to PI-containing cART in the first trimester compared to exposure only after the first trimester to PI- or non-PI-containing cART. Exposure to non-PI-containing regimens in the first trimester was not associated with increased risk of preterm birth.<sup>18</sup> In an analysis of HIV-infected women enrolled in the ANRS French Perinatal Cohort from 1990 to 2009, preterm delivery rates were seen to increase over time, and preterm delivery was associated with cART versus either mono- or dual-ARV regimens and were highest in those who had initiated ARV drugs before pregnancy.<sup>19</sup> A restricted analysis within this cohort of PI-based cART comparing boosted to unboosted PIs showed an association with induced preterm delivery for boosted PI regimens (adjusted odds ratio [AOR] 2.03; 95% CI, 2.06–3.89) that was not seen with spontaneous preterm birth. Boosted PI regimens were also associated with both medical and obstetrical complications, raising the possibility that the association with induced preterm delivery was mediated through these complications.

A secondary analysis of data collected during a randomized, controlled clinical trial conducted in Botswana in women with CD4 cell counts >200 cells/mm<sup>3</sup>—267 randomized to receive lopinavir/ritonavir/zidovudine/lamivudine (PI group) and 263 randomized to receive abacavir/zidovudine/lamivudine (NRTI group) begun between 26 and 34 weeks' gestation for prevention of perinatal transmission and not for maternal health indications—did show an association between PI-containing ARV regimens and preterm delivery. In logistic regression analysis, use of combination PI-based ARV regimens was the most significant risk factor for preterm delivery (OR 2.03; 95% CI, 1.26–3.27).<sup>20</sup> Those receiving the latest initiation of ARV drugs had the highest preterm delivery rates. However the 20% background rate for preterm delivery in this population was not different from that seen in the PI group, and there was no difference between the 2 groups in neonatal morbidity and mortality. An observational study also from Botswana found that use of cART from before conception was not associated with very preterm delivery (AOR 0.78), which could not be assessed in the controlled clinical trial.<sup>21</sup>

Clinicians should be aware of a possible increased risk of preterm birth with use of cART; however, given the clear benefits for maternal health and reduction in perinatal transmission, these agents should not be withheld because of the possibility of increased risk of preterm delivery. Until more information is known, HIV-infected pregnant women who are receiving cART for their HIV infection should continue their provider-recommended regimens. They should receive careful, regular monitoring for pregnancy complications including preterm delivery<sup>22</sup> and for potential toxicities.

**Table 5. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery** (page 1 of 3)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Notes
European Collaborative and Swiss Mother and Child HIV Cohort Study; 1986–2000 <sup>1</sup>	3,920/896	<ul style="list-style-type: none"> <li>• Mono (573)</li> <li>• Multi, no PI (215)</li> <li>• PI-multi (108)</li> </ul>	<ul style="list-style-type: none"> <li>• YES (compared with no ARV)</li> <li>• Multi: 1.82 (1.13–2.92)</li> <li>• PI-multi: 2.60 (1.43–4.7)</li> </ul>	<ul style="list-style-type: none"> <li>• Increase in PTD if ARV begun before pregnancy versus in third trimester</li> </ul>
United States; 1990–1998 <sup>3</sup>	3,266/2,123	<ul style="list-style-type: none"> <li>• Mono (1,590)</li> <li>• Multi (396)</li> <li>• PI-multi (137)</li> </ul>	<ul style="list-style-type: none"> <li>• NO (compared with mono)</li> <li>• Multi: 0.95 (0.60–1.48)</li> <li>• PI-multi: 1.45 (0.81–2.50)</li> </ul>	<ul style="list-style-type: none"> <li>• 7 prospective clinical studies</li> </ul>
European Collaborative Study; 1986–2004 <sup>2</sup>	4,372/2,033	<ul style="list-style-type: none"> <li>• Mono (704)</li> <li>• Dual (254)</li> <li>• Multi (1,075)</li> </ul>	<ul style="list-style-type: none"> <li>• YES (compared with mono/dual)</li> <li>• Multi in pregnancy: 1.88 (1.34–2.65)</li> <li>• Multi prepregnancy: 2.05 (1.43–2.95)</li> </ul>	
United States; 1990–2002 <sup>4</sup>	2,543/not given	<p><u>Early (&lt;25 Weeks):</u></p> <ul style="list-style-type: none"> <li>• Mono (621)</li> <li>• Multi (≥2 without PI or NNRTI) (198)</li> <li>• Multi (with PI or NNRTI) (357)</li> </ul> <p><u>Late (≥32 Weeks):</u></p> <ul style="list-style-type: none"> <li>• Mono (932)</li> <li>• Multi (≥2 without PI or NNRTI) (258)</li> <li>• Multi (with PI or NNRTI) (588)</li> </ul>	<ul style="list-style-type: none"> <li>• NO (compared with mono)</li> <li>• No association between any ARV and PTD</li> </ul>	<ul style="list-style-type: none"> <li>• PTD decreased with ARV compared with no ARV.</li> </ul>
United States; 1990–2002 <sup>23</sup>	1,337/999	<ul style="list-style-type: none"> <li>• Mono (492)</li> <li>• Multi (373)</li> <li>• PI-multi (134)</li> </ul>	<ul style="list-style-type: none"> <li>• YES (compared with other multi)</li> <li>• PI-multi: 1.8 (1.1–3.03)</li> </ul>	<ul style="list-style-type: none"> <li>• PI-multi reserved for advanced disease, those who failed other multi-ARV regimens.</li> </ul>
Brazil, Argentina, Mexico, Bahamas; 2002–2005 <sup>24</sup>	681/681	<ul style="list-style-type: none"> <li>• Mono/dual NRTI (94)</li> <li>• Multi-NNRTI (257)</li> <li>• Multi-PI (330)</li> </ul>	<ul style="list-style-type: none"> <li>• NO (compared with mono/dual NRTI)</li> <li>• No association between any ARV regimen and PTD</li> </ul>	<ul style="list-style-type: none"> <li>• All on ARV for at least 28 days during pregnancy</li> <li>• Preeclampsia/eclampsia, cesarean delivery, diabetes, low BMI associated with PTD</li> </ul>

**Table 5. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery** (page 2 of 3)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Notes
<b>Meta-analysis, Europe and United States; 1986–2004</b> <sup>12</sup>	11,224/not given	<ul style="list-style-type: none"> <li>Multi-no PI [including dual] or multi-PI (2,556)</li> </ul>	<ul style="list-style-type: none"> <li>YES (only comparing PI with multi)</li> <li>PI versus multi-no PI: 1.35 (1.08–1.70)</li> </ul>	<ul style="list-style-type: none"> <li>14 studies, 5 in PTD-ARV comparison.</li> <li>No overall increase in PTD with antepartum ARV.</li> <li>PTD increased in those on ARV pre-pregnancy and in first trimester compared with later use.</li> </ul>
<b>Italy; 2001–2006</b> <sup>7</sup>	419/366	<ul style="list-style-type: none"> <li>Multi-PI second trimester (97)</li> <li>Multi-PI third trimester (146)</li> </ul>	<ul style="list-style-type: none"> <li>YES</li> <li>Multi-PI second trimester: 2.24 (1.22–4.12)</li> <li>Multi-PI third trimester: 2.81 (1.46–5.39)</li> </ul>	<ul style="list-style-type: none"> <li>Multivariate association also with hepatitis C</li> </ul>
<b>United States; 1989–2004</b> <sup>6</sup>	8,793/6,228	<ul style="list-style-type: none"> <li>Mono (2,621)</li> <li>Dual (1,044)</li> <li>Multi-no PI (1,781)</li> <li>Multi-PI (782)</li> </ul>	<ul style="list-style-type: none"> <li>YES (compared with dual)</li> <li>Multi-PI associated with PTD: 1.21 (1.04–1.40)</li> </ul>	<ul style="list-style-type: none"> <li>Lack of antepartum ARV also associated with PTD.</li> <li>PTD and low birthweight decreased over time.</li> </ul>
<b>United Kingdom, Ireland; 1990–2005</b> <sup>5</sup>	5,009/4,445	<ul style="list-style-type: none"> <li>Mono/dual (1,061)</li> <li>Multi-NNRTI or Multi-PI (3,384)</li> </ul>	<ul style="list-style-type: none"> <li>YES (compared with mono/dual)</li> <li>Multi: 1.51 (1.19–1.93)</li> </ul>	<ul style="list-style-type: none"> <li>Similar increased risk with PI or no-PI multi.</li> <li>No association with duration of use.</li> </ul>
<b>Germany, Austria; 1995–2001</b> <sup>8</sup>	183/183	<ul style="list-style-type: none"> <li>Mono (77)</li> <li>Dual (31)</li> <li>Multi-PI (21)</li> <li>Multi-NNRTI (54)</li> </ul>	<ul style="list-style-type: none"> <li>YES (compared with mono)</li> <li>Multi-PI: 3.40 (1.13–10.2)</li> </ul>	
<b>United States; 2002–2007</b> <sup>16</sup>	777/777	<ul style="list-style-type: none"> <li>Mono (6)</li> <li>Dual (11)</li> <li>Multi-no PI (202)</li> <li>Multi-PI (558)</li> </ul>	<ul style="list-style-type: none"> <li>NO (compared PI with all non-PI)</li> <li>Multi-PI: 1.22 (0.70–2.12)</li> </ul>	<ul style="list-style-type: none"> <li>All started ARV during pregnancy.</li> <li>Analyzed only spontaneous PTD.</li> </ul>
<b>Swiss Mother and Child HIV Cohort Study; 1985–2007</b> <sup>13</sup>	1,180/941	<ul style="list-style-type: none"> <li>Mono (94)</li> <li>Dual (53)</li> <li>Multi (PI or no PI) (409)</li> <li>Multi-PI (385)</li> </ul>	<ul style="list-style-type: none"> <li>YES (compared with no ARV)</li> <li>Multi: 2.5 (1.4–4.3)</li> </ul>	<ul style="list-style-type: none"> <li>No association mono/dual with PTD compared with no ARV.</li> <li>No confounding by duration of ARV or maternal risk factors.</li> </ul>



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

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Notes
Botswana; 2006–2008 <sup>20</sup>	530/530	<ul style="list-style-type: none"> <li>Lopinavir/ritonavir plus zidovudine plus lamivudine (267)</li> <li>Abacavir plus zidovudine plus lamivudine (263)</li> </ul>	<ul style="list-style-type: none"> <li>YES</li> <li>Multi-PI versus multi-NRTI: 2.03 (1.26–3.27)</li> </ul>	<ul style="list-style-type: none"> <li>Secondary analysis of data from randomized, controlled clinical trial of ARV begun at 26–34 weeks for prevention of perinatal transmission.</li> <li>All CD4-cell counts &gt;200 cells/mm<sup>3</sup></li> </ul>
Botswana; 2007–2010 <sup>21</sup>	4,347/3,659	<ul style="list-style-type: none"> <li>ARV, regimen unspecified (70)</li> <li>Mono (2,473)</li> <li>Multi, 91% NNRTI (1,116)</li> </ul>	<ul style="list-style-type: none"> <li>NO</li> <li>No association between multi-ART and very PTD (&lt;32 weeks gestation)</li> </ul>	<ul style="list-style-type: none"> <li>Observational multi-ART before conception associated with very small for gestational age and maternal hypertension during pregnancy.</li> </ul>
Spain; 2000–2008 <sup>10</sup>	803/739	<ul style="list-style-type: none"> <li>Mono/dual (32)</li> <li>Multi-no PI (281)</li> <li>Multi-PI (426)</li> </ul>	<ul style="list-style-type: none"> <li>NO</li> <li>No association between ARV and PTD</li> </ul>	<ul style="list-style-type: none"> <li>Greatest PTD risk if no antepartum ARV received.</li> </ul>
Spain; 1986–2010 <sup>17</sup>	519/371	<ul style="list-style-type: none"> <li>Mono/dual NRTI (73)</li> <li>All multi (298)</li> <li>Multi-PI (178)</li> </ul>	<ul style="list-style-type: none"> <li>NO (compared with no ARV plus mono/dual)</li> <li>Spontaneous PTD not associated with multi-ARV or multi-PI before or during pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>Iatrogenic PTD associated with multi-ARV given in second half of pregnancy and with prior PTD.</li> </ul>
United States; 2007–2010 <sup>18</sup>	1,869/1,810	<ul style="list-style-type: none"> <li>Mono/dual (138)</li> <li>Multi-NRTI (193)</li> <li>Multi-NNRTI (160)</li> <li>Multi-PI (1,319)</li> </ul>	<ul style="list-style-type: none"> <li>YES (compared with no ARV in first trimester)</li> <li>Multi-PI in first trimester vs. none in first trimester</li> <li>PTD 1.55 (1.16–2.07); spontaneous PTD 1.59 (1.10–2.30)</li> </ul>	N/A

**Key to Abbreviations:** ARV = antiretroviral; BMI = body mass index; dual = two ARV drugs; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; NNRTI = non-nucleoside analogue reverse transcriptase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; PI = protease inhibitor; PTD = preterm delivery

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## Recommendations for Use of Antiretroviral Drugs during Pregnancy (Last updated April 17, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- In general, the same regimens as recommended for treatment of non-pregnant adults should be used in pregnant women unless there are known adverse effects for women, fetuses or infants that outweigh benefits **(All)**.
- Multiple factors must be considered when choosing a regimen for a pregnant woman including comorbidities, convenience, adverse effects, drug interactions, resistance testing results, pharmacokinetics (PK), and experience with use in pregnancy **(All)**.
- PK changes in pregnancy may lead to lower plasma levels of drugs and necessitate increased dosages, more frequent dosing, or boosting, especially of protease inhibitors **(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

Antiretroviral (ARV) drug recommendations for HIV-infected, pregnant women have been based on the concept that drugs of known benefit to women should not be withheld during pregnancy unless there are known adverse effects to the mother, fetus, or infant and unless these adverse effects outweigh the benefits to the woman.<sup>1</sup> Pregnancy should not preclude the use of optimal drug regimens. The decision to use any ARV drug during pregnancy should be made by a woman after discussing with her health care provider the known and potential benefits and risks to her and her fetus.

The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel) reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration review related to treatment of HIV-infected adult women, both pregnant and non-pregnant. The durability, tolerability, and simplicity of a medication regimen are particularly important for **ensuring adherence and preserving future treatment options**. Regimen selection should be individualized and the following factors should be considered:

- Comorbidities,
- Patient adherence potential,
- Convenience,
- Potential adverse maternal drug effects that may be exacerbated during pregnancy,
- Potential drug interactions with other medications,
- Results of genotypic resistance testing,
- Pharmacokinetic (PK) changes in pregnancy and degree of placental transfer,
- Potential teratogenic effects and other short- and long-term adverse effects on fetuses or newborns including preterm birth, mutagenicity, and carcinogenicity, and
- Experience with use in pregnancy.

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

- Data from randomized, prospective clinical trials, **and cohort studies** that demonstrate durable viral suppression as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short- and long-term drug toxicity of ARV regimens, with special attention to maternal toxicity and potential teratogenicity and fetal safety;
- Specific knowledge about drug tolerability and simplified dosing regimens;

- Known efficacy of ARV drug regimens in reducing perinatal transmission of HIV;
- PK data during the prenatal period; and
- Data from animal teratogenicity studies.

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.<sup>2,3</sup> During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in cellular transporters and drug metabolizing enzymes in the liver and intestine. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug PK in the pregnant woman.

Currently available data on the PKs and dosing of ARV drugs in pregnancy are summarized in [Table 7](#). In general, the PKs of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and non-pregnant women (although data on etravirine and rilpivirine are limited), whereas protease inhibitor (PI) PKs are more variable, particularly in later pregnancy. Current data suggest that with standard adult dosing, plasma concentrations of ritonavir-boosted lopinavir, atazanavir, darunavir, and nelfinavir are reduced during the second and/or third trimesters (see [Table 7](#)). The need for a dose adjustment depends on the PI, an individual patient's treatment experience, and use (if any) of concomitant medications with potential for drug interactions.<sup>4-11</sup> Raltegravir levels in the third trimester were quite variable but not significantly different than postpartum or historical data in non-pregnant individuals.<sup>12</sup> Data on enfuvirtide, maraviroc, and elvitegravir in pregnancy are too limited to allow recommendations on dosing.

Although clinical data are more limited on ARV drugs in pregnant women than in non-pregnant individuals, sufficient data exist on which to base recommendations related to drug choice for many of the available ARV drugs. [Drugs and drug regimens for pregnant antiretroviral-naïve women](#) are classified as preferred, alternative, insufficient data to recommend use, and not recommended ([Table 6](#)).

Categories of ARV regimens include:

- **Preferred:** Drugs or drug combinations are designated as preferred for use in **ARV-naïve** pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific PK data are available to guide dosing; and **no established association with teratogenic effects** or clinically significant adverse outcomes for mothers, fetuses, or newborns have been reported. Drugs in the preferred category may have toxicity concerns based on non-human data that have not been verified or established in humans. Therefore, it is important to read the full discussion of each drug in the Guidelines before using it in your patients (also see [Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)). For example, efavirenz is now listed in the preferred category, but only with initiation after 8 weeks' gestation because of unresolved questions regarding teratogenicity.
- **Alternative:** Drugs or drug combinations are designated as alternatives for initial therapy in **ARV-naïve** pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: experience in pregnancy is limited; data are lacking on teratogenic effects on the fetus; or the drug or regimen is associated with dosing, formulation, administration, or interaction issues.
- **Insufficient Data to Recommend:** The drugs and drug combinations in this category are approved for use in adults but lack pregnancy-specific PK or safety data or such data are too limited to make a recommendation for use in **ARV-naïve pregnant women**.
- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potentially serious maternal or fetal

safety concerns, or pharmacologic antagonism **or are not recommended for ARV-naive populations regardless of pregnancy status.**

**In pregnant women, as in non-pregnant adults,** a combination ARV treatment (cART) regimen with at least three agents is recommended. Recommendations for choice of ARV drug regimen during pregnancy must be individualized according to a pregnant woman's specific ARV history and the presence of comorbidities. Some women may become pregnant and present for obstetrical care while receiving cART for their own health. In general, women who are already on a fully suppressive regimen should continue their regimens (see [HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy](#)).

Other HIV-infected women may not be receiving cART at the time they present for obstetrical care. Some women have never received ARV drugs, and others may have taken ARV drugs for treatment that was stopped, for **prevention of** perinatal transmission of HIV in prior pregnancies, or for pre- or post-exposure prophylaxis. The following sections provide detailed discussions of recommendations based on maternal ARV history **and current and previous resistance testing.**

For ARV-naive women, a cART regimen including two NRTIs and either a **PI with low-dose ritonavir or an NNRTI is preferable (Table 6).**

While zidovudine/lamivudine remains a preferred dual NRTI combination for ARV-naive pregnant women, based on efficacy studies in preventing perinatal transmission and extensive experience with safe use in pregnancy, additional NRTI combinations are also considered in the preferred category. Tenofovir disoproxil fumarate (tenofovir) with emtricitabine or lamivudine is the preferred NRTI component for non-pregnant adults and, based on increased experience with use in pregnancy, once-daily dosing, enhanced activity against hepatitis B, and less frequent toxicity compared to zidovudine/lamivudine, can now be considered a preferred combination in pregnancy. In addition, abacavir offers the advantage of once-daily dosing in combination with lamivudine and has been well tolerated in pregnancy and can be considered a preferred agent.

Data from the Antiretroviral Pregnancy Registry on 1,612 pregnancies with first-trimester exposure to tenofovir have shown no increase in overall birth defects compared with the general population.<sup>13</sup> Animal studies have shown decreased fetal growth and reduction in fetal bone porosity with tenofovir use in pregnancy, and studies in infected children on chronic tenofovir-based therapy have shown bone demineralization in some children. However, increasing experience with tenofovir use in pregnancy has generally been reassuring. Several large case series as well as an analysis from the Pediatric HIV/AIDS Cohort Study (PHACS) including infants born to 449 women taking tenofovir during pregnancy have not shown differences in weight or other growth parameters at birth compared to infants exposed to other ARV regimens *in utero*.<sup>14-18</sup> The PHACS analysis did note slightly lower length and head circumference at 1 year in tenofovir-exposed infants compared to those with other ARV exposures, although this was not reported in other cohorts that had longitudinal follow-up.<sup>16</sup> Additional studies evaluating *in utero* tenofovir exposure are ongoing; given experience with tenofovir in pregnancy to date as well as once daily dosing and decreased toxicity, a tenofovir-based dual NRTI combination has been added as a preferred NRTI combination in pregnancy.

Data from the Antiretroviral Pregnancy Registry on 848 pregnancies with first-trimester exposure to abacavir have shown no increase in overall birth defects compared with the general population.<sup>13</sup> Abacavir was well-tolerated in pregnancy in a large trial in Botswana.<sup>19</sup> 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.

The combination of stavudine/didanosine should not be used in pregnant women because fatal cases of lactic acidosis and hepatic failure have been reported in women who received this combination throughout pregnancy.

**In addition to the dual NRTIs, either a low-dose ritonavir-boosted PI or an NNRTI would be preferred for cART regimens in ARV-naive pregnant women (Table 6).** Ritonavir-boosted lopinavir and ritonavir-boosted atazanavir are the preferred PI drugs for use in ARV-naive pregnant women, based on efficacy studies in



adults and experience with use in pregnancy (see [Table 7](#) for dosing considerations). Alternative PIs include ritonavir-boosted saquinavir or darunavir, although experience is more limited with these regimens in pregnancy.<sup>20-22</sup> PK data and extensive clinical experience do exist for nelfinavir in pregnancy, but the rate of viral response to nelfinavir-based regimens was lower than ritonavir-boosted lopinavir or efavirenz-based regimens in clinical trials of initial therapy in non-pregnant adults. Because of its lower antiviral activity, nelfinavir use is not recommended. Indinavir may be associated with renal stones and has a higher pill burden than many other PI drugs and thus is also not recommended for use in ARV-naive pregnant women. Both atazanavir and indinavir are associated with increased indirect bilirubin levels, which theoretically may increase the risk of hyperbilirubinemia in neonates although pathologic elevations have not been seen in studies to date. In an analysis from PHACS, *in utero* exposure to atazanavir compared to other drugs was associated with risk of late language emergence at 12 months, but that was no longer significant at 24 months.<sup>23,24</sup> Data on use in pregnancy are too limited to recommend routine use of fosamprenavir and ritonavir-boosted tipranavir in pregnant women, although they can be considered for women who are intolerant of other agents or who require tipranavir/ritonavir because of resistance.

Efavirenz is the preferred NNRTI for non-pregnant adults. Although increasing data on use of efavirenz in pregnancy are reassuring,<sup>25</sup> because of concerns regarding potential teratogenicity, efavirenz is not recommended for initiation in ARV-naive women in the first 8 weeks of pregnancy (see [Teratogenicity](#)). Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens. Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the health of the woman. Because the risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized before 4–6 weeks of pregnancy, and because unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz may be continued in pregnant women presenting for prenatal care in the first trimester who have achieved virologic suppression on the regimen (see [HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment](#)). Initiation of efavirenz can be considered in ARV-naive pregnant women after the first 8 weeks of pregnancy with accurate dating parameters, based on clinical indication. Nevirapine would be an alternate NNRTI for ARV-naive pregnant women with CD4 T lymphocyte (CD4) cell counts <250 cells/mm<sup>3</sup> and can be continued in ARV-experienced women already receiving a suppressive nevirapine-based regimen, regardless of CD4 cell count. In general, nevirapine should not be initiated in treatment-naive women with CD4 cell counts >250 cells/mm<sup>3</sup> because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity. Elevated transaminase levels at baseline also may increase the risk of nevirapine toxicity.<sup>26</sup> Safety and PK data on etravirine and rilpivirine in pregnancy are insufficient to recommend use of these NNRTI drugs in ARV-naive women.

Safety and PK data in pregnancy are insufficient to recommend use of the entry inhibitors enfuvirtide and maraviroc in ARV-naive women during pregnancy. Use of these agents can be considered for women who have failed therapy with several other classes of ARV drugs after consultation with HIV and obstetric specialists.

Data on the integrase inhibitor raltegravir during pregnancy are limited but increasing; cART regimens including raltegravir can be considered as alternate regimens when preferred agents cannot be used in ARV-naive pregnant women.<sup>12,21,27-29</sup> Clinical trial data from non-pregnant adults suggest a more rapid viral decay with the use of raltegravir compared to efavirenz.<sup>30</sup> Case series have reported rapid viral decay with the use of raltegravir initiated late in pregnancy given with the goal of achieving viral suppression and reducing risk of perinatal HIV transmission, but no comparative data are available in pregnancy.<sup>27,29,31-34</sup> The rate of viral decay with raltegravir compared to efavirenz or ritonavir-boosted lopinavir in late-presenting pregnant women is currently under investigation in a trial in the IMPAACT network, P1081. A case report of marked elevation of liver transaminases after initiation of raltegravir in late pregnancy, which resolved rapidly after stopping the drug, suggests that monitoring of transaminases may be indicated with use of this strategy.<sup>35</sup>

There are currently no data on the use of elvitegravir with cobicistat in pregnancy, thus these drugs cannot be recommended for ARV-naïve pregnant women at this time.

Although data are insufficient to support or refute the teratogenic risk of ARV drugs when administered during the first trimester, information to date does not support major teratogenic effects for the majority of such agents. (For further data, see [www.APRegistry.com](http://www.APRegistry.com).) However, certain drugs are of more concern than others—for example, efavirenz should be avoided during the first 8 weeks of pregnancy when possible (see [Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy](#)).

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**Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women**  
(page 1 of 2)

These recommendations are for pregnant women who have never received antiretroviral therapy (ART) previously (i.e., ARV-naive) and are predicated on lack of evidence of resistance to regimen components. See [Table 7](#) for more information on specific drugs and dosing in pregnancy. Within each drug class, regimens are listed alphabetically, and the order does not indicate a ranking of preference. It is recommended that women who become pregnant while on a stable ARV regimen with viral suppression remain on that same regimen.

Drug	Comments
<b>Preferred Regimens</b>	
Regimens with clinical trial data in adults demonstrating optimal efficacy and durability with acceptable toxicity and ease of use, PK data available in pregnancy, and no evidence to date of teratogenic effects or established adverse outcomes for mother/fetus/newborn. To minimize the risk of resistance, a PI regimen is preferred for women who may stop ART during the postpartum period.	
<b>Preferred Two-NRTI Backbone</b>	
ABC/3TC	Available as FDC, can be administered once daily, but potential HSR. ABC <b>should not be used</b> in patients who test positive for HLA-B*5701.
TDF/FTC or 3TC	TDF/FTC available as FDC. Either TDF/FTC or TDF and 3TC can be administered once daily. TDF has potential renal toxicity, thus TDF-based dual NRTI combinations should be used with caution in patients with renal insufficiency.
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 toxicity.
<b>PI Regimens</b>	
ATV/r + a Preferred Two-NRTI Backbone	Once-daily administration.
LPV/r + a Preferred Two-NRTI Backbone	Twice-daily administration. Once-daily LPV/r is not recommended for use in pregnant women.
<b>NNRTI Regimen</b>	
<b>EFV + a Preferred Two-NRTI Backbone</b> <b>Note:</b> May be initiated <u>after the first 8 weeks of pregnancy</u>	Concern because of birth defects seen in primate study; risk in humans is unclear (see <a href="#">Teratogenicity</a> and <a href="#">Table 7</a> ). Postpartum contraception must be ensured. Preferred regimen in women requiring co-administration of drugs with significant interactions with PIs.
<b>Alternative Regimens</b>	
Regimens with clinical trial data demonstrating efficacy in adults but one or more of the following apply: experience in pregnancy is limited, data are lacking or incomplete on teratogenicity, or regimen is associated with dosing, formulation, toxicity, or interaction issues	
<b>PI Regimens</b>	
DRV/r + a Preferred Two-NRTI Backbone	Less experience with use in pregnancy than ATV/r and LPV/r.
SQV/r + a Preferred Two-NRTI Backbone	Baseline ECG is recommended before initiation of SQV/r because of potential PR and QT prolongation; contraindicated with pre-existing cardiac conduction system disease. Large pill burden.
<b>NNRTI Regimen</b>	
NVP + a Preferred Two-NRTI Backbone	NVP should be used with caution when initiating ART in women with CD4 T-lymphocyte (CD4) cell count >250 cells/mm <sup>3</sup> . Use NVP and ABC together with caution; both can cause HSRs within the first few weeks after initiation.
<b>Integrase Inhibitor Regimen</b>	
RAL + a Preferred Two-NRTI Backbone	Limited data on RAL use in pregnancy, but may be considered when drug interactions with PI regimens are a concern.



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

Drug	Comments
<b>Insufficient Data in Pregnancy to Recommend Routine Use in ART-Naive Women</b>	
Drugs that are approved for use in adults but lack adequate pregnancy-specific PK or safety data	
DTG	No data on use of DTG in pregnancy
EVG/COBI/TDF/FTC Fixed Drug Combination	No data on use of EVG/COBI component in pregnancy.
FPV/r	Limited data on use in pregnancy.
MVC	MVC requires tropism testing before use. Few case reports of use in pregnancy.
RPV	RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4 cell count <200 cells/mm <sup>3</sup> . Do not use with proton pump inhibitor. Limited data on use in pregnancy.
<b>Not Recommended</b>	
Drugs whose use is not recommended because of toxicity, lower rate of viral suppression or because not recommended in ART-naive populations	
ABC/3TC/ZDV	Generally not recommended due to inferior virologic efficacy.
d4T	Not recommended due to toxicity.
ddl	Not recommended due to toxicity.
IDV/r	Concerns re: kidney stones, hyperbilirubinemia.
NFV	Lower rate of viral suppression with NFV compared to LPV/r or EFV in adult trials.
RTV	RTV as a single PI is not recommended because of inferior efficacy and increased toxicity.
ETR	Not recommended in ART-naive populations
T20	Not recommended in ART-naive populations
TPV	Not recommended in ART-naive populations

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



**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 1 of 15)**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
NRTIs	N/A	N/A	<p>NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection.</p> <p>See text for discussion of potential maternal and infant mitochondrial toxicity.</p>
<p><b>Abacavir</b> (ABC) <i>Ziagen</i></p> <p>(3TC/ABC) <i>Epzicom</i></p> <p>(ZDV/3TC/ABC) <i>Trizivir</i></p>	<p><u>ABC (Ziagen)</u> <i>Tablet:</i> • 300 mg</p> <p><i>Solution:</i> • 20 mg/mL</p> <p><u>Epzicom:</u> • ABC 600 mg plus 3TC 300 mg tablet</p> <p><u>Trizivir:</u> • ABC 600 mg plus 3TC 150 mg plus ZDV 300 mg tablet</p>	<p><u>Standard Adult Doses</u> <i>ABC (Ziagen):</i> • 300 mg twice daily or 600 mg once daily, without regard to food</p> <p><i>Epzicom:</i> • 1 tablet once daily without regard to food</p> <p><i>Trizivir:</i> • 1 table twice daily without regard to food</p> <p><u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.</p> <p><u>Dosing in Pregnancy:</u> • No change in dose indicated.</p>	<p>High placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</p> <p>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.</p>
<p><b>Didanosine</b> (ddl) <i>Videx</i> <i>Videx EC</i> Generic ddl</p>	<p><u>ddl (Videx)</u> <i>Buffered Tablets (Non-EC):</i> • No longer available</p> <p><i>Solution:</i> • 10 mg/mL oral solution</p> <p><u>Videx EC (EC Beadlets)</u> <u>Capsules:</u> • 125 mg • 200 mg • 250 mg • 400 mg</p> <p><u>Generic Delayed-Release Capsules:</u> • 200 mg • 250 mg • 400 mg</p>	<p><u>Standard Adult Doses</u> <i>Body Weight ≥60kg:</i> • 400 mg once daily</p> <p><u>With TDF:</u> • 250 mg once daily; take 1/2 hour before or 2 hours after a meal.</p> <p><i>Body Weight &lt;60kg:</i> • 250 mg once daily</p> <p><u>With TDF:</u> • 200 mg once daily; take 1/2 hour before or 2 hours after a meal.</p> <p><b>Note:</b> 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.</p> <p><u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.</p> <p><u>Dosing in Pregnancy:</u> • No change in dose indicated.</p>	<p>Low-moderate placental transfer to fetus.<sup>b</sup></p> <p>In the APR, an increased rate of birth defects with ddl compared to general population was noted after both first-trimester (20/413, 4.8%, 95% CI, 3.0–7.4%) and later exposure (20/460, 4.3%, 95% CI 2.7–6.6%). No specific pattern of defects was noted and clinical relevance is uncertain.</p> <p>ddl should not be used with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together.</p>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup>** (page 2 of 15)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
<p><b>Emtricitabine</b> (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><u>FTC (Emtriva)</u> <i>Capsules:</i> • 200 mg</p> <p><i>Oral Solution:</i> • 10 mg/mL</p> <p><u>Truvada:</u> • FTC 200 mg plus TDF 300 mg tablet</p> <p><u>Atripla:</u> • FTC 200 mg plus TDF 300 mg plus EFV<sup>c</sup> 600 mg tablet</p> <p><u>Complera:</u> • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet</p> <p><u>Stribild:</u> • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet</p>	<p><u>Standard Adult Dose(s)</u> <i>FTC (Emtriva)</i> <u>Capsule:</u> • 200 mg once daily without regard to food</p> <p><u>Oral Solution:</u> • 240 mg (24 mL) once daily without regard to food</p> <p><i>Truvada:</i> • 1 tablet once daily without regard to food</p> <p><i>Atripla:</i> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.</p> <p><i>Complera:</i> • 1 tablet once daily with food</p> <p><i>Stribild:</i> • 1 tablet once daily with food</p> <p><u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.</p> <p><u>Dosing in Pregnancy:</u> • No change in dose indicated.</p>	<p>High placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</p> <p>If hepatitis B coinfecting, it is possible that a hepatitis B flare may occur if the drug stopped postpartum; see <a href="#">HIV/Hepatitis B Virus Coinfection</a>.</p>
<p><b>Lamivudine</b> (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><u>3TC (Epivir)</u> <i>Tablets:</i> • 150 mg • 300 mg</p> <p><i>Oral Solution:</i> • 10 mg/mL</p> <p><u>Combivir:</u> • 3TC 150 mg plus ZDV 300 mg tablet</p> <p><u>Epzicom:</u> • 3TC 300 mg plus ABC 600 mg tablet</p> <p><u>Trizivir:</u> • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet</p>	<p><u>Standard Adult Dose(s)</u> <i>3TC (Lamivudine):</i> • 150 mg twice daily or 300 mg once daily, without regard to food</p> <p><i>Combivir:</i> • 1 tablet twice daily without regard to food</p> <p><i>Epzicom:</i> • 1 tablet once daily without regard to food</p> <p><i>Trizivir:</i> • 1 tablet twice daily without regard to food</p> <p><u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.</p> <p><u>Dosing in Pregnancy:</u> • No change in dose indicated.</p>	<p>High placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).</p> <p>If hepatitis B coinfecting, it is possible that a hepatitis B flare may occur if the drug stopped postpartum; see <a href="#">HIV/Hepatitis B Virus Coinfection</a>.</p>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 3 of 15)**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
<b>Stavudine</b> (d4T) <i>Zerit</i>	<u>Capsules:</u> <ul style="list-style-type: none"> <li>• 15 mg</li> <li>• 20 mg</li> <li>• 30 mg</li> <li>• 40 mg</li> </ul> <u>Oral Solution:</u> <ul style="list-style-type: none"> <li>• 1 mg/mL following reconstitution</li> </ul>	<u>Standard Adult Dose(s)</u> <u>Body Weight ≥60 kg:</u> <ul style="list-style-type: none"> <li>• 40 mg twice daily without regard to meals</li> </ul> <u>Body Weight &lt;60 kg:</u> <ul style="list-style-type: none"> <li>• 30 mg twice daily without regard to meals</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• PK not significantly altered in pregnancy.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• No change in dose indicated.</li> </ul>	High placental transfer. <sup>b</sup>  No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).  d4T should not be used with ddI or ZDV.  Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together.
<b>Tenofovir Disoproxil Fumarate</b> (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> <ul style="list-style-type: none"> <li>• 300 mg</li> </ul> <u>Powder:</u> <ul style="list-style-type: none"> <li>• 40 mg/1G oral powder</li> </ul> <u>Truvada:</u> <ul style="list-style-type: none"> <li>• TDF 300 mg plus FTC 200 mg tablet</li> </ul> <u>Atripla:</u> <ul style="list-style-type: none"> <li>• TDF 300 mg plus FTC 200 mg plus EFV<sup>c</sup> 600 mg tablet</li> </ul> <u>Complera:</u> <ul style="list-style-type: none"> <li>• TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet</li> </ul> <u>Stribild:</u> <ul style="list-style-type: none"> <li>• TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet</li> </ul>	<u>Standard Adult Dose</u> <u>TDF (Viread)</u> <u>Tablet:</u> <ul style="list-style-type: none"> <li>• 300 mg once daily without regard to food</li> </ul> <u>Powder:</u> <ul style="list-style-type: none"> <li>• 8 mg/kg (up to maximum 300 mg), take with food</li> </ul> <u>Truvada:</u> <ul style="list-style-type: none"> <li>• 1 tablet once daily without regard to food</li> </ul> <u>Atripla:</u> <ul style="list-style-type: none"> <li>• 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.</li> </ul> <u>Complera:</u> <ul style="list-style-type: none"> <li>• 1 tablet once daily with food</li> </ul> <u>Stribild:</u> <ul style="list-style-type: none"> <li>• 1 tablet once daily with food</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• AUC lower in third trimester than postpartum but trough levels adequate.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• No change in dose indicated.</li> </ul>	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).  Studies in monkeys (at doses approximately 2-fold higher than that for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no effect on intrauterine growth, but one study demonstrated lower length and head circumference with exposure.  TDF should be used in combination with 3TC or FTC in women with chronic HBV infection. If hepatitis B coinfecting, it is possible that a hepatitis B flare may occur if the drug stopped postpartum; see <a href="#">HIV/Hepatitis B Virus Coinfection</a> .  Because of potential for renal toxicity, renal function should be monitored.

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 4 of 15)**

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<b>Zidovudine</b> (AZT, ZDV) <i>Retrovir</i> (ZDV/3TC) <i>Combivir</i> (ZDV/3TC/ABC) <i>Trizivir</i>	<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 <u>Combivir:</u> • ZDV 300 mg plus 3TC 150 mg tablet <u>Trizivir:</u> • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	<u>Standard Adult Dose(s)</u> <u>ZDV (Retrovir):</u> • 300 mg twice daily or 200 mg 3 times daily, 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 <u>Combivir:</u> • 1 tablet twice daily, without regard to food <u>Trizivir:</u> • 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. <sup>b</sup> No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).
<b>NNRTI Drugs</b>	N/A	N/A	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.

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 5 of 15)**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
<p><b>Efavirenz<sup>d</sup></b> (EFV) <i>Sustiva</i></p> <p>(EFV/TDF/FTC) <i>Atripla</i></p>	<p><u>EFV (Sustiva)</u> <i>Capsules:</i></p> <ul style="list-style-type: none"> <li>• 50 mg</li> <li>• 200 mg</li> </ul> <p><i>Tablet:</i></p> <ul style="list-style-type: none"> <li>• 600 mg</li> </ul> <p><u>Atripla:</u></p> <ul style="list-style-type: none"> <li>• EFV 600 mg plus TDF 300 mg plus FTC 200 mg tablet</li> </ul>	<p><u>Standard Adult Dose</u> <i>EFV (Sustiva):</i></p> <ul style="list-style-type: none"> <li>• 600 mg once daily at or before bedtime, on empty stomach to reduce side effects</li> </ul> <p><i>Atripla:</i></p> <ul style="list-style-type: none"> <li>• 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester participants exceeded target exposure.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• No change in dose indicated.</li> </ul>	<p>Moderate placental transfer to fetus.<sup>b</sup></p> <p>Potential fetal safety concern: FDA Pregnancy Class D. Cynomolgus monkeys receiving EFV during the first trimester at a dose resulting in plasma levels comparable to systemic human therapeutic exposure had 3 of 20 infants with significant CNS or other malformations.</p> <p>In humans, there is no increase in overall birth defects with first-trimester EFV exposure. However, in humans with first-trimester exposure, there have been 6 retrospective case reports and 1 prospective case report of CNS defects and 1 prospective case report of anophthalmia with facial clefts. The relative risk with first-trimester exposure is unclear.</p> <p>Non-pregnant women of childbearing potential should undergo pregnancy testing before EFV initiation and counseling about potential risk to the fetus and desirability of avoiding pregnancy while on EFV-containing regimens. Alternate ARV regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the health of the woman.</p> <p>Because the risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized before 4–6 weeks of pregnancy, and unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV may be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided there is virologic suppression on the regimen (see <a href="#">HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment</a>).</p>



**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup>** (page 6 of 15)

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<p><b>Etravirine</b> (ETR) <i>Intelence</i></p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• 25 mg</li> <li>• 100 mg</li> <li>• 200 mg</li> </ul>	<p><u>Standard Adult Dose(s):</u></p> <ul style="list-style-type: none"> <li>• 200 mg twice daily with food</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Limited PK data in pregnancy (n = 4) suggest no significant differences from non-pregnant adults.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Insufficient data to make dosing recommendation.</li> </ul>	<p>Moderate placental transfer (data from one mother-infant pair).<sup>b</sup></p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p>
<p><b>Nevirapine</b> (NVP) <i>Viramune</i></p> <p><i>Viramune XR</i> (Extended Release)</p> <p><b>Note:</b> Generic available for 200 mg tablets</p>	<p><u>NVP (Viramune)</u></p> <p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• 200 mg</li> </ul> <p><u>Oral Suspension:</u></p> <ul style="list-style-type: none"> <li>• 50 mg/5 mL</li> </ul> <p><u>Viramune XR Tablets:</u></p> <ul style="list-style-type: none"> <li>• 100 mg</li> <li>• 400 mg</li> </ul>	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Repeat lead-in period if therapy is discontinued for &gt;7 days.</li> <li>• 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.</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• PK not significantly altered in pregnancy.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• No change in dose indicated.</li> </ul>	<p>High placental transfer to fetus.<sup>b</sup></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 counts ≥250/mm<sup>3</sup> 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/mm<sup>3</sup> 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>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 7 of 15)**

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<b>Rilpivirine</b> (RPV) <i>Endurant</i>  (RPV/TDF/FTC) <i>Complera</i>	<u>RPV (Endurant)</u> <u>Tablet:</u> • 25 mg  <u>Complera:</u> • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet	<u>Standard Adult Dose</u> <u>RPV (Endurant):</u> • 25 mg once daily with food  <u>Complera:</u> • 1 tablet once daily with food  <u>PK in Pregnancy:</u> • No PK studies in human pregnancy, no dosing recommendation can be made.  <u>Dosing in Pregnancy:</u> • Insufficient data to make dosing recommendation.	Unknown placental transfer to fetus in humans.  No evidence of teratogenicity in rats or rabbits. Insufficient data to assess for teratogenicity in humans.
<b>Protease Inhibitors</b>	N/A	N/A	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 <a href="#">Combination Antiretroviral Drug Regimens and Pregnancy Outcomes</a> ).

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup>** (page 8 of 15)

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<p><b>Atazanavir</b> (ATV) <i>Reyataz</i></p> <p><b>Note:</b> Must be combined with low-dose RTV boosting in pregnancy</p>	<p><u>Capsules:</u></p> <ul style="list-style-type: none"> <li>• 100 mg</li> <li>• 150 mg</li> <li>• 200 mg</li> <li>• 300 mg</li> </ul>	<p><u>Standard Adult Dose</u> <i>ARV-Naive Patients</i> <u>Without RTV Boosting:</u></p> <ul style="list-style-type: none"> <li>• ATV 400 mg once daily with food; ATV without RTV boosting <b>not</b> recommended when used with TDF, H<sub>2</sub>-receptor antagonist or proton pump inhibitor or during pregnancy.</li> </ul> <p><u>With RTV Boosting:</u></p> <ul style="list-style-type: none"> <li>• ATV 300 mg plus RTV 100 mg once daily with food</li> <li>• When combined with EFV in ARV-naive patients: ATV 400 mg plus RTV 100 mg once daily with food</li> </ul> <p><i>ARV-Experienced Patients:</i></p> <ul style="list-style-type: none"> <li>• ATV 300 mg plus RTV 100 mg once daily with food</li> </ul> <ul style="list-style-type: none"> <li>• Do not use with proton pump inhibitor or EFV.</li> <li>• If combined with an H<sub>2</sub>-receptor antagonist: ATV 300 mg plus RTV 100 mg once daily with food</li> <li>• If combined with an H<sub>2</sub>-receptor antagonist and TDF: ATV 400 mg plus RTV 100 mg once daily with food</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• ATV concentrations reduced during pregnancy, also reduced when given concomitantly with TDF or H<sub>2</sub>-receptor antagonist.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Use of unboosted ATV <b>not</b> recommended during pregnancy.</li> <li>• Use of an increased dose (400 mg ATV plus 100 mg RTV once daily with food) during the second and third trimesters results in plasma concentrations equivalent to those in non-pregnant adults on standard dosing. Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the second and third trimesters also receiving either TDF or an H<sub>2</sub>-receptor antagonist.</li> </ul>	<p>Low placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (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>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>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 9 of 15)**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
<p><b>Darunavir</b> (DRV) <i>Prezista</i></p> <p><b>Note:</b> Must be combined with low-dose RTV boosting</p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• 75 mg</li> <li>• 150 mg</li> <li>• 400 mg</li> <li>• 600 mg</li> </ul>	<p><u>Standard Adult Dose:</u> <i>ARV-Naive Patients:</i></p> <ul style="list-style-type: none"> <li>• DRV 800 mg plus RTV 100 mg once daily with food</li> </ul> <p><i>ARV-Experienced Patients</i> <u>If No DRV Resistance Mutations:</u></p> <ul style="list-style-type: none"> <li>• DRV 800 mg plus RTV 100 mg once daily with food</li> </ul> <p><u>If Any DRV Resistance Mutations:</u></p> <ul style="list-style-type: none"> <li>• DRV 600 mg plus RTV 100 mg twice daily with food</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Decreased exposure in pregnancy.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Once-daily dosing <b>not</b> recommended during pregnancy. Twice-daily dosing recommended for all pregnant women. Increased twice-daily DRV dose (DRV 800 mg plus RTV 100 mg with food) in pregnancy is being investigated.</li> </ul>	<p>Low placental transfer to fetus.<sup>b</sup></p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits.</p> <p>Must be given as low-dose RTV-boosted regimen.</p>
<p><b>Fosamprenavir</b> (FPV) <i>Lexiva (a prodrug of amprenavir)</i></p> <p><b>Note:</b> Must be combined with low-dose RTV boosting in pregnancy</p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• 700 mg</li> </ul> <p><u>Oral Suspension:</u></p> <ul style="list-style-type: none"> <li>• 50 mg/mL</li> </ul>	<p><u>Standard Adult Dose</u> <i>ARV-Naive Patients:</i></p> <ul style="list-style-type: none"> <li>• FPV 1400 mg twice daily without food or</li> <li>• FPV 1400 mg plus RTV 100 or 200 mg once daily without food or</li> <li>• FPV 700 mg plus RTV 100 mg twice daily without food</li> </ul> <p><i>PI-Experienced Patients (Once-Daily Dosing not Recommended):</i></p> <ul style="list-style-type: none"> <li>• FPV 700 mg plus RTV 100 mg twice daily without food</li> </ul> <p><i>Co-Administered with EFV:</i></p> <ul style="list-style-type: none"> <li>• FPV 700 mg plus RTV 100 mg twice daily without food; or</li> <li>• FPV 1400 mg plus RTV 300 mg once daily without food</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• 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</li> </ul>	<p>Low placental transfer to fetus.<sup>b</sup></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>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 10 of 15)**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
<p><b>Fosamprenavir</b>, continued (FPV)</p> <p><i>Lexiva (a prodrug of amprenavir)</i></p> <p><b>Note:</b> Must be combined with low-dose RTV boosting in pregnancy</p>		<p>during the third trimester were adequate for patients without PI resistance mutations.</p> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Use of unboosted FPV <b>not</b> recommended during pregnancy. No change in standard boosted dose (FPV 700 mg plus RTV 100 mg twice daily without food) indicated.</li> </ul>	
<p><b>Indinavir</b> (IDV) <i>Crixivan</i></p> <p><b>Note:</b> Must be combined with low-dose RTV boosting in pregnancy</p>	<p><u>Capsules:</u></p> <ul style="list-style-type: none"> <li>• 100 mg</li> <li>• 200 mg</li> <li>• 400 mg</li> </ul>	<p><u>Standard Adult Dose</u></p> <p><u>Without RTV Boosting:</u></p> <ul style="list-style-type: none"> <li>• IDV 800 mg every 8 hours, taken 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal.</li> </ul> <p><u>With RTV Boosting:</u></p> <ul style="list-style-type: none"> <li>• IDV 800 mg plus RTV 100 mg twice daily without regard to meals</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• 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.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Use of unboosted IDV <b>not</b> recommended during pregnancy.</li> </ul>	<p>Minimal placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (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>



**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 11 of 15)**

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<b>Ritonavir-Boosted Lopinavir</b> (LPV/r) Kaletra	<p><u>Tablets (Co-Formulated):</u></p> <ul style="list-style-type: none"> <li>• LPV 200 mg plus RTV 50 mg</li> <li>• LPV 100 mg plus RTV 25 mg</li> </ul> <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> <li>• LPV 400 mg plus RTV 100 mg/5mL</li> </ul>	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> <li>• LPV 400 mg plus RTV 100 mg twice daily</li> </ul> <p>or</p> <ul style="list-style-type: none"> <li>• LPV 800 mg plus RTV 100 mg once daily</li> </ul> <p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• Take without regard to food.</li> </ul> <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> <li>• Take with food.</li> </ul> <p><u>With EFV or NVP (PI-Naive or PI-Experienced Patients):</u></p> <ul style="list-style-type: none"> <li>• LPV 500 mg plus RTV 125 mg tablets twice daily without regard to meals (use a combination of two LPV 200 mg plus RTV 50 mg tablets plus one LPV 100 mg plus RTV 25 mg tablet) without regard to food</li> </ul> <p>or</p> <ul style="list-style-type: none"> <li>• LPV 533 mg plus RTV 133 mg oral solution (6.5 mL) twice daily with food</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• PK studies suggest increased dose (LPV 600 mg plus RTV 150 mg twice daily without regard to meals) should be used in second and third trimesters, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. No data to address if drug levels are adequate with once-daily dosing in pregnancy.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Once daily dosing is <b>not</b> recommended during pregnancy.</li> <li>• Some experts recommend increased dose of LPV 600 mg plus RTV 150 mg twice daily without regard to meals in second and third trimester.</li> </ul>	<p>Low placental transfer to fetus.<sup>b</sup></p> <p>No evidence of human teratogenicity (can rule out 2-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>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 12 of 15)**

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<b>Nelfinavir</b> (NFV) <i>Viracept</i>	<u>Tablets:</u> <ul style="list-style-type: none"> <li>• 250 mg</li> <li>• 625 mg (Tablets can be dissolved in small amount of water.)</li> </ul> <u>Powder for Oral Suspension:</u> <ul style="list-style-type: none"> <li>• 50 mg/G</li> </ul>	<u>Standard Adult Dose:</u> <ul style="list-style-type: none"> <li>• 1250 mg twice daily or 750 mg three times daily with food</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• 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.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• 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.</li> </ul>	Minimal to low placental transfer to fetus. <sup>b</sup>  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).
<b>Ritonavir</b> (RTV) <i>Norvir</i>  <b>Note:</b> Should be only be used as a low-dose booster with other PIs	<u>Capsules:</u> <ul style="list-style-type: none"> <li>• 100 mg</li> </ul> <u>Tablets:</u> <ul style="list-style-type: none"> <li>• 100 mg</li> </ul> <u>Oral Solution:</u> <ul style="list-style-type: none"> <li>• 80 mg/mL</li> </ul>	<u>Standard Adult Dose as PK Booster for Other PIs:</u> <ul style="list-style-type: none"> <li>• 100–400 mg per day in 1–2 divided doses (Refer to other PIs for specific dosing recommendations.)</li> </ul> <u>Tablet:</u> <ul style="list-style-type: none"> <li>• Take with food.</li> </ul> <u>Capsule or Oral Solution:</u> <ul style="list-style-type: none"> <li>• To improve tolerability, recommended to take with food if possible.</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• Lower levels during pregnancy compared with postpartum but no dosage adjustment necessary when used as booster.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• Use only as low-dose booster with other PIs.</li> </ul>	Low placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).  Oral solution contains 43% alcohol and is not recommended for use in pregnancy.

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 13 of 15)**

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<p><b>Saquinavir</b> (SQV) <i>Invirase</i></p> <p><b>Note:</b> Must be combined with low-dose RTV boosting</p>	<p><u>Tablets:</u></p> <ul style="list-style-type: none"> <li>• 500 mg</li> </ul> <p><u>Capsules:</u></p> <ul style="list-style-type: none"> <li>• 200 mg</li> </ul>	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> <li>• SQV 1000 mg plus RTV 100 mg twice a day with food or within 2 hours after a meal</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Based on limited data, SQV exposure may be reduced in pregnancy but not sufficient to warrant a dose change.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• No change in dose indicated.</li> </ul>	<p>Low placental transfer to fetus.<sup>b</sup></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>Baseline ECG recommended before starting because PR and/or QT interval prolongations have been observed. Contraindicated in patients with pre-existing cardiac conduction system disease.</p>
<p><b>Tipranavir</b> (TPV) <i>Aptivus</i></p> <p><b>Note:</b> must be combined with low-dose RTV boosting</p>	<p><u>Capsules:</u></p> <ul style="list-style-type: none"> <li>• 250 mg</li> </ul> <p><u>Oral Solution:</u></p> <ul style="list-style-type: none"> <li>• 100 mg/mL</li> </ul>	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> <li>• TPV 500 mg plus RTV 200 mg twice daily</li> </ul> <p><u>With RTV Tablets:</u></p> <ul style="list-style-type: none"> <li>• Take with food.</li> </ul> <p><u>With RTV Capsules or Solution:</u></p> <ul style="list-style-type: none"> <li>• Take without regard to food.</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Limited PK data in human pregnancy.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Insufficient data to make dosing recommendation.</li> </ul>	<p>Moderate placental transfer to fetus reported in one patient.<sup>b</sup></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><b>Entry Inhibitors</b></p>	<p>N/A</p>	<p>N/A</p>	<p>N/A</p>
<p><b>Enfuvirtide</b> (T20) <i>Fuzeon</i></p>	<p><u>Injectable:</u></p> <ul style="list-style-type: none"> <li>• Supplied as lyophilized powder. Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.</li> </ul>	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> <li>• 90 mg (1 mL) twice daily without regard to meals</li> </ul> <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• No PK data in human pregnancy.</li> </ul> <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> <li>• Insufficient data to make dosing recommendation.</li> </ul>	<p>Minimal to low placental transfer to fetus.<sup>b</sup></p> <p>No data on human teratogenicity.</p>

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 14 of 15)**

<b>Generic Name</b> (Abbreviation) Trade Name	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Recommendations for Use in Pregnancy</b>
<b>Maraviroc</b> (MVC) Selzentry	<u>Tablets:</u> <ul style="list-style-type: none"> <li>• 150 mg</li> <li>• 300 mg</li> </ul>	<u>Standard Adult Dose:</u> <ul style="list-style-type: none"> <li>• 300 mg twice daily without regard to meals</li> </ul> <u>Dosing Affected by Concomitant Use of Drugs Metabolized by CYP450 3A4</u> <u>Co-Administration with CYP 3A4 Inhibitors:</u> <ul style="list-style-type: none"> <li>• 150 mg twice daily without regard to meals</li> </ul> <u>Co-Administration with CYP 3A4 Inducers:</u> <ul style="list-style-type: none"> <li>• 600 mg twice daily without regard to meals</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• Limited PK data in human pregnancy.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• Insufficient data to make dosing recommendation.</li> </ul>	Minimal to low placental transfer to fetus. <sup>b</sup>  No data on human teratogenicity.
<b>Integrase Inhibitors</b>	N/A	N/A	N/A
<b>Dolutegravir</b> (DTG) Tivicay	<u>Tablets:</u> <ul style="list-style-type: none"> <li>• 50 mg</li> </ul>	<u>Standard Adult Dose</u> <u>ARV-Naive or ARV-Experienced but Integrase Inhibitor-Naive Patients:</u> <ul style="list-style-type: none"> <li>• DTG 50 mg once daily</li> </ul> <u>ARV-Naive or ARV-Experienced but Integrase Inhibitor-Naive if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced:</u> <ul style="list-style-type: none"> <li>• DTG 50 mg twice daily</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• No PK data in human pregnancy.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• Insufficient data to make dosing recommendation.</li> </ul>	Unknown placental transfer to fetus.  Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits.
<b>Elvitegravir plus cobicistat</b> (EVG/COBI) Stribild	<u>Tablet (Co-Formulated):</u> <ul style="list-style-type: none"> <li>• EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg</li> </ul>	<u>Standard Adult Dose:</u> <ul style="list-style-type: none"> <li>• One tablet once daily with food.</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• No PK studies in human pregnancy.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• Insufficient data to make dosing recommendation.</li> </ul>	No data on placental transfer of EVG/COBI are available.  Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

**Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy<sup>a</sup> (page 15 of 15)**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Recommendations for Use in Pregnancy
<b>Raltegravir</b> (RAL) Isentress	<u>Film-Coated Tablets:</u> • 400 mg  <u>Chewable Tablets:</u> • 25 mg • 100 mg	<u>Standard Adult Dose:</u> • 400 mg twice daily without regard to food  <u>With Rifampin:</u> • 800 mg twice daily without regard to food  <u>PK in Pregnancy:</u> • Limited data suggest PK not significantly altered in pregnancy.  <u>Dosing in Pregnancy:</u> • No change in dose indicated.	High placental transfer to fetus. <sup>b</sup>  Insufficient data to assess for teratogenicity in humans. Increased skeletal variants in rats, no increase in defects in rabbits.  Case report of markedly elevated liver transaminases with use in late pregnancy. Severe, potentially life-threatening and fatal skin and hypersensitivity reactions have been reported in non-pregnant adults.  Chewable tablets contain phenylalanine.

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

<sup>b</sup> Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

**High:** >0.6

**Moderate:** 0.3–0.6

**Low:** 0.1–0.3

**Minimal:** <0.1

<sup>c</sup> See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; APR = Antiretroviral Pregnancy Registry; ARV = antiretroviral; ATV = atazanavir; AUC = area under the curve; CD4 = CD4 T lymphocyte; CI = confidence interval; CNS = central nervous system; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; DRV = darunavir; EC = enteric coated; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; IDV = indinavir; IV = intravenous; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = ritonavir-boosted tipranavir; T20 = enfuvirtide; ZDV = zidovudine



## HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- All HIV-infected pregnant women should receive a potent combination antiretroviral (ARV) regimen to reduce the risk of perinatal transmission of HIV (AI). The choice of regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy, and the risk of teratogenicity (see [Table 6](#) and [Table 7](#)).
- The decision as to whether to start the regimen in the first trimester or delay until 12 weeks' gestation will depend on CD4 T lymphocyte count, HIV RNA levels, and maternal conditions (e.g., nausea and vomiting) (AIII). Earlier initiation of a combination ARV regimen may be more effective in reducing transmission, but benefits must be weighed against potential fetal effects of first-trimester drug exposure.
- ARV drug-resistance studies should be performed before starting the ARV regimen if HIV RNA is above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) unless drug-resistance studies have already been performed (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)) (AI). If HIV is diagnosed later in pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing (BIII).
- If there is no evidence of resistance, combination ARV regimens that are preferred for the treatment of antiretroviral-naive HIV-infected pregnant women include: a dual nucleoside reverse transcriptase inhibitor combination (abacavir/lamivudine, tenofovir/emtricitabine or lamivudine, or zidovudine/lamivudine) and either a ritonavir-boosted protease inhibitor (ritonavir-boosted atazanavir or ritonavir-boosted lopinavir) or a non-nucleoside reverse transcriptase inhibitor (efavirenz initiated after 8 weeks of pregnancy) (see [Table 6](#)) (AIII).

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

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

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation. They should be counseled about and offered combination antiretroviral therapy (cART) containing at least 3 drugs for their own health and for prevention of perinatal transmission of HIV, consistent with the principles of treatment for non-pregnant adults.<sup>1</sup> Use of a cART regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal transmission of HIV, lessens the need for consideration of elective cesarean delivery as an intervention to reduce risk of transmission, and reduces risk of ARV drug resistance in the mother. In an analysis of perinatal transmission in 5,151 HIV-infected women between 2000 and 2006 in the United Kingdom and Ireland, the overall perinatal transmission rate was 1.2%. A transmission rate of 0.8% was seen in women on ARV drugs for at least the last 14 days of pregnancy, regardless of the type of ARV regimen or mode of delivery.<sup>2</sup> After adjustment for viral load, mode of delivery, and sex of the infant, longer duration of use of ARV drugs was associated with reduced transmission rates. Similar data from Canada in 1,707 HIV-infected pregnant women followed between 1997 and 2010 showed perinatal transmission was 1% in mothers receiving cART, and 0.4% if more than 4 weeks of cART was received.<sup>3</sup>

ARV drug-resistance testing should be performed before starting an ARV regimen if plasma HIV RNA levels are above the threshold for resistance testing (that is, >500 to 1,000 copies/mL) unless drug-resistance testing has already been performed. For details regarding genotypic and phenotypic resistance testing, see [Adult and Adolescent Antiretroviral Guidelines](#). Given the association of earlier viral suppression with lower risk of transmission as discussed above, if HIV is diagnosed in the second half of pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing, with modification of the regimen, if required, when test results return. Because clinically significant resistance to protease inhibitors (PI) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in ARV-naive individuals, a PI-based cART regimen generally should be considered in this situation.

[Table 6](#) outlines the ARV regimens that are preferred for treatment of HIV-infected pregnant women who have never received ARV drugs, based on available data indicating acceptable toxicity profiles, ease of use, pharmacokinetic data in pregnancy, and lack of evidence of teratogenic effects or established adverse

outcomes for mother, fetus or newborn in addition to optimal ARV efficacy and durability. Preferred dual nucleoside reverse transcriptase inhibitor (NRTI) combinations include abacavir/lamivudine, tenofovir/emtricitabine or lamivudine, or zidovudine/lamivudine in combination with either a ritonavir-boosted PI (ritonavir-boosted atazanavir or ritonavir-boosted lopinavir) or an NNRTI (efavirenz initiated after 8 weeks of pregnancy). Alternative regimens include those demonstrated to be effective in adults but with more limited data on use in pregnancy, lack of or incomplete data on teratogenicity, and dosing, formulation, toxicity or interaction issues. Selection of these regimens should be based on individual patient characteristics and needs (see [Table 7](#)).

Fetuses are most susceptible to the potential teratogenic effects of drugs during the first trimester and the risks of ARV drug exposure during that period are not fully known. Therefore, women in the first trimester who do not require immediate initiation of therapy for symptomatic HIV infection can consider delaying initiation of ARV drugs until after 12 weeks' gestation. This decision should be carefully considered by health care providers and their patients. The discussion should include an assessment of a woman's health status and the benefits and risks to her health of delaying initiation of ARV drugs for several weeks.

Although most perinatal transmission events occur late in pregnancy or during delivery, recent analyses suggest that early control of viral replication may be important in preventing transmission. In a French study, lack of early and sustained control of maternal viral load appeared strongly associated with residual perinatal transmission of HIV.<sup>4</sup> That study evaluated risk factors for perinatal transmission in women with HIV RNA <500 copies/mL at the time of delivery; overall HIV transmission was 0.5%. Women who transmitted were less likely to have received ARV drugs at the time of conception than were nontransmitters and were less likely to have HIV RNA <500 copies/mL at 14, 28, and 32 weeks' gestation. By multivariate analysis, plasma viral load at 30 weeks' gestation was significantly associated with transmission. Among women starting ARV drugs during pregnancy, the gestational age at initiation of therapy did not differ between groups (30 weeks), but viral load tended to decrease earlier in the nontransmitters, although this was not statistically significant. The number of patients initiating therapy during pregnancy was too small to assess whether initiation of ARV drugs in the first trimester was associated with lower rates of transmission. These data suggest that early and sustained control of HIV viral replication is associated with decreasing residual risk of transmission and favor initiating cART sufficiently early in ARV-naive women to suppress viral replication by the third trimester.

Other studies have demonstrated that baseline viral load is significantly associated with the likelihood of viral suppression by delivery, and thus, prompt initiation of cART would be particularly important in HIV-infected pregnant women who have high baseline viral loads.<sup>5,6</sup> However, the potential benefits of earlier initiation of cART must be balanced against the unknown long-term outcome of first-trimester ARV exposure to the fetus.

A cART regimen is recommended for all HIV-infected pregnant women, regardless of viral load. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, there is no threshold below which lack of transmission can be ensured.<sup>7-9</sup> 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.<sup>10-14</sup> Additional mechanisms of protection include pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis of the infant. With PrEP, passage of the ARV drug across the placenta results in presence of drug levels sufficient for inhibition of viral replication in the fetus, particularly during the birth process when there is intensive viral exposure. Therefore, whenever possible, cART regimens initiated during pregnancy should include zidovudine or another NRTI with high transplacental passage, such as lamivudine, emtricitabine, tenofovir, or abacavir (see [Table 7](#)).<sup>15-18</sup> With post-exposure prophylaxis, ARV drugs are administered to the infant after birth.

Some women may wish to restrict fetal exposure to ARV drugs while reducing the risk of HIV transmission to their infants. Use of zidovudine alone during pregnancy for prophylaxis of perinatal transmission is not optimal, but it could be an option for women with low viral loads (i.e., <1,000 copies/mL) on no ARV drugs. In the U.K. study discussed above, transmission rates were 0.7% for women receiving a triple-ARV drug regimen combined with planned cesarean delivery or with planned vaginal delivery and 0.5% in 464 women with HIV RNA levels

<10,000 copies/mL who received single-drug prophylaxis with zidovudine combined with planned cesarean delivery, not significantly different between groups. Zidovudine single-drug prophylaxis is recommended in the British HIV Association guidelines for women with CD4 T lymphocyte counts >350 cells/mm<sup>3</sup> and HIV RNA levels <10,000 copies/mL and wild-type virus who do not require treatment for their own health.<sup>19</sup> Time-limited administration of zidovudine during the second and third trimesters is less likely to induce development of resistance in women with low viral loads than in those with higher viral loads. This lower rate of resistance is likely because of the low level of viral replication and the short duration of exposure.<sup>20,21</sup> Women's choices after counseling to use or not use ARV drugs during pregnancy should be respected.

Raltegravir has been suggested for use in late pregnancy in women who have high viral loads because of its ability to rapidly suppress viral load (approximately 2-log copies/mL decrease by Week 2 of therapy).<sup>22-25</sup> A recent publication reported the effect of adding raltegravir to a standard ARV regimen in 4 women diagnosed with HIV infection in the third trimester.<sup>26</sup> The median viral load at presentation was 271,000 copies/mL and the mean viral load decline per week was 1.12 log (usually not seen until after 1–2 months of standard cART). Although no raltegravir-related side effects were noted in these reports, marked elevations in hepatic transaminases were reported in a single HIV-infected pregnant woman when raltegravir was added to an ARV regimen.<sup>27</sup> Because the efficacy and safety of this approach has only been described in anecdotal reports, it cannot be routinely recommended at this time for women who are ARV-naive.

The cART regimen initiated during pregnancy can be modified after delivery to include simplified regimens that were not used in pregnancy because pregnancy safety data were insufficient. Decisions regarding continuation of an ARV regimen or which specific ARV agents to use should be made by women in consultation with their HIV care providers, taking into account current recommendations and life circumstances (see [General Principles Regarding Use of Antiretroviral Drugs during Pregnancy](#)).

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## HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- In general, HIV-infected pregnant women receiving combination antiretroviral therapy (cART) who present for care during the first trimester should continue treatment during pregnancy, assuming the regimen is tolerated and effective in suppressing viral replication (HIV-1 viral load less than lower limits of detection of the assay) (AII).
- The Panel recommends that efavirenz be continued in pregnant women receiving efavirenz-based cART who present for antenatal care in the first trimester provided the regimen is achieving virologic suppression (see text below) (CIII).
- HIV antiretroviral drug-resistance testing is recommended for pregnant women who have detectable viremia (i.e., >500 to 1,000 copies/mL) on therapy (see [Failure of Viral Suppression](#)) (AI).

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

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

In general, women who have been receiving combination antiretroviral therapy (cART) for their HIV infection should continue that treatment during pregnancy, assuming it is tolerated and effective in suppressing viral replication. Discontinuation of therapy could lead to an increase in viral load with possible decline in immune status and disease progression as well as adverse consequences for the fetus, including increased risk of HIV transmission. Continuation of therapy, therefore, is recommended when pregnancy is identified in HIV-infected women receiving cART.

HIV-infected women receiving cART who present for care during the first trimester should be counseled regarding the benefits and potential risks of administration of antiretroviral (ARV) drugs during this period and that continuation of cART is recommended. There are concerns regarding efavirenz use in the first trimester and potential for neural tube defects, based on preclinical primate data and retrospective case reports (for more details see [Teratogenicity](#)). A recent meta-analysis including data on 1,437 women with first-trimester efavirenz exposure from 19 prospective studies did not find an increased relative risk (RR) of overall birth defects in infants born to women receiving efavirenz-based versus non-efavirenz-based regimens (RR 0.85, 95% confidence interval [CI], 0.6–1.2) and identified 1 neural tube defect, resulting in an incidence of 0.07% (95% CI, 0.002–0.39%).<sup>1</sup> Although a 2- to 3-fold increased incidence of a rare outcome (e.g., neural tube defects [0.02%–0.2% incidence in the United States]) cannot be ruled out given the limited data on first-trimester efavirenz exposure, the available data suggest that first-trimester exposure is not associated with a large (i.e., 10-fold or more) increase in risk of neural tube defects. Analyses from the Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy found that treatment changes during pregnancy significantly increased the risk of incomplete viral suppression at the end of pregnancy.<sup>2</sup> The risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after last menstrual period), pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs in pregnancy may be associated with loss of viral control and, thus, increased risk of transmission to the infant. Therefore, the Panel recommends that efavirenz be continued in pregnant women receiving efavirenz-based cART who present for antenatal care in the first trimester, provided that the regimen is resulting in virologic suppression. In such situations, additional fetal monitoring (such as with second-trimester ultrasound) should be considered to evaluate fetal anatomy.

Resistance testing should be performed in women who are on therapy but in whom viral replication is not fully suppressed (i.e., patient has detectable viremia). The results can be used to select a new regimen with a greater likelihood of suppressing viral replication to undetectable levels. Drug resistance testing is generally done in individuals with HIV RNA levels >1,000 copies/mL; however, in individuals with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered.



Pregnant women for whom nevirapine-containing regimens are achieving virologic suppression and who are tolerating therapy may be continued on that regimen, regardless of current CD4 T lymphocyte (CD4) cell count. Although hepatic toxicity is a concern in women starting a nevirapine-containing regimen who have CD4 cell counts  $>250$  cells/mm<sup>3</sup>, an increased risk of hepatic toxicity has not been seen in women receiving nevirapine-based therapy in whom the therapy has produced immune reconstitution.

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## HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- Obtain an accurate history of all prior antiretroviral (ARV) regimens used for treatment of HIV disease or prevention of transmission, including virologic efficacy, tolerance to the medications, results of prior resistance testing, and any adherence issues (**AIII**).
- If HIV RNA is above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL), ARV drug-resistance studies should be performed before starting an ARV drug regimen (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)) (**AIII**). In women who present late in pregnancy, therapy or prophylaxis should be initiated promptly without waiting for the results of resistance testing (**BIII**).
- Choose and initiate a combination ARV regimen based on results of resistance testing and prior history of antiretroviral therapy while avoiding drugs with teratogenic potential or with known adverse potential for the mother (**AII**).
- Consult specialists in treatment of HIV infection about the choice of a combination ARV regimen in women who previously received ARV drugs for their own health (**AIII**).
- Perform repeat ARV drug-resistance testing (**AI**), assess adherence, and consult with an HIV treatment specialist to guide changes in ARV drugs in women who do not achieve virologic suppression on their ARV regimens (see [Monitoring of the Woman and Fetus During Pregnancy](#)).

**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

During a previous pregnancy, HIV-infected women may have received antiretroviral (ARV) drugs solely for prevention of perinatal transmission. At any time in the past, they also may have discontinued ARV drugs given to them for treatment of their own disease. A small number of clinical trials or observational studies have generated information about how effective combination antiretroviral therapy (cART) is in individuals who previously received ARV prophylaxis. The data are limited to outcomes with therapy containing nevirapine initiated after the use of peripartum single-dose nevirapine.<sup>1-5</sup> **Diminished viral and clinical response to nevirapine-based cART has been observed if cART was initiated within 12 to 24 months after single-dose nevirapine exposure. Adding other ARV drugs to single-dose nevirapine (such as use of an ARV tail) decreases rates of nevirapine resistance<sup>6,7</sup> (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)).**

There is concern that time-limited use of ARV drugs during pregnancy for prophylaxis of perinatal transmission may lead to genotypic resistance and, thus, reduced efficacy of these ARV drugs when used either for indicated HIV therapy in a woman or during a subsequent pregnancy for prevention of perinatal transmission. Rates of resistance appear to be low, based on standard genotyping, after prophylaxis for prevention of perinatal transmission with cART consisting of zidovudine, lamivudine, and nevirapine.<sup>8,9</sup> However, minority populations of virus with resistance to nevirapine or lamivudine have been detected using sensitive allele-specific polymerase chain reaction (PCR) techniques, particularly in women whose virus was inadequately suppressed during prophylaxis.<sup>9-11</sup> **Rates of minor, drug-resistant variants may be lower in women given longer or more complex ARV tails after stopping pregnancy-limited nevirapine-based cART.<sup>12-16</sup> Only limited data are available on the impact of these resistance-conferring minority variants on prediction of virologic or clinical failure of subsequent cART, and the PCR-based assays are not widely available. However, in the OCTANE/A5208 study, while the presence of low-frequency minority viral variants with nevirapine resistance was associated with higher rates of viral failure in women starting nevirapine-based cART after receiving single-dose nevirapine for prevention of perinatal transmission, low-frequency minority variants were not associated with higher rates of nevirapine-cART failure in women who had not had prior single-dose nevirapine exposure.<sup>17</sup> Both standard and sensitive genotyping techniques appear to show a low rate of**

resistance to protease inhibitors (PIs) after pregnancy-limited use of PI-based combination ARV regimens for prophylaxis, but these results reflect assessments in only small numbers of women.<sup>11,18</sup>

To date, treatment failure has not been demonstrated with reinitiation of combination ARV regimens following prophylactic use in pregnancy for prevention of transmission. In ACTG 5227, 52 women who had previously received combination ARV regimens for prevention of perinatal transmission, had no evidence of HIV drug resistance, and had an indication for restarting cART were prescribed a fixed-dose combination of efavirenz plus tenofovir/emtricitabine once daily. After 6 months of therapy, 81% achieved plasma viral loads below the limit of detection; the virologic suppression rate was similar regardless of the drug class of the prior combination ARV regimen and whether women had received such ARV regimens in 1 or more than 1 previous pregnancy.<sup>19</sup> Data from the French Perinatal Cohort assessed virologic suppression with a PI-based combination ARV regimen administered for prevention of perinatal transmission to women who had received ARV prophylaxis during a previous pregnancy. No differences in rates of undetectable viral load at delivery were noted among ARV-naive women when compared with those with previous prophylaxis or according to type of previous prophylaxis regimens received.<sup>20</sup> In addition, the United Kingdom- and Ireland-based National Study of HIV in Pregnancy and Childhood found no increased risk of perinatal transmission in sequential pregnancies compared with 1 pregnancy at a time when most women received interventions for prevention of perinatal HIV transmission.<sup>21</sup> However, in a subsequent comparison between 5,372 ARV-naive pregnant women and 605 women who had previously received ARV but were on no ARV prior to the current pregnancy, there was a slight increase in the risk of detectable viral load among the ARV-experienced women at delivery after receiving antenatal cART (aOR 1.27; 95% CI, 1.01, 1.60). This risk was confined to those ARV-experienced women who received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based as opposed to PI-based therapy.<sup>22</sup> Sufficiently large, prospective, observational studies and clinical trials are lacking by which we can definitively assess the effect of pregnancy-limited ARV prophylaxis on virologic outcomes of subsequent ARV therapy.

Given the lack of substantive data, it is reasonable to use results of initial resistance testing, if available, to make preliminary decisions about ARV regimens in women whose only previous exposure to ARV drugs was during pregnancy for prophylaxis of perinatal transmission. However, interpretation of resistance testing after discontinuation of ARV drugs can be complex because drug-resistance testing is most accurate if performed while an individual is taking the ARV regimen or within 4 weeks of treatment discontinuation. In the absence of selective drug pressure, resistant virus may revert to wild-type virus, and although detection of drug-resistance mutations is informative for choosing a regimen, a negative finding does not rule out the presence of archived drug-resistant virus that could re-emerge once drugs are reinitiated. Therefore, when selecting a new regimen for use during the current pregnancy, all information from the previous pregnancy—including regimens received, viral response, laboratory testing (including HLA-B\*5701 results), and any tolerance or adherence issues—and the results of resistance testing should be taken into consideration. In women who present late in pregnancy, ARVs should be started pending results of resistance testing. Careful monitoring of virologic response to the chosen ARV regimen is important.

If the chosen regimen produces an insufficient viral response, decisions about switching regimens should be guided by repeat resistance testing and assessment of medication adherence. These measures should be undertaken in consultation with an HIV treatment specialist.

Some women who receive cART for their own health choose to discontinue the drugs for a variety of reasons, and the length of time between treatment termination and pregnancy may vary. In these cases, careful clinical and laboratory assessments are necessary before therapy is reinitiated during pregnancy. The evaluations should include a review of a woman's prior history of virologic response and medication toxicity and her adherence to therapy. The appropriate choice of ARV regimen to be initiated during pregnancy will vary according to a woman's history of cART; the indication for stopping therapy; the effect of prior therapy on clinical, virologic, and immunologic status; and the results of past and current testing for resistance and for HLA-B\*5701. It may be possible, for example, to restart the same regimen in women with a history of

prior cART associated with successful suppression of viral load who then stopped all drugs simultaneously (or staggered discontinuation, if therapy was NNRTI-based) and who have no evidence of resistance. On the other hand, the selection of an appropriate ARV regimen may be challenging even for health care providers experienced in HIV care in women with advanced HIV disease, a history of extensive prior cART, or previous significant toxicity or nonadherence to ARV drugs. In such cases, restarting the prior regimen for a week or two before performing a resistance assay may yield more accurate results. In addition to obtaining genotypic resistance testing, it is strongly recommended that specialists in the treatment of HIV infection be consulted early during the pregnancy about the choice of a suitable combination ARV regimen.

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## Monitoring of the Woman and Fetus During Pregnancy (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- Plasma HIV RNA levels should be monitored at the initial visit (AI); 2 to 4 weeks after initiating (or changing) antiretroviral (ARV) drug regimens (BI); monthly until RNA levels are undetectable (BIII); and then at least every 3 months during pregnancy (BIII). HIV RNA levels also should be assessed at approximately 34 to 36 weeks' gestation to inform decisions about mode of delivery (see [Transmission and Mode of Delivery](#)) (AIII).
- CD4 T lymphocyte (CD4) cell count should be monitored at the initial antenatal visit (AI) and at least every 3 months during pregnancy (BIII). Monitoring of CD4 cell count can be performed every 6 months in patients on combination ARV therapy (cART) with consistently suppressed viral load who have immune reconstitution (CD4 count increase well above threshold for opportunistic infection risk) related to use of the regimen (CIII).
- Genotypic ARV drug-resistance testing should be performed at baseline in all HIV-infected pregnant women with HIV RNA levels above the threshold for resistance testing (that is, >500 to 1,000 copies/mL), whether they are ARV-naive or currently on therapy (AIII). However, it is not necessary to repeat a genotype in pregnancy if the woman already had a genotype prior to pregnancy and was ARV-naive. Repeat testing is indicated following initiation of an ARV regimen in women who have suboptimal viral suppression or who have persistent viral rebound to detectable levels after prior viral suppression on an ARV regimen (AII).
- Monitoring for complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs a woman is receiving (AIII).
- HIV-infected women taking cART during pregnancy should undergo standard glucose screening at 24 to 28 weeks' gestation (AIII). Some experts would perform earlier glucose screening in women receiving ongoing protease inhibitor-based regimens initiated before pregnancy, similar to recommendations for women with high risk factors for glucose intolerance (BIII).
- Early ultrasound is recommended to confirm gestational age and, if scheduled cesarean delivery is necessary, to guide timing of the procedure (see [Transmission and Mode of Delivery](#)) (AII).
- In women on effective cART, no perinatal transmissions have been reported after amniocentesis, but a small risk of transmission cannot be ruled out. If amniocentesis is indicated in HIV-infected women, it should be done only after initiation of an effective cART regimen and, if possible, when HIV RNA levels are undetectable (BIII). In women with detectable HIV RNA levels in whom amniocentesis is deemed necessary, consultation with an expert should be considered.

**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

Viral load should be monitored in HIV-infected pregnant women at the initial visit, 2 to 4 weeks after initiating or changing antiretroviral (ARV) regimens, monthly until undetectable, and at least every 3 months thereafter. If adherence is a concern, more frequent monitoring is recommended because of the potential increased risk of perinatal HIV infection associated with detectable HIV viremia during pregnancy. More frequent viral load monitoring is recommended in pregnant versus non-pregnant individuals because of the urgency to lower viral load as rapidly as possible to reduce the risk of perinatal transmission. Therefore, there is a need to identify pregnant women in whom the decline in viral load is slower than expected. Adult ARV guidelines note that for most individuals who are adherent to their ARV regimen and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 12 to 24 weeks, although it may take longer in some patients.<sup>1</sup> Viral load also should be assessed at approximately 34 to 36 weeks' gestation to inform decisions about mode of delivery (see [Transmission and Mode of Delivery](#)).

In HIV-infected pregnant women, CD4 T lymphocyte (CD4) cell count should be monitored at the initial visit and at least every 3 months during pregnancy. CD4 cell counts can be performed every 6 months in patients who are clinically stable with consistently suppressed viral load who have ARV regimen-related immune reconstitution (CD4 count increase well above threshold for opportunistic infection risk).<sup>1,2</sup>

Whenever feasible, ARV drug-resistance testing should be performed in HIV-infected pregnant women before initiation of ARV drugs, if HIV RNA levels are above the threshold for resistance testing, unless a

delay in getting results back would lead to a delay in starting ARV for prevention of perinatal transmission. Testing also should be performed on women taking an ARV regimen who have suboptimal viral suppression or who have persistent viral rebound to detectable levels after prior viral suppression on an ARV regimen (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)). Drug-resistance testing in the setting of virologic failure should be performed while patients are receiving ARV drugs or within 4 weeks after discontinuation of drugs. Genotypic testing is preferable to phenotypic testing because it costs less, has a faster turnaround time, and is more sensitive for detection of mixtures of wild-type and resistant virus.

Monitoring for potential complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs a woman is receiving. For example, routine hematologic monitoring is recommended for women receiving zidovudine-containing regimens and routine renal monitoring should be recommended for women on tenofovir. Liver function should be monitored in all women receiving ARV drugs. Hepatic dysfunction has been observed in pregnant women on protease inhibitors (PI), and hepatic steatosis and lactic acidosis in pregnancy have been related to nucleoside reverse transcriptase inhibitor use. Women with CD4 cell counts >250 cells/mm<sup>3</sup> are thought to be at particular risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity within the first 18 weeks after initiation of therapy. However, recent data **either do** not show the same association between nevirapine toxicity and CD4 cell counts among pregnant women,<sup>3</sup> **or found only weak evidence of an association.**<sup>4</sup> Additional data from a 2010 study suggest that abnormal liver transaminase levels at baseline may be more predictive of risk than CD4 cell count.<sup>5</sup> Transaminase levels should be monitored more frequently and carefully in pregnant women initiating therapy with nevirapine, and they should also be watched for clinical symptoms of potential hepatotoxicity (see [Nevirapine and Hepatic/Rash Toxicity](#)). The drug can be used cautiously with careful monitoring in women with mildly abnormal liver function tests at the time of ARV drug initiation.

**Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported in HIV-infected patients taking PIs.<sup>6-9</sup> In addition, pregnancy is itself a risk factor for hyperglycemia. To date, however, the majority of studies have not shown an increased risk of glucose intolerance with PI-based regimens during pregnancy. A prospective study including detailed evaluations for glucose intolerance and insulin resistance among HIV-infected pregnant women did not find differences between women on PI-containing and non-PI-containing regimens.<sup>10</sup> In both groups, however, the rate of impaired glucose tolerance was high (38%); this is likely related to high body mass index and race/ethnicity among trial subjects. HIV-infected women receiving ARV regimens during pregnancy should receive standard glucose screening at 24 to 28 weeks' gestation. Some experts would perform earlier glucose screening in women with ongoing PI-based ARV regimens initiated before pregnancy (particularly those of minority race/ethnicity), similar to recommendations for women with high risk factors for glucose intolerance, such as maternal obesity, advanced maternal age, and family history of type II diabetes mellitus.**

First-trimester ultrasound is recommended to confirm gestational age and, if scheduled cesarean delivery is necessary, to guide potential timing because such deliveries for prevention of perinatal transmission of HIV should be performed at 38 weeks' gestation (see [Transmission and Mode of Delivery](#)).<sup>11,12</sup> In patients who are not seen until later in gestation, second-trimester ultrasound can be used for both anatomical scanning and determination of gestational age.

Although data are still somewhat limited, the risk of transmission does not appear to be increased with amniocentesis or other invasive diagnostic procedures in women receiving effective combination ARV therapy (cART) resulting in viral suppression. This is in contrast to the era before effective cART, during which invasive procedures such as amniocentesis and chorionic villus sampling (CVS) were associated with a two- to four-fold increased risk of perinatal transmission of HIV.<sup>13-16</sup> Although no transmissions have occurred among 159 cases reported to date of amniocentesis or other invasive diagnostic procedures among women on effective cART, a small increase in risk of transmission cannot be ruled out.<sup>17-20</sup> HIV-infected women who have indications for invasive testing in pregnancy (e.g., abnormal ultrasound or aneuploidy screening) should be counseled about the potential risk of transmission of HIV along with other risks of the

procedure and allowed to make an informed decision about testing. Some experts consider CVS and cordocentesis too risky to offer to HIV-infected women and they recommend limiting invasive procedures to amniocentesis,<sup>18</sup> but existing data on transmission risk associated with these procedures are limited. At a minimum, HIV-infected pregnant women should receive effective cART before undergoing any invasive prenatal testing and, ideally, have an undetectable HIV RNA level at the time of the procedure. **Consideration can also be given to non-invasive testing using cell-free, fetal DNA to reduce the need for amniocentesis.**<sup>21</sup> In women with detectable HIV RNA levels for whom amniocentesis is deemed necessary, consultation with an expert should be considered. These procedures should be done under continuous ultrasound guidance and, if possible, the placenta should be avoided.

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## Antiretroviral Drug Resistance and Resistance Testing in Pregnancy (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- HIV drug-resistance studies should be performed before starting antiretroviral (ARV) regimens in all ARV-naive pregnant women whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) unless they have already been tested for ARV resistance (AIII).
- HIV drug-resistance studies should be performed before modifying ARV regimens for those entering pregnancy with detectable HIV RNA levels that are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) while receiving ARV drugs or who have suboptimal viral suppression after starting ARV drugs during pregnancy (AII).
- In women who present late in pregnancy, an empiric ARV regimen should be initiated promptly without waiting for the results of resistance testing, with adjustment as needed after test results are available, for optimal prevention of perinatal transmission and maternal health (BIII).
- Women who have documented zidovudine resistance and are on regimens that do not include zidovudine for their own health should still receive intravenous zidovudine during labor along with their established ARV regimens if they have HIV RNA levels >1,000 copies/mL near delivery (see [Intrapartum Antiretroviral Therapy/ Prophylaxis](#)), unless a history of hypersensitivity is documented (AII).
- The optimal prophylactic regimen for newborns of women with ARV resistance is unknown. Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery (see [Infant Antiretroviral Prophylaxis](#)) (AIII).
- HIV-infected pregnant women should be given combination ARV therapy (cART) to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission (AII).
- 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).
- To minimize development of resistance, pregnant women who receive a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination ARV regimen that is discontinued after delivery should receive either dual nucleoside analogue reverse transcriptase inhibitor agents alone (AI) or with a protease inhibitor (BII) for 7 to 30 days (AII) after stopping the NNRTI drug. The optimal interval between stopping an NNRTI and the other ARV drugs is unknown (see [Stopping Antiretroviral Drugs During Pregnancy](#) and [Postpartum Follow-Up of HIV-Infected Women](#)).

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

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

### Indications for Antiretroviral Drug-Resistance Testing in HIV-Infected Pregnant Women

Because identification of baseline resistance mutations allows selection of more effective and durable ARV regimens, in addition to a comprehensive history of antiretroviral (ARV) drug use, genotypic resistance testing is recommended:

- Before initiating combination antiretroviral therapy (cART) in ARV-naive HIV-infected pregnant women with HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) who have not been previously tested for ARV resistance;
- Before initiating cART in HIV-infected pregnant women who have received ARVs for prevention of perinatal transmission in prior pregnancies and who are restarting ARV drugs for prevention of perinatal transmission if HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL);
- Before modifying ARV regimens in HIV-infected pregnant women entering pregnancy with detectable HIV RNA levels that are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) while receiving cART or who have suboptimal viral suppression after starting cART during pregnancy.



In most settings, the results of resistance testing guide selection of the initial ARV regimen. In some situations in pregnant women, however, the clinician may choose to initiate an empiric ARV drug regimen before resistance-testing results are available to optimize prevention of perinatal transmission of HIV. Most experts believe that for women in the third trimester, the benefits of immediate initiation of ARV drugs for prevention of perinatal transmission, pending results of resistance testing, outweigh the possible risks of short-term use of a regimen that could be suboptimal because of pre-existing resistance. Once resistance-test results are obtained, the ARV drug regimen can be modified as needed.

### ***Incidence and Significance of Antiretroviral Drug Resistance in Pregnancy***

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in HIV-infected individuals. Additionally, pre-existing resistance to a drug in a cART regimen may diminish the regimen's efficacy in preventing perinatal transmission. The development of resistance to drugs used during pregnancy for prophylaxis of perinatal transmission may limit future maternal treatment options or decrease the effectiveness of prophylactic regimens in the current pregnancy or during future pregnancies. Infant treatment options also may be limited if maternal drug resistance is present or develops and resistant virus is transmitted to the fetus.

Several factors unique to pregnancy may increase the risk of development of resistance. If drugs with significant differences in half-life **and a low genetic barrier to resistance** (e.g., non-nucleoside reverse transcriptase inhibitors combined with two nucleoside analogue drugs) are included in the ARV regimen, simultaneous postpartum discontinuation of all regimen components may result in persistent sub-therapeutic drug levels and increase the risk of development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (see [Stopping Antiretroviral Drugs During Pregnancy](#)).<sup>1,2</sup> **Issues relating to discontinuation of NNRTI-based combination therapy are discussed in [Prevention of Antiretroviral Drug Resistance](#).** Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to sub-therapeutic drug levels, increasing the risk that resistance will develop.

### ***The Impact of Resistance on the Risk of Perinatal Transmission of HIV and Maternal Response to Subsequent Therapy***

#### **Perinatal Transmission**

Perinatal transmission of resistant virus has been reported, but appears to be unusual. There is little evidence that presence of resistance mutations increases risk of transmission when current recommendations for ARV management in pregnancy are followed. A sub-study of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV infection in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count;<sup>3</sup> however, women in this cohort had characteristics that would indicate a need for cART under the current Department of Health and Human Services recommendations for maternal health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild-type and virus with low-level zidovudine resistance, only wild-type virus was detected in their infants,<sup>4</sup> and other studies have suggested that drug-resistance mutations may diminish viral fitness,<sup>5</sup> possibly leading to a decrease in transmissibility. In another study, prevalence of ARV drug resistance among HIV-infected newborns in New York State was examined. Eleven (12.1%) of 91 infants born between 1989 and 1999 and 8 (19%) of 42 infants born between 2001 and 2002 had mutations associated with decreased drug susceptibility. However, perinatal exposure to ARVs was not found to be a significant risk factor for the presence of resistance during either time period.<sup>6,7</sup> 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.<sup>8,9</sup>

## **Maternal Response to Subsequent Treatment Regimens**

Few studies have evaluated response to subsequent therapy in women who receive current combination ARV regimens for prophylaxis and discontinue the drugs postpartum. In theory, however, resistance should not occur if the regimen that was discontinued had fully suppressed viral replication. The French Perinatal Cohort evaluated the association between exposure to ARV drugs for perinatal transmission during a previous pregnancy and presence of a detectable viral load with exposure to ARV drugs during the current pregnancy in women followed between 2005 and 2009.<sup>10</sup> In 1,166 women not receiving ARVs at the time of conception, 869 were ARV-naïve and 247 had received ARV drugs for perinatal transmission during a previous pregnancy. Previous ARV prophylaxis was protease inhibitor (PI) based in 48%, non-PI based in 4%, nucleoside reverse transcriptase inhibitor (NRTI) dual ARVs in 19%, and zidovudine as a single ARV in 29%. A PI-based ARV regimen was initiated in 90% of the women during the current pregnancy; in multivariate analysis, previous ARV exposure in a prior pregnancy was not associated with detectable viral load in the current pregnancy. A separate study reported in abstract form—ACTG A5227—evaluated viral suppression in 52 women with prior combination ARV exposure for perinatal transmission who had stopped ARV at least 24 weeks before study entry and were now initiating cART (efavirenz, tenofovir, and emtricitabine) for treatment.<sup>11</sup> None of the women had prior or recent resistance detected on standard bulk genotyping. Viral suppression was observed in 81% of women after 24 weeks of follow-up, with no difference in response by number of prior ARV exposures for perinatal transmission or the drug class of prior exposure.

## ***Management of Antiretroviral Drug Resistance during Pregnancy***

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, the drug still should be given intravenously (IV) during labor when indicated (i.e., HIV RNA >1,000 copies/mL near delivery; see [Intrapartum Antiretroviral Drug Therapy/Prophylaxis](#)). Other ARVs should be continued orally during labor to the extent possible. The rationale for including zidovudine intrapartum when a woman is known to harbor virus with zidovudine resistance is based on several factors. Data thus far have suggested that only wild-type virus appears to be transmitted to infants by mothers who have mixed populations of wild-type virus and virus with low-level zidovudine resistance.<sup>4</sup> Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.<sup>5</sup> 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.<sup>12-14</sup> Zidovudine crosses the placenta readily and has a high maternal-to-cord blood ratio. In addition, zidovudine is metabolized to the active triphosphate within the placenta,<sup>15,16</sup> which may provide additional protection against transmission. Metabolism to the active triphosphate, which is required for activity of all nucleoside analogue agents, has not been observed within the placenta with other nucleoside analogues that have been evaluated (didanosine and zalcitabine). Zidovudine penetrates the central nervous system (CNS) better than do other nucleoside analogues except stavudine, which has similar CNS penetration; this may help to eliminate a potential reservoir for transmitted HIV in the infant.<sup>17,18</sup> Thus, intrapartum IV administration of zidovudine when indicated currently is recommended even in the presence of known resistance because of the drug's unique characteristics and its proven record in reducing perinatal transmission.

The optimal prophylactic regimen for newborns of women with ARV drug-resistant virus is unknown. Therefore, ARV prophylaxis for infants born to women with known or suspected drug-resistant virus should be determined with a pediatric HIV specialist, preferably before delivery (see [Infant Antiretroviral Prophylaxis](#)).

## ***Prevention of Antiretroviral Drug Resistance***

The most effective way to prevent development of ARV drug resistance in pregnancy is to use and adhere to an effective cART regimen to achieve maximal viral suppression. More frequent monitoring of viral load in pregnant women than in non-pregnant individuals is recommended because of the potential increased risk of perinatal HIV infection associated with detectable HIV viremia during pregnancy (see [Monitoring of the](#)

## Woman and Fetus During Pregnancy).

Several studies have demonstrated that women's adherence to cART may worsen in the postpartum period.<sup>19-23</sup> Clinicians caring for postpartum women receiving ART should specifically address adherence, including evaluating specific factors that facilitate or impede adherence.

Because of the prolonged half-life of NNRTI drugs, if an NNRTI-based ARV regimen is stopped postpartum, there is a risk of development of NNRTI-resistance mutations if all drugs in the regimen are stopped simultaneously. This has been demonstrated for nevirapine and efavirenz but may also be a problem with newer NNRTI drugs with long half-lives, such as etravirine and rilpivirine. Several studies have shown that development of NNRTI resistance is significantly decreased (but not eliminated) when zidovudine/lamivudine is given intrapartum and administered for 3 to 7 days postpartum in women who have received single-dose intrapartum nevirapine.<sup>24-27</sup> A variety of other regimens (e.g., tenofovir/emtricitabine, zidovudine/didanosine, zidovudine/didanosine/lopinavir/ritonavir) given for 7 to 30 days postpartum following maternal single-dose nevirapine have also been shown to be very effective in reducing the development of NNRTI resistance.<sup>26,28,29,30,31,32</sup> These data suggest that the NRTI components of an NNRTI-based regimen should be continued for 7 to 30 days after discontinuation of the NNRTI to minimize the risk of resistance. An alternative equally effective strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time.<sup>33</sup> The optimal duration for continuation of either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is unknown.<sup>34</sup> NNRTI drugs have long half-lives, and drug levels can persist for up to 1 to 3 weeks after stopping the drugs; efavirenz levels persist longer than nevirapine levels.<sup>35,36</sup> **Despite the use of various multiple drug regimens, ARV drug resistance may still develop in some women.<sup>34</sup>** More research is needed on the optimal duration of time and regimen to cover this period of prolonged NNRTI exposure to prevent the emergence of resistance after discontinuation of an NNRTI-based ARV regimen.

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## Failure of Viral Suppression (Last updated March 28, 2014; last reviewed March 28, 2014)

Panel's Recommendations
<ul style="list-style-type: none"><li>• If an ultrasensitive HIV RNA assay indicates failure of viral suppression (that is, <b>persistent HIV viral load &gt;20 to 75 copies/mL, depending on the assay used</b>) after an adequate period of treatment:<ul style="list-style-type: none"><li>◦ Assess resistance and adherence (<b>All</b>).</li><li>◦ Consult an HIV treatment expert (<b>All</b>).</li></ul></li><li>• Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels &gt;1,000 copies/mL near the time of delivery (<b>All</b>).</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> 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>

A three-pronged approach is indicated for management of women on antiretroviral (ARV) regimens who have suboptimal suppression of HIV RNA (that is, detectable virus at any time during pregnancy using ultrasensitive assays). They should be:

- Evaluated for resistant virus (if plasma HIV RNA is >500 to 1,000 copies/mL);
- Assessed for adherence, tolerability, incorrect dosing, or potential problems with absorption (e.g., nausea/vomiting, lack of attention to food requirements); and
- **Considered for ARV regimen modification.**

Experts in the care of ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary. Hospitalization can be considered for directly observed drug administration, adherence education, and treatment of comorbidities such as nausea and vomiting.

Among 662 pregnancies followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with an HIV-1 RNA level >400 copies/mL in late pregnancy (adjusted odds ratio, 1.66; 95% confidence interval, 1.07–2.57;  $P = 0.024$ ), highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize need to modify treatment.<sup>1</sup>

HIV RNA levels should be assessed 2 to 4 weeks after an ARV drug regimen is initiated or changed to provide an initial assessment of effectiveness.<sup>2</sup> 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.**<sup>3,4</sup> Most patients with an adequate viral response at 24 weeks have had at least a 1 log copies/mL HIV RNA decrease within 1 to 4 weeks after starting therapy.<sup>2</sup> **In a retrospective multicenter cohort of 378 pregnant women, 77.2% achieved HIV RNA <50 copies/mL by delivery, with success of viral suppression varying by baseline HIV RNA level. With baseline <10,000 copies/mL, gestational age at initiation did not affect success up to 26.3 weeks. With baseline >10,000 copies/mL, however, delaying initiation past 20.4 weeks significantly reduced ability for achieving maximal suppression at delivery.**<sup>3</sup> In data on 1,070 HIV-infected treatment-naïve pregnant women participating in IMPAACT P1025, a prospective cohort study, later initiation of combination antiretroviral therapy (cART) at >32 weeks' gestation also was associated with a significantly higher risk of having viral load >400 copies/mL at delivery.<sup>5</sup> The role of therapeutic drug monitoring in reducing the risk of virologic failure is still undefined.<sup>6,7</sup>

**A recent systematic review and meta-analysis of adherence to cART during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the United States) found that a pooled estimate of 73.5% of pregnant women had adequate (>80%) adherence to cART.**<sup>8</sup> Evaluation of and support

for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

Because maternal antenatal viral load correlates with risk of perinatal transmission of HIV, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible. The addition of raltegravir in late pregnancy has been suggested for women who have high viral loads and/or in whom multiple drug-resistant mutations have resulted in incomplete suppression of viremia because of the ability of raltegravir to rapidly suppress viral load (approximately 2 log copies/mL decrease by Week 2 of therapy).<sup>9-12</sup> However, the efficacy and safety of this approach have not been evaluated and only anecdotal reports are available. In the setting of a failing regimen related to non-adherence and/or resistance, there are concerns that the addition of a single agent may further increase risk of resistance and potential loss of future effectiveness with raltegravir. A recent report found a 10- to 23-fold increase in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with return to normal levels after raltegravir discontinuation.<sup>13</sup> Therefore, at the current time, this approach cannot be routinely recommended. Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL.

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## Stopping Antiretroviral Drugs during Pregnancy (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- HIV-infected women receiving combination antiretroviral therapy who present for care during the first trimester should continue treatment during pregnancy (**AII**). If an antiretroviral (ARV) drug regimen is stopped acutely for severe or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to antiemetics, or other acute illnesses that preclude oral intake, all ARV drugs should be stopped and reinitiated at the same time (**AIII**).
- If an ARV drug regimen is being stopped for non-life-threatening reasons and the patient is receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI), consideration should be given to either:
  - Stopping the NNRTI first and continuing the other ARV drugs for a period of time; or
  - Switching from an NNRTI to a protease inhibitor (PI) before interruption and continuing the PI with the other ARV drugs for a period of time before electively stopping.
- The optimal interval between stopping an NNRTI and the other ARV drugs is unknown; at least 7 days is recommended. Given the potential for prolonged detectable efavirenz concentrations for >3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other ARV agents or substituting a PI plus 2 other agents for up to 30 days after stopping the NNRTI drug (**CIII**).
- If nevirapine is stopped and more than 7 days have passed before restarting therapy, nevirapine should be restarted with the 2-week half-dose escalation period (**AII**).

**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, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or at patients' request.

HIV-infected women receiving combination antiretroviral therapy (cART) who present for care during the first trimester should continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load with possible decline in immune status and disease progression as well as adverse consequences for the fetus, including increased risk of *in utero* transmission of HIV. An analysis from a prospective cohort of 937 HIV-infected mother-child pairs found that interruption of cART during pregnancy, including interruption in the first and third trimesters, was independently associated with perinatal transmission. In the first trimester, the median time at interruption was 6 weeks' gestation and length of time without therapy was 8 weeks (interquartile range [IQR], 7–11 weeks); in the third trimester, the median time at interruption was 32 weeks and length of time without therapy was 6 weeks (IQR, 2–9 weeks). Although the perinatal transmission rate for the entire cohort was only 1.3%, transmission occurred in 4.9% (95% confidence interval [CI], 1.9%–13.2%; adjusted odds ratio [AOR] 10.33;  $P = .005$ ) with first-trimester interruption and 18.2% (95% CI, 4.5%–72.7%; AOR 46.96;  $P = .002$ ) with third-trimester interruption.<sup>1</sup> Although the use of efavirenz should be avoided during the first trimester when possible, therapy should not be interrupted in women receiving an efavirenz-based regimen who present in the first trimester, provided the regimen produces viral suppression (see [HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy](#)).

Continuation of all drugs during the intrapartum period generally is recommended. Women who are having elective cesarean delivery can take oral medications before the procedure and restart drugs following surgery. Because most drugs are given once or twice daily, it is likely that no doses would be missed or that at most the postpartum dose would be given a few hours late.

When short-term drug interruption is indicated, in most cases, all ARV drugs should be stopped and reintroduced at the same time. This can be problematic with drugs that have a long half-life. However, in

conditions such as serious or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to antiemetics, or other acute illnesses precluding oral intake, the clinician has no choice but to stop all therapy at the same time. In the rare case in which a woman has limited oral intake that does not meet food requirements for certain ARV agents, decisions about the ARV regimen administered during the antepartum or intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert.

Non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs (e.g., nevirapine, efavirenz) have very long half-lives and can be detected for 21 days or longer after discontinuation; efavirenz has a longer half-life than nevirapine.<sup>2-6</sup> Because other drugs in the ARV regimen have shorter half-lives and are cleared more rapidly, only detectable NNRTI drug levels persist, resulting in subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, certain genetic polymorphisms, which may be more common among ethnic groups such as African Americans and Hispanics, may have the potential to result in a slower rate of clearance.<sup>4,6</sup> To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other ARV drugs for a period of time.<sup>3</sup> Detectable levels of NNRTIs may be present from <1 week to >3 weeks after discontinuation, with the longer duration primarily observed with efavirenz.<sup>6</sup> An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI and to continue the PI with dual nucleoside reverse transcriptase inhibitors (NRTIs) for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI- to a PI-based regimen before interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of HIV RNA re-suppression after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual NRTIs.<sup>7</sup>

The optimal duration for continuing either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI **has not been definitively established**, but a minimum of 7 days is recommended based on past studies to reduce resistance following single-dose nevirapine.<sup>8,9</sup> **More recently, among 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or ritonavir-boosted lopinavir for either 7 or 21 days, there was an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific polymerase chain reaction emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%],  $P = .019$ ).**<sup>10</sup>

A pharmacokinetic study of nevirapine elimination in African adults following cessation of steady-state nevirapine-containing regimens found that nevirapine concentrations were estimated to have fallen below 20 ng/mL in 3 of 19 (16%) and 14 of 19 (74%) subjects by 7 and 14 days, respectively, after the cessation of dosing.<sup>11</sup> Elimination half-life was 39 hours in these subjects, considerably shorter than that observed after peripartum exposure to single doses of nevirapine (average 55–60 hours), likely related to induction of nevirapine metabolism with chronic nevirapine exposure.<sup>2,12,13</sup> Because efavirenz concentrations have the potential to be detectable for more than 3 weeks, some experts suggest that if efavirenz-based therapy is stopped, the dual NRTIs or PI may need to be continued for up to 30 days. Further research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens.

Another consideration is reintroduction of nevirapine if it is temporarily stopped and subsequently restarted. A 2-week, half-dose escalation currently is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing cytochrome P450 3A4 liver metabolic enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. In cases where nevirapine has been discontinued for more than 7 days, another 2-week dose escalation is recommended when it is reintroduced.

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## HIV/Hepatitis B Virus Coinfection (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- All HIV-infected pregnant women should be screened during pregnancy for hepatitis B virus (HBV) and hepatitis C virus (HCV), unless they are known to be coinfecting or have already been screened during the current pregnancy (see [HIV/Hepatitis C Virus Coinfection](#)) (AIII).
- All pregnant women who screen negative for HBV (i.e., HBV surface antigen [HBsAg]-negative, HBV core antibody-negative, and HBV surface antibody [anti-HBs]-negative) should receive the HBV vaccine series (AII).
- Women with chronic HBV infection should also be screened for hepatitis A virus (HAV) because they are at increased risk of complications from coinfection with other viral hepatitis infections (AIII).
- Women with chronic HBV infection who are negative for hepatitis A immunoglobulin G should receive the HAV vaccine series (AII).
- The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV is strongly recommended (AIII).
- Interferon alfa and pegylated interferon alfa are not recommended during pregnancy (AII).
- All pregnant women with HIV/HBV coinfection should receive combination antiretroviral therapy (cART), including a dual nucleoside reverse transcriptase inhibitor (NRTI)/nucleotide analogue reverse transcriptase inhibitor (NtRTI) backbone with two drugs active against both HIV and HBV (AII). Tenofovir plus lamivudine or emtricitabine is the preferred dual NtRTI/NRTI backbone of antepartum cART in HIV/HBV-coinfecting pregnant women (AI).
- Pregnant women with HIV/HBV coinfection receiving antiretroviral (ARV) drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter during pregnancy (BIII).
- If ARV drugs are discontinued postpartum in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt reinstitution of treatment for both HIV and HBV if a flare is suspected (BIII).
- Decisions concerning mode of delivery in HIV/HBV-coinfecting pregnant women should be based on standard obstetric and HIV-related indications alone (see [Intrapartum Care](#)) (BIII).
- Within 12 hours of birth, infants born to women with HBV infection should receive hepatitis B immune globulin and the first dose of the HBV vaccine series. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively (AI). Post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 9 months to 18 months.

**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 Antiretroviral Guidelines](#) (<http://AIDSInfo.nih.gov>)<sup>1</sup> and [Hepatitis B Virus Infection](#) in the [Adult Opportunistic Infections Guidelines](#).<sup>2</sup> The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended.

All HIV-infected women should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. Pregnant HIV-infected women should be rescreened for HBV and HCV unless they are known to be coinfecting or have already been screened during the current pregnancy. Women who screen negative for HBV (i.e., hepatitis B surface antigen [HBsAg]-negative, hepatitis B core antibody [anti-HBc]-negative, and hepatitis B surface antibody [anti-HBs]-negative) should receive the HBV vaccine series. Data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg and should cause no risk to fetuses.<sup>3</sup> A positive test for anti-HBc alone can be false-positive, or it may signify past exposure with subsequent loss of anti-HBs or “occult” HBV infection, which can be confirmed by detection of HBV DNA.<sup>4,5</sup> The clinical significance of isolated anti-HBc is unknown.<sup>6,7</sup>

Some experts recommend that HIV-infected individuals with anti-HBc alone be tested for HBV DNA before vaccination for HBV or before treatment or prophylaxis with antiretroviral (ARV) drugs is initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS).<sup>2</sup> HIV-infected pregnant women with isolated anti-HBc and occult HBV infection have very low levels of HBV DNA and are thought to be at extremely low risk of transmitting HBV to their infants.<sup>8</sup>

Because of the added risk of acute infection with hepatitis A virus (HAV) in individuals with chronic HBV, women who are found to have chronic HBV infection should also be screened for HAV. Women with chronic HBV infection who are hepatitis A immunoglobulin G-negative should receive the HAV vaccine series. Although the safety of HAV vaccination during pregnancy has not been determined, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.<sup>3</sup>

An ARV regimen that includes drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection who require HBV treatment or who are starting ARV drugs, including pregnant women. Initiation of an ARV regimen that does not include anti-HBV drugs may be associated with reactivation of HBV and development of IRIS; IRIS-related flare of HBV activity during pregnancy can occur even in women with relatively high CD4 T lymphocyte (CD4) cell counts at the time of ARV initiation. In addition, use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia, potentially increasing the efficacy of neonatal hepatitis B immune globulin (HBIG) and hepatitis B vaccine in prevention of perinatal transmission of HBV. High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.<sup>9-11</sup> Several small studies and a recent meta-analysis suggest that lamivudine or telbivudine may reduce the risk of perinatal transmission of HBV if given during the third trimester to HBV-infected, HIV-seronegative women with high HBV DNA viremia.<sup>12-18</sup> Although a high HBV viral load clearly is important, it is not the only factor predisposing to failure of prophylaxis.<sup>19</sup>

Because lamivudine, tenofovir, and emtricitabine have activity against both HIV and HBV, the recommended dual-nucleoside reverse transcriptase/nucleotide analogue reverse transcriptase inhibitor (NRTI) backbone for HIV/HBV-coinfected individuals, including pregnant women, is tenofovir/emtricitabine or tenofovir/lamivudine. Lamivudine has been extensively studied and is recommended for use in pregnancy (see Table 6). The Antiretroviral Pregnancy Registry includes reports on the outcomes of 4,273 pregnancies that involved administration of lamivudine in the first trimester and there is no indication that the exposure was associated with an increased risk of birth defects.<sup>20</sup> Similarly, no increase in birth defects has been noted in 1,230 cases of first-trimester exposure to emtricitabine, which, like lamivudine, is recommended for use in pregnancy (see Table 6). Tenofovir is not teratogenic in animals, but reversible bone changes at high doses have been seen in multiple animal species. A total of 1,800 cases of first-trimester exposure have been reported to the Antiretroviral Pregnancy Registry, with no increase in birth defects noted.<sup>20</sup> Tenofovir with emtricitabine or lamivudine is a preferred dual NRTI backbone in women who are HIV-infected or HIV/HBV-coinfected (see Table 6).

Several other antivirals with activity against HBV, including entecavir, adefovir, and telbivudine, have not been well evaluated in pregnancy. Entecavir is associated with skeletal anomalies in rats and rabbits but only at doses high enough to cause toxicity to the mother. Fewer than 52 cases of exposure to each of these drugs during pregnancy have been reported to the Antiretroviral Pregnancy Registry prospectively, with no increased risk of birth defects.<sup>20</sup> Telbivudine was given to 135 HBV-positive, HIV-seronegative women during the third trimester and was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers (0% vs. 8%;  $P = 0.002$ ).<sup>15,21</sup> In a larger meta-analysis of the effects of telbivudine in late pregnancy in women infected with HBV alone, telbivudine was effective in interrupting intrauterine HBV infection without significant adverse effects or complications.<sup>16</sup> Each of these anti-HBV drugs should be administered only in addition to a fully suppressive regimen for HIV. Because these other anti-HBV drugs also have weak activity against HIV, they may select for anti-HIV drug resistance in the absence of fully suppressive cART regimen as well as confer the potential for developing cross-resistance to other ARV

drugs. (Entecavir, for example, can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine.) Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; <http://www.apregistry.com>).

Interferon alfa and pegylated interferon alfa are not recommended for use in pregnancy and should be used only if the potential benefits outweigh the potential risks. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents.<sup>22</sup>

Following initiation of ARV drugs, an elevation in hepatic enzymes can occur in HIV/HBV-coinfected women—particularly those with low CD-cell counts at the time of treatment initiation—as a result of an immune-mediated flare in HBV disease triggered by immune reconstitution with effective HIV therapy. HBV infection also can increase hepatotoxic risk of certain ARV drugs, specifically protease inhibitors and nevirapine. Pregnant women with HIV/HBV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter. If hepatic toxicity occurs, it may be necessary to consider substituting a less hepatotoxic regimen or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between a flare in HBV disease due to immune reconstitution and drug toxicity often can be difficult, and consultation with an expert in HIV and HBV coinfection is strongly recommended. Because tenofovir has potential to cause renal toxicity, kidney function also should be monitored regularly in women receiving this drug, based on toxicity seen in non-pregnant adults.

Following delivery, considerations regarding continuation of the ARV drug regimen are the same as for other non-pregnant individuals (see [General Principles Regarding Use of Antiretroviral Drugs During Pregnancy](#)). Discontinuing agents with anti-HBV activity may be associated with hepatocellular damage resulting from reactivation of HBV. Frequent monitoring of liver function tests for potential HBV flare is recommended in women with HIV/HBV coinfection whose ARV drugs are discontinued postpartum, with prompt re-initiation of treatment for both HIV and HBV if a flare is suspected.

Within 12 hours of birth, all infants who weigh >2,000 g born to mothers with chronic HBV infection should receive HBIG and the first dose of the HBV vaccination series. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively. This regimen is >95% effective in preventing HBV infection in these infants. Consult the CDC Morbidity and Mortality Weekly Report recommendations for similar infants with birth weights <2,000 g at birth.<sup>23</sup>

Post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 9 months to 18 months. Testing should not be performed before age 9 months to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti-HBc testing of infants is not recommended because passively acquired maternal anti-HBc might be detected in infants born to HBV-infected mothers up to age 24 months. HBsAg-negative infants with anti-HBs levels >10 mIU/mL are protected and need no further medical management. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1–2 months after the final dose of vaccine.

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## HIV/Hepatitis C Virus Coinfection (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- All HIV-infected pregnant women should be screened during pregnancy for hepatitis B virus (HBV) and hepatitis C virus (HCV), unless they are known to be coinfecting or have already been screened during the current pregnancy (see [HIV/Hepatitis B Virus Coinfection section](#)) (AIII).
- Screening for HCV infection should use the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood (AIII).
- All pregnant women who screen negative for HBV (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) should receive the HBV vaccine series (AII).
- Women with chronic HCV infection should also be screened for hepatitis A virus (HAV) because they are at increased risk of complications from coinfection with other viral hepatitis infections (AIII).
- Women with chronic HCV who are negative for hepatitis A immunoglobulin G should receive the HAV vaccine series (AII).
- The management of HIV/HCV coinfection in pregnancy is complex, given currently approved medications for HCV. If considering treatment of HCV in an HIV coinfecting pregnant woman, consultation with an expert in HIV and HCV is strongly recommended (AIII).
- Interferon alfa and pegylated interferon alfa are not recommended and ribavirin is contraindicated during pregnancy (AII).
- Recommendations for antiretroviral (ARV) drug use during pregnancy are the same for HIV-infected women who have chronic HCV as for those without HCV coinfection (BIII).
- Pregnant women with HIV/HCV coinfection receiving ARV drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter during pregnancy (BIII).
- Decisions concerning mode of delivery in HIV/HCV-coinfecting pregnant women should be based on standard obstetric and HIV-related indications alone (see [Intrapartum Care](#)) (BIII).
- Infants born to women with HIV/HCV coinfection should be evaluated for HCV infection with anti-HCV antibody testing after age 18 months (AII). Infants who screen positive should undergo confirmatory HCV RNA testing. HCV RNA virologic testing can be done after age 2 months, if earlier diagnosis is indicated (AIII). Because HCV viremia can be intermittent, two negative HCV RNA tests at or after age 2 months, including one at or after age 12 months, are needed to definitively exclude HCV infection (BIII). Children are considered to be HCV-infected if they have two or more positive HCV RNA results or are HCV antibody-positive beyond age 18 months (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

For additional information on hepatitis C virus (HCV) and HIV, see [HIV/Hepatitis C Coinfection](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)<sup>1</sup> and [Hepatitis C Virus Infection](#) in the [Adult Opportunistic Infections Guidelines](#).<sup>2</sup> The management of HIV/HCV coinfection in pregnancy is complex and consultation with an expert in HIV and HCV infection is strongly recommended, particularly if treatment of HCV infection during pregnancy is being considered.

All HIV-infected women should be screened for hepatitis B virus (HBV) and HCV at entry into general HIV care. Pregnant HIV-infected women should be re-screened for HBV and HCV unless they are known to be coinfecting or have already been screened during the current pregnancy. HCV coinfection is not uncommon in HIV-infected women, particularly those infected via parenteral use of drugs; among HIV-infected pregnant women, the HCV seroprevalence rate ranges from 17% to 54%.<sup>3</sup> Screening for chronic HCV infection using a sensitive immunoassay for HCV antibody is recommended for all HIV-infected individuals, including pregnant women. False-negative anti-HCV immunoassay results can occur in HIV-infected individuals, particularly those with very low CD4 T lymphocyte (CD4) cell counts, but it is uncommon with the most

sensitive immunoassays. Individuals who have a positive HCV antibody test should undergo confirmatory testing for plasma HCV RNA using a commercially available quantitative diagnostic assay. Testing for HCV RNA also should be performed on individuals whose serologic test results are indeterminate or negative but in whom HCV infection is suspected because of elevated aminotransaminase levels or risk factors such as a history of intravenous drug use.

Women who screen negative for HBV (i.e., hepatitis B surface antigen (HBsAg)-negative, hepatitis B core antibody-negative, and hepatitis B surface antibody-negative) should receive the HBV vaccine series. Data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg and should cause no risk to fetuses.<sup>4</sup>

Because of the added risk of acute infection with hepatitis A virus (HAV) in individuals with chronic HCV, women who are found to have chronic HCV infection should also be screened for HAV. Women with chronic HCV infection who are hepatitis A immunoglobulin G-negative should receive the HAV vaccine series. Although the safety of HAV vaccination during pregnancy has not been determined, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.<sup>4</sup>

Few data exist on the optimal management of HIV-infected pregnant women with HCV coinfection. Recommendations for antiretroviral (ARV) drug use during pregnancy for treatment of HIV and/or prevention of perinatal transmission are the same for women who have HCV coinfection as for those with HIV alone (see [HIV/Hepatitis C Coinfection](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). However, currently available anti-HCV treatments are not recommended during pregnancy. Interferons are not recommended for use in pregnancy because they are abortifacient at high doses in monkeys and have direct antigrowth and antiproliferative effects,<sup>5</sup> and ribavirin is contraindicated (Food and Drug Administration [FDA] Pregnancy Category X) because of teratogenicity at low doses in multiple animal species. Ribavirin-associated defects in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Concerns have been raised about potential mutagenic effects of ribavirin in the offspring of men taking ribavirin before conception because of possible accumulation of ribavirin in spermatozoa. However, in a small number of inadvertent pregnancies occurring in partners of men receiving ribavirin therapy, no adverse outcomes were reported.<sup>6</sup> Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or <http://www.ribavirinpregnancyregistry.com>). There are no data in pregnancy on telaprevir or boceprevir, both approved in 2011 by the FDA for treatment of HCV, or simeprevir or sofosbuvir, also approved for HCV treatment by the FDA in 2013. Telaprevir, boceprevir, and sofosbuvir are Pregnancy Category B agents and simeprevir is a Pregnancy Category C agent; however, these agents currently must be used in combination with pegylated interferon and ribavirin, which should not be used in pregnancy. In addition, potential drug interactions between these newer anti-HCV drugs and ARV drugs, particularly certain ritonavir-boosted protease inhibitor (PI) regimens, may reduce the effectiveness of these medications if used together (for more detailed information see [Adult and Adolescent Antiretroviral Guidelines](#)).<sup>7</sup> Pregnancy does not appear to influence the course of HCV infection and women with chronic HCV generally do quite well during pregnancy, provided that their infections have not progressed to decompensated cirrhosis.<sup>8</sup>

In a majority of studies, the incidence of perinatal HCV transmission increases if the mother is coinfecting with HIV, with transmission rates between 10% and 20%.<sup>9-12</sup> These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impact on HCV disease activity.<sup>13</sup> A European study of perinatal transmission of HCV found that use of effective combination antiretroviral therapy (cART) for HIV was associated with a strong trend toward reduction in HCV transmission (odds ratio 0.26, 95% confidence interval, 0.07–1.01).<sup>14</sup> Maternal HIV/HCV coinfection also may increase the risk of perinatal transmission of HIV.<sup>15</sup> Therefore, potent cART with at least three drugs is recommended for all HIV/HCV-coinfecting pregnant women, regardless of CD4 cell count or HIV viral load.

As with chronic HBV infection, an elevation in hepatic enzymes following initiation of cART can occur in HIV/HCV-coinfecting women—particularly in those with low CD4 cell counts at treatment initiation—as a result of an immune-mediated flare in HCV disease triggered by immune reconstitution with effective cART.

Like HBV, HCV infection may increase the hepatotoxic risk of certain ARV agents, specifically PIs and nevirapine. Pregnant women with HIV/HCV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiation of ARV drugs and then every 3 months thereafter. If hepatic toxicity occurs, consideration may need to be given to substituting a less hepatotoxic drug regimen, and if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between a flare in HCV disease associated with immune reconstitution and drug toxicity often can be difficult; therefore, consultation with an expert in HIV and HCV coinfection is strongly recommended.

As with transmission of HIV, risk of perinatal transmission of HCV may be increased by use of internal fetal monitoring, amniocentesis, and rupture of membranes for more than 6 hours.<sup>11,16</sup> The majority of studies of elective cesarean delivery that have included HIV-infected women have found that the procedure does not reduce the risk of perinatal transmission of HCV.<sup>14,17-19</sup> Thus, the general recommendations for intrapartum management are the same in women with HIV/HCV coinfection as in those with HIV infection alone (see [Intrapartum Care](#)).

Infants born to women with HIV/HCV coinfection should be assessed for HCV infection with anti-HCV antibody testing after age 18 months. Infants who screen positive should undergo confirmatory HCV RNA testing. HCV RNA virologic testing can be done after age 2 months, if earlier diagnosis is indicated or desirable.<sup>20,21</sup> Because HCV viremia can be intermittent, 2 negative HCV RNA tests at or after age 2 months, including 1 at or after age 12 months, are needed to definitively exclude HCV infection. Children are considered to be HCV-infected if they have 2 or more positive HCV RNA polymerase chain reaction results or are HCV antibody-positive beyond age 18 months.

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## HIV-2 Infection and Pregnancy (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- HIV-2 infection should be suspected in pregnant women who are from—or have partners from—countries in which the disease is endemic, who are HIV antibody-positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot along with HIV-1 RNA viral loads at or below the limit of detection (**BII**).
- A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted protease inhibitor (PI) currently is recommended for HIV-2-infected pregnant women who require treatment for their own health because they have significant clinical disease or CD4 T-lymphocyte (CD4-cell) counts <500 cells/mm<sup>3</sup> (**AIII**).
- Lopinavir/ritonavir plus zidovudine/lamivudine or abacavir/lamivudine or tenofovir/emtricitabine is the preferred ART regimen for HIV-2-infected pregnant women who require treatment, based on safety data on use of these drugs in HIV-1-infected pregnant women (**AIII**).
- Optimal prophylactic regimens have not been defined for HIV-2-infected pregnant women who do not require treatment for their own health (i.e., CD4 cell counts >500 cells/mm<sup>3</sup> and no significant clinical disease). Experts have recommended the following approaches:
  - A boosted PI-based regimen (two NRTIs plus ritonavir-boosted lopinavir) for prophylaxis, with the drugs stopped postpartum (**BIII**); or
  - Zidovudine prophylaxis alone during pregnancy and intrapartum (**BIII**).
- Non-nucleoside reverse transcriptase inhibitors and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis (**AIII**).
- All infants born to HIV-2-infected mothers should receive the standard 6-week zidovudine prophylactic regimen (**BIII**).
- In the United States, where safe infant formula is readily available, breastfeeding is not recommended for infants of HIV-2-infected mothers (**AIII**).

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

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

HIV-2 infection is endemic in West African countries including Ivory Coast, Ghana, Cape Verde, Gambia, Mali, Senegal, Liberia, Guinea, Burkina Faso, Nigeria, Mauritania, Sierra Leone, Guinea Bissau, Niger, Sao Tome, and Togo; Angola; Mozambique; and in parts of India.<sup>1-4</sup> It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.<sup>5</sup> HIV-2 remains rare in the United States. Between 1998 and 2010, a total of 242 HIV-2 cases were reported to the Centers for Disease Control and Prevention (CDC), with 166 cases meeting criteria for HIV-2 diagnosis. These 166 cases constituted only 0.01% of the more than 1.4 million U.S. cases of HIV infection.<sup>6</sup> Of the 50 women aged 15 to 44 years at diagnosis, 24 (48%) were pregnant at or after HIV-2 diagnosis.<sup>6</sup> HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic, who are HIV-1 antibody positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot along with HIV-1 RNA viral loads at or below the limit of detection.<sup>7-9</sup> Note that this pattern of HIV testing can also be seen in patients who have a false-positive HIV-1 test.

The FDA has approved the first rapid diagnostic test that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen, the Alere Determine HIV-1/2 Ag/Ab Combo, which can be used on human serum, plasma, and venous or fingerstick whole-blood specimens. However, this test does not distinguish between antibodies to HIV-1 and HIV-2. Specimens which are reactive on the rapid test must be tested with an FDA-approved 2nd generation antibody assay to distinguish HIV-1 from HIV-2 antibodies. The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is FDA-approved for differentiating HIV-1 from HIV-2 infections. In some commercial and public health laboratories, HIV-2 supplemental tests, such as HIV-2 immunoblot or HIV-2-specific Western



blot, are available. However, none of these tests has been FDA approved for diagnosis or clinical management of HIV-2. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2 and no HIV-2 commercial viral load assays are currently available. All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department, which can arrange for additional confirmatory testing for HIV-2 by the CDC.<sup>10</sup> No validated HIV-2 genotype or phenotype resistance assays are available in the United States. Recently, European experts developed a rule set and an automated tool for HIV-2 drug resistance analyses that is freely available on the Internet (see <http://www.hiv-grade.de>).<sup>11</sup>

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.<sup>3,12,13</sup> Several studies confirm that rates of perinatal transmission of HIV-2 are low with and without interventions (0%–4%), which may be a result of reduced plasma viral loads and less cervical viral shedding, compared with that seen in HIV-1-infected women.<sup>14–17</sup> HIV-2 also can be transmitted through breastfeeding. HIV-2 infection does not protect against HIV-1 and dual infection, which carries the same prognosis as HIV-1 mono-infection, can occur.

Few data exist on which to base treatment decisions or strategies for prevention of perinatal transmission in patients infected with HIV-2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis.<sup>18,19</sup> HIV-2 has variable sensitivity to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity against the virus.<sup>20</sup> The integrase inhibitors raltegravir and elvitegravir also appear to be effective against HIV-2.<sup>3,21–24</sup> 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.<sup>25,26</sup>

The care of HIV-2-infected pregnant women has been based on expert opinion. A regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted PI currently is recommended for HIV-2-infected pregnant women who require treatment for their own health because they have significant clinical disease or CD4 T lymphocyte (CD4) cell counts <500 cells/mm<sup>3</sup>.<sup>27</sup> Based on efficacy and available data on safety in HIV-1-infected pregnant women, ritonavir-boosted lopinavir plus zidovudine/lamivudine or abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine would be preferred.<sup>28,29</sup> NNRTIs should not be used because they are not active against HIV-2. All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen.

For HIV-2-infected pregnant women with CD4 cell counts >500 cells/mm<sup>3</sup> and no significant clinical disease, who do not require treatment for their own health, some experts would use a boosted PI-based regimen for prophylaxis and stop the drugs postpartum. Other experts would consider zidovudine prophylaxis alone during pregnancy and intrapartum.<sup>15</sup> Because HIV-2 has a significantly lower risk of perinatal transmission than does HIV-1, single-drug prophylaxis with zidovudine alone can be considered for prevention of perinatal transmission. All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen.<sup>29</sup> The possible risks and benefits of antiretroviral (ARV) prophylaxis should be discussed with the mothers.

Pregnant women who have HIV-1/HIV-2 coinfection should be treated according to the guidelines for HIV-1-monoinfected patients, making sure that the ARV regimen chosen is also appropriate for HIV-2.

Other than the standard obstetrical indications, no data exist regarding the role of elective cesarean delivery in women who are infected with HIV-2. The risk to infants from breastfeeding is lower for HIV-2 than for HIV-1, but breastfeeding should be avoided in the United States and other resource-rich countries where safe infant formula is readily available.<sup>15</sup>

Infants born to HIV-2-infected mothers should be tested for HIV-2 infection with HIV-2-specific virologic assays at time points similar to those used for HIV-1 testing.<sup>30</sup> HIV-2 virologic assays are not commercially available, but the National Perinatal HIV Hotline (888-448-8765) can provide a list of sites that perform this testing.

Testing of infants at age 18 months (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) also is recommended to confirm clearance of HIV-2 antibodies.<sup>29</sup>

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## Acute HIV Infection (Last updated March 28, 2014; last reviewed March 28, 2014)

### 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 an HIV antibody test (see [Identifying, Diagnosing, and Managing Acute HIV-1 Infection](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)) (AI).
- Repeat HIV antibody 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, are receiving care in facilities that have an HIV incidence in pregnant women of at least 1 per 1,000 per year, 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](#)) (AI).
- All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) drug regimen 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 the combination ARV regimen, and the ARV regimen should be adjusted, if necessary, to optimize virologic response (AIII).
- Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors in ARV-naive individuals in general, a ritonavir-boosted PI-based regimen should be initiated (AIII).

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

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

Primary or acute HIV infection in pregnancy or during breastfeeding is associated with an increased risk of perinatal transmission of HIV and may represent a significant proportion of residual perinatal transmission in the United States.

In North Carolina, from 2002 to 2005, 5 of 15 women found to have acute HIV infection on nucleic acid amplification testing of pooled HIV antibody-negative specimens were pregnant at the time of testing.<sup>1</sup> All 5 women received antiretroviral (ARV) drugs and delivered HIV-uninfected infants.

From 2002 to 2006, 3,396 HIV-exposed neonates were born in New York State—22% (9 of 41) of infants born to mothers who acquired HIV during pregnancy became infected with HIV, compared with 1.8% of those born to mothers who did not acquire HIV during pregnancy (odds ratio 15.19; 95% confidence interval, 3.98–56.30). Maternal acquisition of HIV during pregnancy was documented in only 1.3% of perinatal HIV exposures, but it was associated with 9 (13.8%) of the 65 perinatal transmission cases.<sup>2</sup> A case series from China reported a perinatal transmission rate of 35.8% in 106 breastfeeding infants of mothers who acquired HIV postnatally through blood transfusion.<sup>3</sup> The high rate of transmission associated with acute infection likely is related to the combination of the high viral load in plasma, breast milk, and the genital tract associated with acute infection<sup>4,5</sup> and the fact that the diagnosis is easy to miss, which results in lost opportunities for implementation of prevention interventions.

Health care providers should maintain a high level of suspicion of acute HIV infection in women who are pregnant or breastfeeding and have a compatible clinical syndrome, even when they do not report high-risk behaviors, because it is possible that their sexual partners are practicing high-risk behaviors of which the women are unaware.

An estimated 40% to 90% of patients with acute HIV infection will experience symptoms of acute retroviral syndrome, characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms.<sup>4,6-11</sup> Providers often do not recognize acute HIV infection, however, because the symptoms are similar to those of other common illnesses and individuals with the condition also can be asymptomatic. When acute retroviral syndrome is suspected, a plasma HIV RNA test typically is used in conjunction with an HIV antibody test to diagnose acute infection. A low-positive HIV RNA level (<10,000 copies/mL) may



represent a false-positive test because values in acute infection generally are very high (>100,000 copies/mL).<sup>4,10</sup> In individuals infected with non-B HIV-1 subtypes, however, HIV RNA levels may be lower, even with acute infection, because those subtypes may not amplify as well as subtype B. In that situation, consultation with an HIV treatment specialist is recommended. Confirmatory serologic testing should be performed within 3 months on patients whose acute HIV infection is diagnosed with virologic testing but who are antibody-negative or whose antibody levels cannot be determined.

Recent HIV infection also can be detected by repeat HIV antibody testing later in pregnancy in women whose initial HIV antibody testing earlier in pregnancy was negative.<sup>12</sup> A report from the Mother-Infant Rapid Intervention at Delivery study found that 6 (11%) of 54 women whose HIV was identified with rapid HIV testing during labor had primary infection.<sup>12,13</sup> In the United States, of 10,308 HIV-infected pregnant women who delivered live infants from 2005 to 2010 in 15 areas conducting Enhanced Perinatal Surveillance (EPS), 124 (1.2%) were identified as seroconverting during pregnancy. The rate of perinatal transmission was 8 times higher among women who seroconverted during pregnancy (12.9%) than in those who became infected prior to pregnancy (1.6%) ( $P < 0.0001$ ).<sup>14</sup> 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](#)).<sup>15</sup>

Whether treatment of acute or recent HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown, and in non-pregnant adults, therapy currently is considered optional.<sup>16</sup> In pregnant or breastfeeding women, however, acute or recent HIV infection is associated with a high risk of perinatal transmission of HIV. All HIV-infected pregnant women with acute or recent infection should start a combination ARV regimen as soon as possible, with the goal of preventing perinatal transmission by optimal suppression of plasma HIV RNA below detectable levels. Data from the United States and Europe demonstrate that in 6% to 16% of patients, transmitted virus may be resistant to at least one ARV drug.<sup>17,18</sup> Therefore, baseline genotypic resistance testing should be performed to guide selection or adjustment of an optimal ARV drug regimen. If results of resistance testing or the source virus's resistance pattern are known, that information should be used to guide selection of the drug regimen, but initiation of the combination ARV regimen should not be delayed. Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors in ARV-naive persons, a PI-based ARV drug regimen generally should be initiated. Choice of regimen should be based on recommendations for use of ARV drugs in pregnancy (see [Table 6](#) and [Table 7](#)). Following delivery, considerations regarding continuation of the ARV regimen for treatment are the same for mothers as for other non-pregnant individuals.

When acute HIV infection is diagnosed during pregnancy, and particularly if it is documented in late pregnancy, cesarean delivery is likely to be necessary because there may be insufficient time to fully suppress a patient's viral load. In nursing mothers in whom seroconversion is suspected, breastfeeding should be interrupted and it should not resume if infection is definitively confirmed (see [Breastfeeding Infants of Mothers Diagnosed with HIV Infection in Infant Antiretroviral Prophylaxis](#)). In such a situation, consultation with a pediatric HIV specialist regarding appropriate infant management is recommended.

All women who are pregnant or breastfeeding should be counseled about prevention of acquisition of HIV (see [Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis](#) and [Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States](#)). Several studies suggest that pregnancy may be a time of increased risk of transmission of HIV,<sup>19,23</sup> even when controlling for sexual risk behaviors.<sup>19</sup> It is hypothesized that the heightened risk may be attributable to hormonal changes that affect the genital tract mucosa or immune responses.<sup>19</sup> Although no reliable data on HIV serodiscordance rates in the United States exist, data on women from sub-Saharan Africa show that women in serodiscordant relationships may be particularly vulnerable to acquisition of HIV.<sup>24,25</sup> HIV testing



of the sexual partners of pregnant women should be encouraged. The importance of using condoms should be reinforced in pregnant and breastfeeding women who may be at risk of acquisition of HIV, including those whose partners are HIV-infected, and the potential use of pre- or post-exposure antiretroviral prophylaxis also should be emphasized (see [Reproductive Options for HIV-Concordant and Serodiscordant Couples](#)).

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## Intrapartum Antiretroviral Therapy/Prophylaxis

### Panel's Recommendations

- Women should continue their antepartum combination antiretroviral (ARV) drug regimen on schedule as much as possible during labor and before scheduled cesarean delivery (**AIII**).
- **Intravenous (IV)** zidovudine should be administered to HIV-infected women with HIV RNA **>1,000** copies/mL (or unknown HIV RNA) near delivery (**AI**), but is not required for HIV-infected women receiving combination ARV regimens who have HIV RNA **≤1,000** copies/mL **consistently during late pregnancy and near delivery and no concerns regarding adherence to the regimen (BII)**.
- For women who have suboptimal viral suppression near delivery (i.e., HIV RNA >1,000 copies/mL), scheduled cesarean delivery is recommended (see [Transmission and Mode of Delivery](#)) (**AI**).
- Women whose HIV status is unknown who present in labor should undergo rapid HIV antibody testing (**AII**). If the results are positive, a confirmatory HIV test should be done as soon as possible and maternal (IV zidovudine)/infant (combination ARV prophylaxis) ARV drugs should be initiated pending results of the confirmatory test (**AII**). If the confirmatory HIV test is positive, infant ARV drugs should be continued for 6 weeks (see [Infant Antiretroviral Prophylaxis](#)) (**AI**); if the **confirmatory HIV** test is negative, the infant ARV drugs should be stopped.

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

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

## Women Who Have Received Antepartum Antiretroviral Drugs

### Use of Intravenous Zidovudine During Labor

The PACTG 076 zidovudine regimen included a continuous intravenous (IV) infusion of zidovudine during labor for all women. Combination antiretroviral (ARV) regimens are now recommended for treatment and prevention of perinatal transmission of HIV; the additional benefit of IV zidovudine in women receiving combination regimens has not been evaluated in randomized clinical trials.

The French Perinatal Cohort evaluated transmission in **>11,000** HIV-infected pregnant women receiving ARV drugs (**10%** zidovudine alone, **18%** dual ARV, and **72%** triple ARV) who delivered between 1997 and **2010**, stratified by viral load at delivery; **95%** received IV intrapartum zidovudine.<sup>1</sup> **The overall rate of perinatal transmission was 0.9% (95/10,239) with IV zidovudine and 1.8% (9/514,  $P = 0.06$ ) without IV zidovudine. Among women with HIV RNA <1,000 copies/mL at delivery, no transmission occurred among 369 who did not receive IV zidovudine compared to a rate of 0.6% (47/8,132,  $P > 0.20$ ) among those receiving IV zidovudine. Among women with HIV RNA >1,000 copies/mL, the risk of transmission was increased without IV zidovudine (10.2%) compared to 2.5% with IV zidovudine ( $P < 0.01$ ) if neonates received only zidovudine for prophylaxis, but was not different (4.8% versus 4.1%,  $P = 0.83$ ) without or with intrapartum zidovudine if the neonate received intensified prophylaxis with two or more ARV drugs. In a cohort of 717 women delivering between 1996 and 2008 in Miami, the majority of whom were on a combination ARV regimen and had HIV RNA <1,000 copies/mL at delivery, lack of receipt of IV zidovudine during labor was not associated with an increased risk of transmission.<sup>2</sup> Among a European cohort of infants considered at high risk of transmission, lack of IV zidovudine in labor was associated with transmission on univariate analysis but was not significantly associated once adjusted for maternal HIV RNA and other factors (adjusted odds ratio with IV zidovudine 0.79, 95% confidence interval 0.55-1.15,  $P = 0.23$ ).<sup>3</sup> In a cohort of Irish women on a combination ARV regimen for at least 4 weeks before delivery with HIV RNA <1,000 copies/mL, no transmission occurred among 61 who received either no zidovudine in labor or <4 hours of IV zidovudine.<sup>4</sup>**

Based on **these studies**, IV zidovudine is not required for HIV-infected women receiving combination ARV regimens with HIV RNA **≤1,000** copies/mL **consistently in late pregnancy and/or near delivery and with no**

indication of concerns about adherence to or tolerance of their ARV regimens; IV zidovudine should continue to be administered to HIV-infected women with HIV RNA >1,000 copies/mL near delivery (or unknown HIV RNA levels), regardless of antepartum regimen.

Previously, these guidelines specified that the threshold for not requiring intrapartum IV zidovudine was <400 copies/mL. However, based on more recent studies that have used a threshold of 1,000 copies/mL,<sup>1,2,4</sup> a threshold of ≤1,000 copies/mL is now recommended for consideration of eliminating the requirement for IV zidovudine. This recommendation is now consistent with the mode of delivery recommendations that specify that a scheduled cesarean delivery is not recommended for women receiving combination ARV drugs with plasma HIV RNA levels ≤1,000 copies/mL. In addition, the previous guidelines did not specify that viral suppression had to be sustained. This guidance has been clarified to state that the viral loads should be consistently suppressed when intrapartum IV zidovudine is not used. However, regardless of viral load, the clinician may elect to use intrapartum IV zidovudine based on clinical judgement.

In women with HIV RNA >1,000 copies/mL receiving a scheduled cesarean delivery for prevention of transmission, IV zidovudine administration should begin 3 hours before the scheduled operative delivery. This recommendation is based on a pharmacokinetic (PK) study of zidovudine given orally during pregnancy and as a continuous infusion during labor. Maternal zidovudine levels were measured at baseline, after the initial IV loading dose and then every 3 to 4 hours until delivery, and in cord blood.<sup>5</sup> Systemic and intracellular zidovudine levels increased from baseline but appeared to stabilize after 3 hours of infusion; cord blood zidovudine levels were associated with maternal levels and maternal infusion duration. If cesarean section is being performed for other indications and maternal viral load is ≤1,000 copies/mL near the time of delivery, administration of IV zidovudine is not required.

If antenatal use of zidovudine was precluded by known or suspected zidovudine resistance, intrapartum use of the drug still should be recommended in women with HIV RNA >1,000 copies/mL near delivery, except in women with documented histories of hypersensitivity. This intrapartum use of the drug is recommended because of the unique characteristics of zidovudine and its proven record in reducing perinatal transmission, even in the presence of maternal resistance to the drug (see [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)).

In some international studies, oral rather than IV zidovudine has been administered during labor. Data are limited on the PKs of oral compared with IV zidovudine during labor. Additionally, the drug levels needed for prophylaxis are unknown, although extrapolations have been made using therapeutic drug level targets. In a study of oral intrapartum zidovudine 300 mg every 3 hours in Thailand, most cord blood zidovudine levels were at therapeutic levels but were lower than those reported after continuous IV administration; 17% of infants had subtherapeutic levels at birth.<sup>6</sup> In another study, the PKs of two dosing regimens of oral zidovudine during labor were evaluated in 10 HIV-infected pregnant women.<sup>7</sup> The oral regimen was well tolerated; plasma zidovudine concentrations were substantially lower with 300 mg every 3 hours given orally during labor than previously reported with continuous IV therapy. A revised regimen with a 600 mg oral loading dose, followed by 400 mg every 3 hours, resulted in increased zidovudine concentrations but inter-patient variance was significant. In both cohorts, PK parameters suggested erratic absorption during labor. Therefore, in women with HIV RNA >1,000 copies/mL near delivery for whom zidovudine is recommended, IV would be preferred to oral administration in the United States; in situations where IV administration is not possible, oral administration can be considered.

### **Continuation of Antenatal Antiretroviral Drugs during Labor**

Women who are receiving an antepartum combination ARV drug regimen should continue that regimen on schedule as much as possible during the intrapartum period to provide maximal virologic effect and to minimize the chance of development of drug resistance. If the woman's HIV-1 RNA level is >1,000 copies/mL and oral zidovudine is part of the antepartum regimen, the oral zidovudine component of the regimen can be held while she receives IV zidovudine. When cesarean delivery is planned, oral medications can be



continued preoperatively with sips of water. Medications requiring food ingestion for absorption can be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist in the preoperative period. If the maternal ARV regimen must be interrupted temporarily (meaning for less than 24 hours) during the peripartum period, all drugs should be stopped and 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 combination ARV drug regimens may not achieve complete viral suppression by the time of delivery because of factors such as poor adherence, viral resistance, or late entry into care. Regardless of the reason, all women who have HIV RNA levels >1,000 copies/mL near the time of delivery should be offered a scheduled cesarean delivery at 38 weeks, which may significantly reduce risk of transmission (see [Transmission and Mode of Delivery](#)).

Women with incomplete viral suppression at the time of delivery should receive IV zidovudine along with their other ARVs orally, as described above. In certain high-risk situations, additional medications for prophylaxis in infants may be warranted, such as in cases where maternal HIV RNA levels are high at or near the time of delivery, especially if delivery is not a scheduled cesarean delivery (see [Infant Antiretroviral Prophylaxis](#) and [Table 8](#)).

### ***Women Who Have Not Received Antepartum Antiretroviral Drugs***

#### **Women Who Present in Labor without Documentation of HIV Status**

All women without documentation of HIV status at the time of labor should be screened with rapid HIV testing unless they decline (opt-out screening). Rapid HIV testing is also recommended for women presenting in labor who tested negative for HIV in early pregnancy but are at increased risk of HIV infection and were not retested in the third trimester.<sup>8</sup> Factors that may increase risk of infection include diagnosis of a sexually transmitted disease, illicit drug use or exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of HIV infection, signs/symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age and not undergoing repeat HIV testing in the third trimester.<sup>8</sup>

Rapid HIV antibody testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit. Statutes and regulations regarding rapid testing vary from state to state (see [http://www.nccc.ucsf.edu/consultation\\_library/state\\_hiv\\_testing\\_laws](http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws) for a review of state HIV testing laws). Current information on rapid testing also should be available at all facilities with a maternity service and/or neonatal intensive care unit.

Women with positive rapid HIV antibody tests should be presumed to be infected until standard HIV antibody confirmatory testing clarifies their infection status. IV zidovudine should be started immediately in all women with positive rapid HIV tests in labor to prevent perinatal transmission of HIV, as discussed below.

In the postpartum period, along with confirmatory HIV antibody testing, these women should receive appropriate assessments as soon as possible to determine their health status, including CD4 T lymphocyte count and HIV-1 RNA viral load. Arrangements also should be made for establishing HIV care and providing ongoing psychosocial support after discharge.

#### **Choice of Intrapartum/Postpartum Antiretroviral Regimen for Women without Antepartum Antiretroviral Therapy**

All HIV-infected women who have not received antepartum ARV drugs should have IV zidovudine started immediately to prevent perinatal transmission of HIV. Although intrapartum/neonatal ARV medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to or during labor



and delivery. Pre-exposure prophylaxis for the fetus can be provided by giving mothers a drug that rapidly crosses the placenta, producing fetal systemic ARV drug levels during intensive exposure to HIV in maternal genital secretions and in blood during birth. In general, zidovudine and other nucleoside reverse transcriptase inhibitor drugs and non-nucleoside reverse transcriptase inhibitors cross the placenta well, whereas protease inhibitors do not (see [Table 7](#)).

A large international trial (NICHD-HPTN 040/PACTG 1043) demonstrated that adding ARV agents to the neonatal portion of the intrapartum/neonatal zidovudine regimen can further reduce perinatal transmission of HIV for mothers who have received no antepartum ARV drugs (see [Infant Antiretroviral Prophylaxis](#)). In this study, women who had not received antepartum ARV drugs received IV zidovudine if they were identified in labor or no zidovudine when diagnosed immediately postpartum; their infants received either 6 weeks of zidovudine alone or zidovudine in combination with other agents. The combination infant regimens resulted in a 50% reduction in transmission compared with zidovudine alone. Therefore, no additional intrapartum drugs, including intrapartum maternal single-dose nevirapine, are indicated for a woman in this situation.<sup>9</sup>

Women diagnosed with HIV infection during labor or the early postpartum period should be counseled against breastfeeding in the United States, where replacement feeding is affordable, feasible, acceptable, sustainable, and safe.

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## Transmission and Mode of Delivery (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- Scheduled cesarean delivery at 38 weeks' gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral drugs (**AII**). Data are insufficient to evaluate the potential benefit of cesarean delivery used solely for prevention of perinatal transmission in women receiving combination antiretroviral therapy with HIV RNA levels ≤1000 copies/mL, and given the low rate of transmission in these patients, it is unclear whether scheduled cesarean delivery would confer additional benefit in reducing transmission (**BIII**). In women with HIV RNA levels ≤1000 copies/mL, cesarean delivery performed for standard obstetrical indications should be scheduled at 39 weeks' gestation.
- It is not clear whether cesarean delivery after rupture of membranes or onset of labor provides benefit in preventing perinatal transmission. Management of women originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized at the time of presentation based on duration of rupture and/or labor, plasma HIV RNA level, and current antiretroviral regimen (**BII**).
- Women should be informed of the risks associated with cesarean delivery. If the indication for cesarean delivery is prevention of perinatal transmission of HIV, the risks to a woman should be balanced with potential benefits expected for the neonate (**AII**).

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

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

### Basis for Current Recommendations

Scheduled cesarean delivery, defined as cesarean delivery performed before the onset of labor and before rupture of membranes, is recommended for prevention of perinatal transmission of HIV in women with HIV RNA levels >1000 copies/mL near delivery and for women with unknown HIV RNA levels.

This recommendation is based on findings from a multicenter, randomized clinical trial<sup>1</sup> and from a large individual patient data meta-analysis.<sup>2</sup> These two studies were conducted at a time when the majority of HIV-infected women received no antiretroviral (ARV) medications or zidovudine as a single drug and before the availability of viral load information. Study results have since been extrapolated to make current recommendations about the mode of delivery in an era when combination ARV regimens during pregnancy are recommended and viral load information is readily available.

In the randomized clinical trial, 1.8% of infants born to women randomized to undergo cesarean delivery were HIV-infected compared with 10.5% of infants born to women randomized to vaginal delivery ( $P < .001$ ). When adjusted for ARV use in pregnancy (zidovudine alone), scheduled cesarean delivery lowered risk of HIV transmission by 80%, although the results were no longer statistically significant (odds ratio [OR] 0.2; 95% confidence interval [CI], 0–1.7). The protective effect still remained for scheduled delivery (adjusted OR [AOR] 0.3; 95% CI, 0.1–0.8) but not for emergency cesarean delivery (AOR 1.0; 95% CI, 0.3–3.7) when the data were analyzed by actual mode of delivery rather than by the group to which women were allocated.<sup>1</sup> Results from a large meta-analysis of individual patient data from 15 prospective cohort studies also demonstrated the benefit of scheduled cesarean delivery, with a 50% reduction in risk.<sup>2</sup>

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

The American College of Obstetricians and Gynecologists (ACOG)<sup>3</sup> recommends that women with HIV RNA >1000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery. Initially, the threshold of 1000 copies/mL was based largely on data from the Women and Infants Transmission Study, a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels less than 1000 copies/mL.<sup>4</sup> 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  $\leq 1000$  copies/mL, cesarean delivery (scheduled or urgent) reduced risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications; however, zidovudine alone was the regimen primarily used as prophylaxis (AOR 0.30;  $P = 0.022$ ).<sup>5</sup> Among infants born to 834 women with HIV RNA  $\leq 1000$  copies/mL receiving ARV medications, 8 (1%) were HIV-infected. In a more recent report from a comprehensive national surveillance system in the United Kingdom and Ireland, 3 (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA levels  $< 50$  copies/mL and 50 to 999 copies/mL, respectively, were HIV infected.<sup>6</sup>

The recent studies demonstrate that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission in this group, it is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. Although decisions about mode of delivery for women **receiving combination ARV** therapy (cART) with HIV RNA levels  $\leq 1000$  copies/mL should be individualized based on discussion between the obstetrician and the mother, women should be informed that there is no evidence of benefit for scheduled cesarean delivery performed solely for prevention of perinatal transmission in women **receiving** cART with HIV RNA  $\leq 1000$  copies/mL and that it is not routinely recommended in this group.

### **Scheduled Cesarean Delivery in the Combination Antiretroviral Therapy Era**

In surveillance data from the United Kingdom and Ireland, pregnant women receiving cART (i.e., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery.<sup>6</sup> Given the low transmission rates achievable with use of maternal cART, the benefit of scheduled cesarean delivery is difficult to evaluate. Both the randomized clinical trial<sup>1</sup> and meta-analysis<sup>2</sup> documenting the benefits of cesarean delivery included mostly women who were receiving either no ARVs or zidovudine alone. However, other data partially address this issue.

In a report from the European Collaborative Study that included data from 4,525 women, the overall transmission rate in the subset of women on cART was 1.2% (11 of 918).<sup>7</sup> In the subset of 560 women with undetectable HIV RNA levels ( $\leq 50$  to  $\leq 200$  copies/mL, depending on site), scheduled cesarean delivery was associated with a significant reduction in perinatal transmission in univariate analysis (OR 0.07; 95% CI, 0.02–0.31;  $P = .0004$ ). However, after adjustment for ARV drug use (none vs. any), the effect was no longer significant (AOR 0.52; 95% CI, 0.14–2.03;  $P = .359$ ). Similarly, data from a European surveillance study did not demonstrate a statistically significant difference in transmission rates between scheduled cesarean delivery and planned vaginal delivery (AOR 1.24; 95% CI, 0.34–4.5) in women on cART.<sup>6</sup> The transmission rate in all women who received at least 14 days of ARV medications was 0.8% (40 of 4,864), regardless of mode of delivery. Therefore, no evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving cART for several weeks and who have achieved virologic suppression.

When the delivery method selected is scheduled cesarean delivery and the maternal viral load is  $> 1000$  copies/mL, administer a 1-hour loading dose and continuous intravenous (IV) zidovudine for 2 hours (3 hours total) before scheduled cesarean delivery. In a study of the pharmacokinetics of IV zidovudine in 28 pregnant women, the ratio of cord blood to maternal zidovudine levels increased significantly in women who received IV zidovudine for 3 to 6 hours compared with  $< 3$  hours before delivery (1.0 vs 0.55, respectively)<sup>8</sup> This suggests that an interval of at least 3 hours may provide adequate time to reach equilibrium across the placenta, although the relationship between specific cord blood zidovudine levels or cord blood-to-maternal-zidovudine levels and efficacy in preventing perinatal transmission of HIV is unknown.

Because unscheduled cesarean delivery is performed for both maternal and fetal indications, when an unscheduled cesarean delivery is indicated in a woman who has a viral load  $> 1000$  copies/mL, consideration can be given to shortening the interval between initiation of IV zidovudine administration and delivery. For example, some experts recommend administering the 1-hour loading dose of IV zidovudine and not waiting to complete additional administration before proceeding with delivery.

## Women Presenting Late in Pregnancy

HIV-infected women who present late in pregnancy and are not receiving ARV drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be  $\leq 1000$  copies/mL at baseline. Even if cART was begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the kinetics of viral decay for a particular drug regimen.<sup>9,10</sup> In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing the risk of perinatal transmission of HIV for women, unless viral suppression can be documented before 38 weeks' gestation.

## Timing of Scheduled Cesarean Delivery

**For the general obstetric population**, ACOG recommends that scheduled cesarean delivery not be performed before 39 weeks' gestation because of the risk of iatrogenic prematurity.<sup>11,12</sup> 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.<sup>3</sup> 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.<sup>12</sup> Gestational age should be determined by best obstetrical dating criteria, including last menstrual period and early ultrasound for dating purposes. Amniocentesis to document lung maturity should be avoided when possible in HIV-infected women and is rarely indicated before scheduled cesarean section for prevention of HIV transmission.

Among 1,194 infants born to HIV-infected mothers, 9 (1.6%) infants born vaginally had respiratory distress syndrome (RDS) compared with 18 (4.4%) infants born by scheduled cesarean delivery ( $P < 0.001$ ). There was no statistically significant association between mode of delivery and infant RDS in an adjusted model that included infant gestational age and birth weight.<sup>13</sup> Although newborn complications may be increased in planned births  $< 39$  weeks' gestation, the benefits of planned cesarean delivery at 38 weeks are generally thought to outweigh the risks if the procedure is performed for prevention of HIV transmission. When cesarean delivery is performed in HIV-infected women for an indication other than decreasing HIV transmission, cesarean delivery should be scheduled at 39 weeks, based on ACOG guidelines.

## Risk of Maternal Complications

Administration of perioperative antimicrobial prophylaxis is recommended for all women to decrease maternal infectious morbidity associated with cesarean delivery. Most studies have demonstrated that HIV-infected women have increased rates of postoperative complications, mostly infectious, compared with HIV-uninfected women and that risk of complications is related to degree of immunosuppression **and the receipt of suppressive** cART.<sup>14-19</sup> Furthermore, a Cochrane review of six studies of HIV-infected women concluded that urgent cesarean delivery was associated with the highest risk of postpartum morbidity, scheduled cesarean delivery was intermediate in risk, and vaginal delivery had the lowest risk of morbidity.<sup>20</sup> Complication rates in most studies<sup>1,21-25</sup> were within the range reported in populations of HIV-uninfected women with similar risk factors and not of sufficient frequency or severity to outweigh the potential benefit of reduced perinatal HIV transmission. Therefore, HIV-infected women should be counseled regarding the risks associated with undergoing cesarean delivery and the potential benefits in decreasing perinatal transmission of HIV if HIV RNA levels at term are  $> 1000$  copies/mL.

## Management of Women Who Present in Early Labor or With Ruptured Membranes

Few data are available to address the question of whether performing cesarean delivery after the onset of labor or membrane rupture decreases risk of perinatal transmission of HIV. Most studies have shown a similar risk of transmission for cesarean delivery performed for obstetric indications after labor and membrane rupture and for vaginal delivery. In one study, the HIV transmission rate was similar in women undergoing emergency cesarean delivery and those delivering vaginally (1.6% vs. 1.9%, respectively).<sup>6</sup> A meta-analysis of HIV-infected women, most of whom were on zidovudine as a single drug or receiving no



ARV medications, demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes.<sup>26</sup> However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.<sup>27</sup> Therefore, the decision about whether to deliver by expeditious cesarean section for prevention of perinatal transmission in women originally scheduled for cesarean delivery who then present with ruptured membranes or in labor must be individualized, taking into account duration of rupture or labor upon presentation, plasma RNA level, and current ARV drug regimen status. The ARV drug regimen should be continued and IV zidovudine initiated, if previously planned.

When membrane rupture occurs before 37 weeks' gestation, decisions about timing of delivery should be based on best obstetrical practices, taking into account risks to the infant of prematurity and of HIV transmission. Steroids should be given, if appropriate, to accelerate fetal lung maturity because no data exist to suggest that these recommendations need to be altered for HIV-infected women. When the decision is made to deliver, route of delivery should be according to obstetrical indications.

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## Other Intrapartum Management Considerations (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- The following should generally be avoided because of a potential increased risk of transmission, unless there are clear obstetric indications:
  - Artificial rupture of membranes (BIII)
  - Routine use of fetal scalp electrodes for fetal monitoring (BIII)
  - Operative delivery with forceps or a vacuum extractor and/or episiotomy (BIII)
- The antiretroviral drug regimen a woman is receiving should be taken into consideration when treating excessive postpartum bleeding resulting from uterine atony:
  - In women who are receiving a cytochrome P (CYP) 3A4 enzyme inhibitor such as a protease inhibitor, methergine should be used only if no alternative treatments for postpartum hemorrhage are available and the need for pharmacologic treatment outweighs the risks. If methergine is used, it should be administered in the lowest effective dose for the shortest possible duration (BIII).
  - In women who are receiving a CYP3A4 enzyme inducer such as nevirapine, efavirenz, or etravirine, additional uterotonic agents may be needed because of the potential for decreased methergine levels and inadequate treatment effect.

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

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

If spontaneous rupture of membranes occurs before or early during the course of labor, interventions to decrease the interval to delivery (e.g., administration of oxytocin) can be considered in HIV-infected women with viral suppression and no indications for cesarean delivery. Artificial rupture of membranes should be avoided and used only for a clear obstetric indication in women with intact membranes and detectable viral loads who present in labor and will be allowed to proceed to vaginal delivery. Data are limited on artificial rupture of membranes in women with undetectable viral loads and planned vaginal delivery. **Data on the association of duration of membrane rupture and perinatal transmission in the era of effective combination antiretroviral therapy (cART) are more reassuring on this issue. A recent prospective cohort study of 707 HIV-infected pregnant women on cART included 493 women with delivery HIV-RNA <1000 copies/mL with no cases of perinatal transmission with up to 25 hours of membrane rupture; logistic regression found that HIV viral load >10,000 copies/mL was the only independent risk factor for transmission.**<sup>1</sup> In general, the procedure should be performed only for clear obstetrical indications because of the potential, albeit small, of an increased risk of HIV transmission.

Obstetric procedures that increase the risk of fetal exposure to maternal blood, such as invasive fetal monitoring, have been implicated in increasing vertical transmission rates by some, but not all, investigators, primarily in studies performed in the pre-ART era.<sup>2-5</sup> Data are limited on use of fetal scalp electrodes in labor in women receiving suppressive antiretroviral (ARV) regimens who have undetectable viral loads; routine use of fetal scalp electrodes for fetal monitoring should be avoided in the setting of maternal HIV infection unless there are clear obstetric indications.

Similarly, data are limited to those obtained in the pre-cART era regarding the potential risk of perinatal transmission of HIV associated with operative vaginal delivery with forceps or the vacuum extractor and/or use of episiotomy.<sup>3,5</sup> These procedures should be performed only if there are clear obstetric indications. Delayed cord clamping has been associated with improved iron status in both term and preterm infants and benefits such as decreased risk of intraventricular hemorrhage in preterm births to HIV-uninfected mothers.<sup>6,7</sup> Even though HIV-specific data on the practice are lacking, there is no reason to modify it in HIV-infected mothers.

## ***Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use***

Oral or parenteral methergine or other ergot alkaloids are often used as first-line treatment for postpartum hemorrhage resulting from uterine atony. However, methergine should not be coadministered with drugs that are potent cytochrome P (CYP) 3A4 enzyme inhibitors, including protease inhibitors (PIs). Concomitant use of ergotamines and PIs has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving PIs, methergine should be used only if alternative treatments such as prostaglandin F<sub>2</sub>-alpha, misoprostol, or oxytocin are unavailable. If no alternative medications are available and the need for pharmacologic treatment outweighs the risks, methergine should be used in as low a dose and for as short a period as possible. In contrast, additional uterotonic agents may be needed when other ARV drugs that are CYP3A4 inducers (e.g., nevirapine, efavirenz, etravirine) are used because of the potential for decreased methergine levels and inadequate treatment effect.

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## Postpartum Care (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- Decisions regarding continuing combination antiretroviral therapy (cART) after delivery should be made in consultation with the woman and her HIV provider, ideally before delivery (**AIII**). cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission, although the strength and evidence for this recommendation varies by pre-treatment CD4 T lymphocyte (CD4) count. Decisions should take into account current recommendations for initiation of cART in adults, pre-treatment CD4 cell counts and trajectory, HIV RNA levels, adherence issues, whether a woman has an HIV-uninfected sexual partner, and patient preference.
- For women continuing cART postpartum, arrangements for new or continued supportive services should be made before hospital discharge because the immediate postpartum period poses unique challenges to adherence (**AII**).
- Contraceptive counseling should be a critical aspect of postpartum care (**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. If infection is confirmed, a full health assessment is warranted, including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of need for cART and opportunistic infection prophylaxis (**AII**).
- Breastfeeding is not recommended for HIV-infected women in the United States, including those receiving cART (**AII**).

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

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

### Postpartum Follow-Up of HIV-Infected Women

The postpartum period provides an opportunity to review and optimize women's health care. Comprehensive medical care and supportive services are particularly important for HIV-infected women and their families, who often face multiple medical and social challenges. Components of comprehensive care include the following services as needed:

- Primary, gynecologic/obstetric, and HIV specialty care for the HIV-infected woman;
- Pediatric care for her infant;
- Family planning services;
- Mental health services;
- Substance abuse treatment;
- Support services; and
- Coordination of care through case management for a woman, her child(ren), and other family members.

Support services should be tailored to the individual woman's needs and can include case management; child care; respite care; assistance with basic life needs, such as housing, food, and transportation; peer counseling; and legal and advocacy services. Ideally, this care should begin before pregnancy and continue throughout pregnancy and the postpartum period.

During the postpartum period, maternal medical services must be coordinated between obstetric care providers and HIV specialists. Decisions about continuing combination antiretroviral therapy (cART) after delivery should be made in consultation with the woman and her HIV provider, ideally prior to delivery. It is especially critical to ensure continuity of cART between the antepartum and postpartum periods.

cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission; the strength and evidence for this recommendation varies by

pretreatment CD4 T lymphocyte (CD4) cell count.<sup>1</sup> Randomized clinical trials have demonstrated clear evidence of individual clinical benefit for starting cART in persons with CD4 <350 cells/mm<sup>3</sup>. Data from observational studies support initiation of cART in individuals with CD4 cell counts of 350 to 500 cells/mm<sup>3</sup>. Data from observational studies are conflicting regarding individual clinical benefit for starting cART in individuals with CD4 cell counts >500 cells/mm<sup>3</sup>. The HPTN 052 clinical trial, which evaluated immediate versus delayed initiation of cART to HIV-infected individuals with CD4 cell counts between 350 and 550 cells/mm<sup>3</sup>, showed that earlier initiation of antiretroviral (ARV) drugs led to a significant reduction in sexual transmission of HIV to uninfected partners in serodiscordant couples (see [Preconception Counseling](#)). The [Adult and Adolescent Guidelines](#) note that when discussing initiation of cART at high CD4 cell counts, clinicians should inform patients that the data on clinical benefit of starting treatment at study levels are not conclusive, but that viral suppression can reduce the risk of sexual transmission to others.<sup>1</sup> It is important to counsel the woman that no single method (including treatment of the infected partner) is fully protective against HIV transmission and safer sexual practices must be continued.

In a study of postpartum women in Haiti, women who stopped ARVs after delivery with antepartum CD4 cell counts between 350 and 499 cells/mm<sup>3</sup> near delivery progressed to CD4 cell counts <350 cells/mm<sup>3</sup> by 19 months post-delivery, whereas women with CD4 cell counts ≥500 cells/mm<sup>3</sup> took significantly longer (5 to 7 years) to progress to CD4 cell counts <350 cells/mm<sup>3</sup>; mortality was confined to women with CD4 cell counts <350 cells/mm<sup>3</sup>.<sup>2</sup> Similar data were reported in the HPTN 046 study in Africa, in which 37% of women with CD4 cell counts 400 to 549 cells/mm<sup>3</sup> near delivery had CD4 cell counts decline to <350 cells/mm<sup>3</sup> by 12 months post-delivery, whereas only 7% of women with CD4 cell counts ≥550 cells/mm<sup>3</sup> had a similar decline.<sup>3</sup> Factors to be taken into consideration regarding continuation of postpartum cART should include current recommendations for initiation of cART in adults, pretreatment CD4 cell counts and trajectory, HIV RNA levels, adherence issues, partner HIV status, and patient preference. The risks versus benefits of stopping cART postpartum in women with high CD4 cell counts are being evaluated in the ongoing PROMISE study (clinical trial number NCT00955968). Unplanned changes in ARV regimens and discontinuations of cART in the postpartum period have led to viral load rebound, although no change in viral setpoint has been observed.<sup>4,5</sup> In contrast to results from treatment interruption studies in adults, in a study of biomarkers in postpartum HIV-infected women with pre-cART CD4 cell counts >350 cells/mm<sup>3</sup> who received cART during pregnancy, significant decreases in the levels of D-dimer, highly sensitive C-reactive protein, and interleukin-6 in the postpartum period were seen in both women who stopped as well as those who continued cART postpartum.<sup>6</sup>

Systematic monitoring of retention in HIV care is recommended for all HIV-infected individuals but special attention is warranted during the postpartum period. Retention in care is associated with improved individual health outcomes, including HIV biomarker and clinical variables, and may reduce community-level viral burden.<sup>7</sup> Because the postpartum period is a particularly vulnerable period for a new mother with HIV, interventions to improve adherence to medical care—to ensure follow-up medical appointments and cART adherence—can include medication management services, community outreach, one-on-one adherence support, group education and support, peer support, reminder devices, and home visits by medical HIV case managers.<sup>7</sup> A number of studies have suggested that postpartum depression may be common among HIV-infected women.<sup>8-11</sup> Health care providers should be vigilant for signs of depression and illicit drug or alcohol use that may require intervention assessment to avoid problems with adherence. Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of cART.<sup>12-14</sup> Simplification of a cART regimen (e.g., to once-daily medications) can be considered. For women who are unable to adhere to their regimens postpartum, it may be preferable to temporarily interrupt cART while they work with their health care provider on strategies to improve adherence. Efforts to maintain adequate adherence during the postpartum period may prolong the effectiveness of therapy (see the section on [Adherence in the Adult and Adolescent Antiretroviral Guidelines](#)).

The postpartum period also is a critical time for addressing the issue of safer sex practices, secondary transmission prevention, and contraception. It is important that comprehensive family planning and



preconception care be integrated into routine health visits. Women who receive family planning counseling during prenatal care are more likely to use effective contraception postpartum.<sup>15</sup> 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.<sup>16</sup> Interpregnancy intervals of less than 18 months have been associated with increased risk of poor perinatal and maternal outcomes in HIV-uninfected women.<sup>17</sup> Because of the stresses and demands of a new baby, women may be more receptive to use of effective contraception, yet simultaneously at higher risk of nonadherence to contraceptive use and, thus, unintended pregnancy.<sup>4</sup> This is an important concern in women who are on an efavirenz-containing regimen because of the potential risk of teratogenicity in the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after the last menstrual period). A dual-protection strategy (e.g., use of condoms plus a second highly effective contraceptive) is ideal for HIV-infected women because it provides simultaneous protection against unintended pregnancy, transmission of HIV, and acquisition or transmission of sexually transmitted disease.<sup>18</sup> Longer-term reversible contraceptive methods, such as injectables, implants, and intrauterine devices (IUDs) should be included as options.

Drug interactions have been documented between oral contraceptives and many ARV drugs; however, data primarily come from pharmacokinetic studies and the clinical implications have not been well studied. The magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy or increase contraceptive-associated adverse effects is unknown. Hormonal contraceptives can be used with cART in women who have no other contraindications. Additional or alternative methods of contraception can be recommended where drug interactions are known. ARV-contraceptive interactions are discussed in [Preconception Counseling and Care for HIV-Infected Women of Childbearing Age](#) and [Table 3](#). A systematic review conducted for the World Health Organization has summarized the research on hormonal contraception, IUD use, and risk of HIV infection.<sup>19,20</sup> Permanent sterilization is appropriate only for women who are certain they do not desire future childbearing.

Concerns have been raised about adherence to ARV regimens during the postpartum period, because a number of studies have found significant decreases in adherence postpartum.<sup>21–24</sup> 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.<sup>25–27</sup>

For women whose antepartum regimen included a non-nucleoside reverse transcriptase inhibitor (NNRTI) and who plan to stop ART after delivery, consideration should be given to stopping the NNRTI and continuing the other ARV drugs for a period of time before stopping electively. The optimal interval between stopping an NNRTI and the other ARV drugs is unknown; a minimum of 7 days is recommended. Because efavirenz-based therapy has potential to result in prolonged, detectable NNRTI concentrations for more than 3 weeks, some experts recommend that patients receiving efavirenz continue their other ARV drugs or substitute a protease inhibitor (PI) for the NNRTI drug in combination with their other ARV drugs for up to 30 days after stopping efavirenz (see [Stopping Antiretroviral Drugs during Pregnancy](#) and [Antiretroviral Drug Resistance and Resistance Testing in Pregnancy](#)). Women whose antepartum regimen did not include an NNRTI and who plan to stop cART after delivery should stop all ARV drugs at the same time. Doses of some PIs may be increased during pregnancy. For women continuing cART, available data suggest that standard doses can be used again, beginning immediately after delivery.

Immediate linking to care, comprehensive medical assessment, counseling, and follow-up are required for women who test positive on rapid HIV antibody assay during labor or at delivery. To minimize the delay in definitive diagnosis, confirmatory HIV antibody testing should be performed as soon as possible after an initial positive rapid test.<sup>28</sup> Women who test positive on rapid HIV antibody assay should not breastfeed unless a confirmatory HIV test is negative. Women with a new HIV diagnosis postpartum should receive the same thorough evaluation as other newly identified infected patients, including consideration of cART and prophylaxis for opportunistic infections, as indicated. Other children and partner(s) should be referred for HIV testing.

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## Infant Antiretroviral Prophylaxis (Last Updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is **generally** recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV (**AI**). **However, a 4-week neonatal chemoprophylaxis regimen can be considered when the mother has received standard combination antiretroviral therapy (cART) during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence (BII).**
- Zidovudine, at gestational age-appropriate doses, should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (**AI**).
- Infants born to HIV-infected women who have not received cART should receive prophylaxis with zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (i.e., at birth, 48 hours later, and 96 hours after the second dose), begun as soon after birth as possible (**AI**).
- In other scenarios, the decision to combine other drugs with the 6-week zidovudine regimen should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by maternal counseling on the potential risks and benefits of this approach (**BIII**).
- **For infants born to mothers with unknown HIV status, expedited (rapid) HIV testing of mothers and/or infants is recommended as soon as possible, either during labor or after birth, with immediate initiation of infant antiretroviral (ARV) prophylaxis if the initial expedited test is positive (AI). If supplemental testing is negative, ARV prophylaxis can be discontinued.**
- In the United States, the use of ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants as **prophylaxis to prevent transmission** because of lack of dosing and safety data (**BIII**).
- The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV, including infant care.

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

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

### General Considerations for Choice of Infant Prophylaxis

All HIV-exposed infants should receive postpartum antiretroviral (ARV) drugs to reduce perinatal transmission of HIV. The 6-week neonatal zidovudine chemoprophylaxis regimen is **generally** recommended for all HIV-exposed infants.<sup>1,2</sup> **However, a 4-week neonatal chemoprophylaxis regimen can be considered when the mother has received standard combination antiretroviral therapy (cART) during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence (see [Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression](#) below).**<sup>3,4</sup> [Table 8](#) shows recommended zidovudine dosing based on gestational age, birth weight and the status of maternal antepartum ARV regimens.

The risk of transmission is increased when maternal viral load at delivery is high or maternal antepartum and/or intrapartum prophylaxis was **incomplete or** not received. **In these situations,** the potential benefit of combining zidovudine infant prophylaxis with additional ARV drugs **must be weighed against the potential risks to infants of multiple drug exposure.** **In the following sections, we present available data and recommendations for management of infants** born to mothers:

- Who received antepartum/intrapartum ARV drugs with effective viral suppression;
- Who received antepartum and intrapartum ARV drugs but who had suboptimal viral suppression at delivery, particularly if delivery was vaginal;
- Who received only intrapartum ARV drugs;
- Who received neither antepartum nor intrapartum ARV drugs;
- **With unknown HIV status;** and
- With known ARV drug-resistant virus.



In each of these situations, there is a spectrum of transmission risk that depends on a number of maternal and infant factors, including maternal viral load, mode of delivery, and gestational age at delivery. The risks and benefits of infant exposure to ARV drugs in addition to zidovudine will differ depending on where the mother/child falls in the risk spectrum. Thus, a generic recommendation cannot be made regarding use of combination drug regimens for infant prophylaxis. Each situation needs to be considered individually, balancing potential benefits (in terms of preventing perinatal transmission of HIV) with risks (in terms of toxicity to the infant). In addition, appropriate drug formulations and dosing regimens for neonates are incompletely defined and data are minimal on the safety of combination drugs in the neonate (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis and the [Pediatric Antiretroviral Guidelines](#)).

Data from the NICHD-HPTN 040/PACTG 1043 study have provided guidance for management of infants born to women who received no ARV prophylaxis during pregnancy. In this study, 1,746 formula-fed infants born to HIV-infected women who did not receive any ARV drugs during pregnancy were randomized to one of three infant prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. The risk of intrapartum transmission was significantly lower in the two- and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone;  $P = .046$  for each experimental arm vs. zidovudine alone).<sup>5</sup> Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or zidovudine-alone regimen (27.5% vs. 15%,  $P < .0001$ ). In other studies, significantly higher rates of neutropenia and anemia have been reported with co-administration of zidovudine and lamivudine to infants.<sup>6</sup> Thus, based on comparable efficacy and reduced toxicity, the Panel recommends 6 weeks of zidovudine plus three doses of nevirapine for infants whose mothers have not received antepartum ARVs ([Table 8](#)).

Despite the paucity of available data, the use of combination ARV prophylaxis for infants in high-risk situations is increasing. Surveillance of obstetric and pediatric HIV infection in the United Kingdom and Ireland through the National Study of HIV in Pregnancy and Childhood noted that between 2001 and 2004, 9% of HIV-exposed infants received triple-drug prophylaxis compared with 13% between 2005 and 2008.<sup>7</sup> Similarly, in an Internet-based poll of 134 U.S.-based perinatal HIV service providers, 62% reported using combination postnatal prophylaxis in high-risk situations in the past year. Zidovudine, lamivudine, and nevirapine was the combination regimen used most often.<sup>8</sup> The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) has pooled data from 5,285 mother-infant pairs included in eight European cohorts and evaluated the use of combination prophylaxis. Among the 1,105 infants receiving combination prophylaxis, 13.5% received zidovudine plus lamivudine, 22.7% received zidovudine plus single-dose nevirapine, 55.8% received zidovudine plus single-dose nevirapine plus lamivudine, and 4.4% received a regimen including a protease inhibitor (PI). In these observational cohorts, there was no difference in infant infection rates between one drug and combination prophylactic regimens.<sup>9</sup> The authors concluded that the lack of difference may be related to residual confounding or the fact that combination prophylaxis may only be effective in a subset of infants.

A case of a “functional cure” of HIV in an infant was recently reported.<sup>10</sup> The infant was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and was diagnosed as HIV-infected by rapid testing during labor; delivery occurred before maternal intrapartum ARV prophylaxis could be given. At age 30 hours, the infant initiated a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher therapeutic dose rather than standard prophylactic dosing). The infant was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these tests, the infant was continued on treatment for HIV infection, thought to be acquired *in utero*. Nevirapine was replaced by ritonavir-boosted lopinavir at day 7 of life (Note: This decision preceded warnings from the Food and Drug Administration (FDA) against use of ritonavir-boosted lopinavir in infants younger than age 14 days). At age 18 months, therapy was discontinued by the mother; levels of plasma RNA, proviral DNA, and HIV antibodies have remained undetectable in the child through age 30 months on



no therapy. Further investigation is ongoing, and clinical trials are planned to address whether administration of a therapeutic combination ARV regimen to HIV-exposed high-risk infants could alter the establishment and long-term persistence of HIV infection and assess the safety of such an approach for the infant.

There are two key safety issues related to the choice of ARV drugs in this infant. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birth-weight infants (see [Antiretroviral Drug Dosing for Premature Infants](#)), these prophylaxis-dose regimens target trough drug levels of 100 ng/mL, with peak levels averaging 1,000 to 1,500 ng/mL. However, there have been no studies in neonates under age 2 weeks or preterm infants to determine the appropriate dosing or safety of nevirapine administered at therapeutic doses, designed to maintain trough drug concentrations above 3,000 ng/mL and peak levels below 10,000 ng/mL for treatment of HIV-infected individuals. Second, ritonavir-boosted lopinavir is not recommended for neonates younger than age 14 days because of the potential for significant toxicity (see [Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis](#)). Therefore, the risks of this approach in terms of infant toxicity (particularly in preterm infants), as well as whether the functional cure can be replicated in additional infants, require further study before a general recommendation can be made.

In this and all other scenarios, decisions about use of combination ARV prophylaxis in infants should be made in consultation with a pediatric HIV specialist before delivery, if possible, and should be accompanied by a discussion with the mothers about potential risks and benefits of this approach.

### **The National Perinatal HIV Hotline**

The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for HIV-infected pregnant women and their infants, and can provide referral to local or regional pediatric HIV specialists.

## ***Recommendations for Infant Antiretroviral Prophylaxis in Specific Clinical Situations***

### **Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression**

The risk of HIV acquisition is small in infants born to women who received standard ARV prophylaxis regimens during pregnancy and labor and had undetectable viral loads at delivery or by scheduled cesarean section to mothers with low viral loads at delivery. **The optimal minimum duration of neonatal zidovudine chemoprophylaxis has not been established in clinical trials.** In the United States, the standard 6-week infant zidovudine regimen has been recommended, based on data from PACTG studies 076 and 316 (both performed during an era when a greater proportion of women did not receive antenatal cART). In the United Kingdom and many other European countries, a 4-week neonatal chemoprophylaxis regimen is now recommended for infants born to mothers who have received cART regimens and have viral suppression, with no apparent increase in the overall HIV perinatal transmission rate.<sup>3,4</sup> Additionally, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy infants compared with the 6-week zidovudine regimen.<sup>11</sup> Therefore, a 4-week zidovudine neonatal chemoprophylaxis regimen can be considered when a mother has received standard cART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence.

**In infants born to women with effective viral suppression, combining zidovudine with additional ARV drugs to reduce transmission risk is not recommended because the risk of transmission is low and any potential benefit would be very limited. Any potential benefits must be balanced by the known toxicities of ARV drugs in infants.**

### **Infants Born to Mothers Who Have Received Antepartum/Intrapartum Antiretroviral Drugs But Have Suboptimal Viral Suppression Near Delivery**

All infants born to women who have received antepartum/intrapartum ARVs but with suboptimal viral suppression near delivery should receive zidovudine for 6 weeks. No specific data address whether a more

intensive combination infant prophylaxis regimen (two or three drugs) provides additional protection against transmission when maternal antepartum/intrapartum prophylaxis is received but viral replication near delivery is significant. Extrapolation of findings from the previously discussed NICHD-HPTN 040/PACTG 1043 study<sup>5</sup> suggests that combination infant prophylaxis should be considered, depending on assessment of risk based on maternal viral load and mode of delivery. That decision should be made in consultation with a pediatric HIV specialist before delivery and accompanied by maternal counseling on the potential risks and benefits of this approach.

Many data support the observation that the risk of perinatal transmission is related to maternal antepartum viral load in women on no ARV drugs as well as women receiving ARVs.<sup>12-14</sup> Scheduled cesarean delivery is recommended for prevention of perinatal transmission in women who have received antepartum ARV drugs but have detectable viremia (HIV RNA >1,000 copies/mL) near the time of delivery (see Intrapartum Care and Transmission and Mode of Delivery). In PACTG 316, transmission occurred in 0% of 17 infants when maternal HIV RNA levels at delivery were >10,000 copies/mL and delivery was by scheduled cesarean delivery.<sup>2</sup> However, not all women with detectable viremia near delivery will undergo cesarean delivery. The risk of acquisition of HIV will be higher in infants born to mothers with higher viral loads near delivery, particularly if delivery is vaginal. The gradient of transmission risk is based on HIV RNA levels. In the Women and Infants Transmission Study (WITS), the risk of transmission of HIV was ≤1.8% in women who received cART and had HIV RNA levels <30,000 copies/mL at delivery; it increased to 4.8% in women with HIV RNA levels ≥30,000 copies/mL.<sup>14</sup>

### **Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs**

All infants whose mothers have received only intrapartum ARV drugs should receive the two-drug regimen of 6 weeks of zidovudine plus three doses of nevirapine in the first week of life (first dose at birth to 48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose), based on the results of the NICHD-HPTN 040/PACTG 1043 study. Infant prophylaxis should be initiated as soon after delivery as possible. Infant prophylaxis is a critical component of prevention when no maternal antepartum ARV drugs have been received. The PETRA study demonstrated that intrapartum prophylaxis alone, without infant prophylaxis, is ineffective in reducing perinatal transmission.<sup>15</sup> A study in Thailand indicated that longer infant prophylaxis with zidovudine (6 weeks versus 3 days) is required for optimal efficacy when maternal antenatal exposure to zidovudine is <4 weeks.<sup>16</sup> In the NICHD-HPTN 040/PACTG 043 trial, 41% of women received zidovudine during labor. Administration of intrapartum zidovudine did not affect transmission rates.<sup>5</sup>

### **Infants Born to Mothers Who Did Not Receive Antepartum or Intrapartum Antiretroviral Drugs**

The two-drug regimen of 6 weeks of zidovudine plus three doses of nevirapine in the first week of life (first dose at birth to 48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose) is recommended for infants born to mothers who did not receive antepartum or intrapartum ARVs based on the results of the NICHD-HPTN 040/PACTG 1043 study, which demonstrated increased efficacy of combination regimens in reducing intrapartum transmission compared with use of zidovudine alone in infants.<sup>5</sup> Prophylaxis should be initiated as soon after delivery as possible.

The interval during which infant prophylaxis can be initiated and still be of benefit is undefined. In the New York State study, when prophylaxis was delayed beyond 48 hours after birth, no efficacy could be demonstrated.<sup>17</sup> Data from animal studies indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, ARV prophylaxis initiated 24 to 36 hours after exposure usually has been ineffective in preventing infection, although a delay in administration has been associated with decreased viremia.<sup>18-20</sup> In the NICHD-HPTN 040/PACTG 1043 study, infant regimens were initiated within 48 hours of life and usually within 12 hours of life.<sup>5</sup> Initiation of infant prophylaxis after age 2 days is not likely to be efficacious in preventing transmission and, by age 14 days, infection already would be established in most infants.<sup>21</sup> Initiating prophylaxis as soon after delivery as possible increases its potential efficacy and minimizes potential harm, such as development of resistant virus, if infection has occurred.

### **Infants Born to Mothers with Unknown HIV Infection Status**

Expedited (previously referred to as “rapid”) HIV testing of mothers is recommended during labor for women with unknown HIV status and for mothers and/or infants as soon as possible after birth if expedited HIV testing was not performed during labor. Expedited test results should be available within 60 minutes. Commercially available antigen/antibody tests are preferred to those that test only for antibody. Oral fluid-based tests are not recommended for infant testing; blood or serum testing has notably better sensitivity in infants than does oral fluid testing.<sup>22</sup> If expedited testing is positive, infant ARV prophylaxis should be initiated immediately, without waiting for the results of supplemental tests (see scenario: [Infants Born to Mothers Who Did Not Receive Antepartum or Intrapartum Antiretroviral Drugs](#)). Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care, special care or newborn nursery. A positive initial test result in mothers or infants should be presumed to indicate maternal HIV infection until standard supplemental testing clarifies maternal status. A positive HIV antibody test in an infant indicates maternal but not necessarily infant HIV infection; diagnosis of HIV infection in infants younger than age 18 months requires virologic testing using a viral nucleic amplification test (NAT; includes DNA and RNA PCR and related assays). Initial positive HIV antibody tests can be confirmed using a recommended HIV-1/2 diagnostic testing algorithm.<sup>23</sup> Supplemental tests should be performed on mothers (or their infants) as soon as possible after the initial positive test. If the supplemental test results on a mother (or infant) are negative, ARV prophylaxis can be discontinued. If the supplemental test results are positive, an HIV NAT should be obtained urgently from the newborn to determine the infant’s HIV infection status. If the HIV NAT is positive, ARV prophylaxis should be promptly discontinued and the infant should receive treatment for HIV infection with standard cART according to the [Pediatric Antiretroviral Guidelines](#).

Breastfeeding should be stopped until HIV infection is confirmed or ruled out in a woman who is suspected of being HIV-infected based on an initial positive antibody test result. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV infection is ruled out, breastfeeding can resume. If HIV infection is confirmed, breastfeeding should be discontinued permanently.

### **Infants Born to Mothers with Antiretroviral Drug-Resistant Virus**

The optimal prophylactic regimen for newborns delivered by women with ARV drug-resistant virus is unknown. ARV prophylaxis for infants born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery.

Data from WITS suggest that in women who have mixed zidovudine-resistant and -sensitive viral populations, the zidovudine-sensitive rather than -resistant virus may be preferentially transmitted.<sup>24,25</sup> Thus, the 6-week infant zidovudine prophylaxis (along with maternal intravenous [IV] intrapartum zidovudine prophylaxis) continues to be recommended, even when maternal zidovudine-resistant virus with thymidine-associated mutations is identified.

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.<sup>25</sup> However, perinatal transmission of multidrug-resistant virus has been reported **both in the United States and international settings**.<sup>26-30</sup>

For these newborns, use of zidovudine in combination with other ARV drugs, selected on the basis of maternal virus resistance testing, should be considered. The efficacy of this approach for prevention of transmission, however, has not been proven in clinical trials, and for many drugs, appropriate dosing regimens for neonates have not been established. Decisions regarding use of additional drugs should be made in consultation with a pediatric HIV specialist and will depend on maternal history of past and current ARV drug exposure, HIV RNA levels at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant.

## ***Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis***

Infant prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see [Initial Postnatal Management](#)). Data are limited on the toxicity to infants of exposure to multiple ARV drugs.

The latest information on neonatal dosing for ARV drugs can be found in the [Pediatric Antiretroviral Guidelines](#). Other than zidovudine, lamivudine is the nucleoside reverse transcriptase inhibitor (NRTI) with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1<sup>15,31,32</sup> or 2 weeks.<sup>5</sup> Six weeks of infant zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the infants also had *in utero* exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in infants exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and infant zidovudine. Anemia was reported in 15% and neutropenia in 18% of infants exposed to zidovudine/lamivudine, with 2% of infants requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.<sup>6</sup> Similarly, in a Brazilian study of maternal antepartum and 6-week infant zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of infants.<sup>33</sup>

Tenofovir with and without emtricitabine has been investigated in several small studies to define the safety and pharmacokinetics (PKs) of the agents in newborns.<sup>34,35,36</sup> However, at this time, tenofovir and emtricitabine are not generally recommended for use in infant prophylaxis by the Panel because data on appropriate dosing are limited and the safety of these agents in the neonate is not well defined.

Experience with other NRTI drugs for neonatal prophylaxis is more limited.<sup>37,38</sup> Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.<sup>6,39-42</sup>

Nevirapine is the only non-nucleoside reverse transcriptase inhibitor drug with a pediatric drug formulation and neonatal **prophylactic (but not therapeutic)** dosing information (see the [Adult and Adolescent Antiretroviral Guidelines](#)).<sup>43</sup> In rare cases, chronic multiple-dose therapeutic nevirapine therapy has been associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving prophylactic dosing with single-dose nevirapine, the 2-drug zidovudine regimen plus 3 doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding infants receiving nevirapine prophylaxis daily for 6 weeks to 6 months to prevent transmission of HIV via breast milk.<sup>5,44-47</sup> Resistance to nevirapine can occur, however, with exposure to nevirapine in infants who become infected despite prophylaxis.<sup>48,49</sup> ARV drug-resistance testing is recommended for all HIV-infected infants before initiation of cART (see the [Adult and Adolescent Antiretroviral Guidelines](#)).

Of the PIs, pediatric drug formulations are available for ritonavir-boosted lopinavir, ritonavir, **darunavir**, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended **due to lack of dosing and safety information**. No PK data are available for any PIs in the first 2 weeks of life. PK data are available for treatment of HIV-infected infants aged 2 to 6 weeks with ritonavir-boosted lopinavir. Although the lopinavir area under the curve (AUC) was significantly lower with dosing 300 mg lopinavir/75 mg ritonavir/m<sup>2</sup> body surface area twice daily than observed for infants >6 weeks of age, treatment was well tolerated and 80% of 10 infants had viral control at 6 months.<sup>50</sup> Studies are ongoing but data are not yet available for infants aged <2 weeks. However, in 4 premature infants (2 sets of twins) started on ritonavir-boosted lopinavir from birth, heart block developed that resolved after drug discontinuation.<sup>51,52</sup> In studies of adults, both ritonavir and ritonavir-boosted lopinavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of ritonavir-boosted lopinavir compared with zidovudine in the neonatal period. Levels of 17-hydroxyprogesterone were greater in infants who were also exposed to ritonavir-boosted lopinavir *in utero* compared with those exposed only in the neonatal



period. Term infants were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.<sup>53</sup> 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,<sup>54</sup> predominantly in preterm neonates, the Food and Drug Administration now recommends that ritonavir-boosted lopinavir **not** be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

Raltegravir is the only integrase inhibitor with an available pediatric drug formulation. However, it is not FDA-approved for use in infants aged <2 years and there are no PK and safety data on its use during the first weeks of life. Raltegravir competes with bilirubin for albumin binding sites, which could increase unconjugated bilirubin levels in the neonate. An *in vitro* study has demonstrated that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant unless raltegravir concentrations 50- to 100-fold higher than typical peak concentrations with usual dosing are reached.<sup>55</sup> Use of raltegravir in neonates is not recommended until adequate PK and safety data are available.

## Neonatal Antiretroviral Drug Dosing

**Table 8. Recommended Neonatal Dosing for Prevention of Perinatal Transmission of HIV**

All HIV-Exposed Infants (initiated as soon after delivery as possible)		
Zidovudine (ZDV)	Dosing	Duration
ZDV	≥35 weeks' gestation at birth: 4 mg/kg/dose PO twice daily, started as soon after birth as possible and preferably within 6–12 hours of delivery (or, if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 hours of delivery, then every 12 hours)	Birth through 4-6 weeks <sup>a</sup>
ZDV	≥30 to <35 weeks' gestation at birth: 2 mg/kg/dose PO (or 1.5 mg/kg/dose IV), started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours at age 15 days	Birth through 6 weeks
ZDV	<30 weeks' gestation at birth: 2 mg/kg body weight/dose PO (or 1.5 mg/kg/dose IV) started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours after age 4 weeks	Birth through 6 weeks
Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants of Women who Received No Antepartum Antiretroviral Prophylaxis (initiated as soon after delivery as possible)		
In addition to ZDV as shown above, administer NVP	Birth weight 1.5–2 kg: 8 mg/dose PO Birth weight >2 kg: 12 mg/dose PO	3 doses in the first week of life <ul style="list-style-type: none"> <li>• 1st dose within 48 hrs of birth (birth–48 hrs)</li> <li>• 2nd dose 48 hrs after 1st</li> <li>• 3rd dose 96 hrs after 2nd</li> </ul>

<sup>a</sup> A 6-week course of neonatal zidovudine is generally recommended. A 4-week neonatal zidovudine chemoprophylaxis regimen may be considered when the mother has received standard ART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence.

**Key to Abbreviations:** IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine

The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 4 mg/kg body weight orally (PO) twice daily, beginning as soon after birth as possible and preferably within 6 to 12 hours of delivery<sup>15,44,56-63</sup> (see Table 8). If an infant is unable to tolerate oral medications, the zidovudine prophylaxis regimen can be administered intravenously (IV). The zidovudine dosing requirements differ for



premature infants and term infants (see [Table 8](#) and Antiretroviral Drug Dosing for Premature Infants).

PKs and safety of the single-dose nevirapine regimen to mother and infant<sup>64</sup> and chronic prophylactic nevirapine administration to infants to prevent HIV transmission during breastfeeding have been studied.<sup>65</sup> The 3-dose extended nevirapine regimen that was used in NICHD-HPTN 040/PACTG1043 and is recommended for HIV-exposed infants whose mothers did not receive ARV during the antepartum period has also been studied.<sup>43</sup> Nevirapine concentrations were measured in 14 newborns participating in a PK substudy during the second week of life and in single samples from 30 more newborns on Days 10 to 14. The median nevirapine elimination half-life was 30.2 hours (range: 17.8–50.3 hours) and the concentration remained greater than the target of 100 ng/mL in all infants through Day 10 of life.

### Antiretroviral Drug Dosing for Premature Infants

Dosing recommendations for premature infants are available for only zidovudine (prophylaxis and therapy) and nevirapine (prophylaxis only) (see [Table 8](#)). Zidovudine is primarily cleared through hepatic glucuronidation to an inactive metabolite; this metabolic pathway is immature in neonates, leading to prolonged zidovudine half-life and **decreased** clearance compared with older infants. Clearance is further **decreased** in premature infants because their hepatic metabolic function is less mature than in term infants.<sup>66,67</sup> The recommended zidovudine dosage for preterm infants is shown in [Table 8](#).

Nevirapine PKs have been described in low-birth-weight **neonates** receiving a single **postnatal** prophylaxis dose of the drug. In a study of 81 infants <37 weeks' gestation, of which 29.6% were small for gestational age, half-lives were very long—median 59 hours in infants whose mothers received single-dose nevirapine and 69 hours in infants whose mothers did not receive single-dose nevirapine. AUC of nevirapine was higher and clearance lower ( $P < .0001$ ) in small-for-gestational-age infants.<sup>68</sup>

Use of ARV drugs other than zidovudine and nevirapine cannot be recommended at this time in premature infants because data on dosing and safety are lacking. Immature renal and hepatic metabolism can increase the risk of overdosing and toxicity. However, in situations where there is a high risk of infant HIV infection, consultation with a pediatric HIV specialist is recommended to determine if the **benefits** of combination ARV prophylaxis **with drugs in addition to or** other than zidovudine and nevirapine outweigh the potential **risks**.

### Breastfeeding Infants of Mothers Diagnosed with HIV Infection Postpartum

Breastfeeding should be stopped until infection is confirmed or ruled out in women who are breastfeeding and suspected to have become HIV infected. Pumping and temporarily discarding **or freezing** breast milk can be recommended to mothers who are suspected of being HIV infected but whose infection is not yet confirmed and who want to continue to breastfeed. If HIV infection is ruled out, breastfeeding can resume. **Breastfeeding is not recommended for women with documented HIV infection in the United States, including those receiving cART (see [Infant Feeding Practices and Risk of HIV Transmission](#)).**<sup>69</sup>

The risk of acquisition of HIV associated with breastfeeding depends on multiple infant and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.<sup>70</sup> Infants of women who develop acute HIV infection while breastfeeding are at greater risk of becoming infected than are those of women with chronic HIV infection<sup>71</sup> because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.<sup>72</sup>

Other than discontinuing breastfeeding, optimal strategies for managing infants born to HIV-infected mothers who breastfed their infants prior to HIV diagnosis have yet to be defined. Some experts would consider the use of post-exposure prophylaxis in infants for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance compared with other non-occupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure.<sup>73</sup>

Several studies of infants breastfed by women with chronic HIV infection have shown that daily infant nevirapine or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.<sup>44-46</sup>

The NICHD-HPTN 040/PACTG 1043 study demonstrated that combination ARV prophylaxis was more effective than zidovudine prophylaxis alone for preventing intrapartum transmission in mothers who have not received antepartum ARV drugs.<sup>5</sup> However, whether the combination regimens in this trial are effective for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection is unknown.

Because of the high risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some experts would be to offer a combination ARV regimen that would be effective for treatment of HIV, should an infant become infected. If this route is chosen, current recommendations for treatment should guide selection of an appropriate combination ARV regimen (see the [Pediatric Antiretroviral Guidelines](#)). Regardless of whether post-exposure prophylaxis or “pre-emptive therapy” is chosen, the optimal duration of the intervention is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.<sup>73</sup> As in other situations, decisions regarding administration of a prophylactic or preemptive treatment regimen should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach.

Infants should be tested for HIV infection at baseline and 4 to 6 weeks, 3 months, and 6 months after recognition of maternal infection to determine HIV status. In infants younger than age 18 months, HIV NAT should be used for diagnosis. HIV DNA PCR testing may be preferable for infants who are receiving combination ARV prophylaxis or preemptive treatment, because HIV RNA assays may be less sensitive in the presence of combination ARVs, which might lower infant plasma viral RNA to undetectable levels. However, HIV DNA PCR assays available in the United States may not detect non-subtype B or group O HIV as well as many HIV RNA assays. Therefore, if non-subtype B or group O HIV infection in an infant is considered possible, both HIV DNA and RNA assays should be obtained from the infant. HIV antibody assays can be used in infants older than age 18 months.

If an infant is already receiving post-exposure ARV prophylaxis and is found to be HIV-infected, prophylaxis should be discontinued and treatment for HIV infection initiated with standard cART according to the [Pediatric Antiretroviral Guidelines](#). Resistance testing should be performed and the cART regimen modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

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## Initial Postnatal Management of the HIV-Exposed Neonate (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- A complete blood count and differential should be performed on newborns as a baseline evaluation (**BIII**).
- If hematologic abnormalities are identified in infants receiving prophylaxis, decisions on whether to continue infant antiretroviral (ARV) prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered (**CIII**).
- Decisions about the timing of subsequent monitoring of hematologic parameters in infants depend on baseline hematologic values, gestational age at birth, clinical condition of the infants, the zidovudine dose being administered, receipt of other ARV drugs and concomitant medications, and maternal antepartum therapy (**CIII**).
- Some experts recommend more intensive monitoring of hematologic and serum chemistry and liver function assays at birth and when diagnostic HIV polymerase chain reaction tests are obtained in infants exposed to combination ARV drug regimens *in utero* or during the neonatal period (**CIII**).
- A recheck of hemoglobin and neutrophil counts is recommended 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens (**A**).
- Routine measurement of serum lactate is not recommended. However, measurement can be considered if an infant develops severe clinical symptoms of unknown etiology (particularly neurologic symptoms) (**CIII**).
- Virologic tests are required to diagnose HIV infection in infants aged <18 months and should be performed within the first 14 to 21 days of life and at age 1 to 2 months and age 4 to 6 months (**AII**).
- To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to HIV-infected women should begin PCP prophylaxis at ages 4 to 6 weeks, after completing their ARV prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see the [Pediatric Opportunistic Infections Guidelines](#)) (**AII**).
- Health care providers should routinely inquire about premastication, instruct HIV-infected caregivers to avoid this practice, and advise on safer feeding options (**AII**).

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

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

A complete blood count (CBC) and differential should be performed on HIV-exposed newborns before initiation of infant antiretroviral (ARV) drug prophylaxis. Decisions about the timing of hematologic monitoring of infants after birth depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the infants, which ARV drugs are being administered, receipt of concomitant medications, and maternal antepartum ARV drug regimen. Anemia is the primary complication seen in neonates given the standard 6-week postnatal zidovudine regimen. In PACTG 076, infants in the zidovudine group had lower hemoglobin levels at birth than those in the placebo group, with the maximal difference (1 g/dL) occurring at age 3 weeks.<sup>1</sup> The lowest mean value for hemoglobin levels (10 g/dL) occurred at age 6 weeks in the zidovudine group. By age 12 weeks, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed between groups.

Some experts recheck hematologic values in healthy infants receiving zidovudine prophylaxis only if symptoms are present. Hematologic safety data are limited on administration of 4 mg/kg of zidovudine twice daily in infants. When administering this dosing regimen, some experts recheck hemoglobin and neutrophil counts routinely after 4 weeks of zidovudine prophylaxis and/or when diagnostic HIV polymerase chain reaction (PCR) tests are obtained.

*In utero* exposure to maternal combination ARV drug regimens may be associated with some increase in anemia and/or neutropenia compared with that seen in infants exposed to zidovudine alone.<sup>2-5</sup> In PACTG 316, where 77% of mothers received antenatal combination therapy, significant Grade 3 or higher anemia

was noted in 13% and neutropenia in 12% of infants, respectively. Depending on the combination regimen the mother has received, some experts advise more intensive laboratory monitoring, including serum chemistry and transaminases at birth plus a CBC at the time of diagnostic HIV PCR testing; monitoring of bilirubin levels can be considered for infants exposed antenatally to atazanavir.

In addition, data are limited on infants receiving zidovudine in combination with other ARVs for prophylaxis. However, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine combination prophylaxis compared with those receiving zidovudine alone or zidovudine plus nevirapine.<sup>6</sup> A recheck of hemoglobin levels and neutrophil counts, therefore, is recommended for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens 4 weeks after initiation of prophylaxis and/or at the time that diagnostic HIV PCR testing is done.<sup>7</sup>

If hematologic abnormalities are found, decisions on whether to continue infant ARV prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether related symptoms are present, duration of infant prophylaxis, risk of HIV infection (as assessed by the mother's history of ARV prophylaxis, viral load near delivery, and mode of delivery), and the availability of alternative interventions such as erythropoietin and transfusion. Consideration can be given to reducing the duration of infant prophylaxis from 6 to 4 weeks, as is the case in many European centers. In a recent prospective, observational study, the 4-week regimen was found to allow earlier recovery from anemia in otherwise healthy infants compared with the 6-week regimen.<sup>8</sup> Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.

Hyperlactatemia has been reported in infants with *in utero* exposure to ARVs, but it appears to be transient and, in most cases, asymptomatic.<sup>9,10</sup> 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.<sup>9,10</sup> Serum lactate measurement should be considered, however, for infants who develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms. In infants with symptoms, if the levels are significantly abnormal (>5 mmol/L), ARV prophylaxis should be discontinued and an expert in pediatric HIV infection should be consulted regarding potential alternate prophylaxis.

To prevent *Pneumocystis jirovecii* pneumonia, all infants born to HIV-infected women should begin trimethoprim-sulfamethoxazole prophylaxis at age 6 weeks, after completion of the infant ARV prophylaxis regimen, unless there is adequate virologic test information to presumptively exclude HIV infection (see the [Pediatric Opportunistic Infections Guidelines](#)).<sup>11</sup>

HIV infection in infants should be diagnosed using HIV nucleic acid amplification virologic assays (NATs), which include DNA and RNA PCR and related assays. Maternal HIV antibody crosses the placenta and will be detectable in all HIV-exposed infants up to age 18 months; therefore, standard antibody tests should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed within the first 14 to 21 days of life and at age 1 to 2 months and age 4 to 6 months.<sup>12</sup> Some experts also perform a virologic test at birth, especially in women who have not had good virologic control during pregnancy or if adequate follow-up of the infant may not be assured. A positive HIV virologic test should be confirmed as soon as possible with a second HIV virologic test on a different specimen. Two positive HIV tests constitute a diagnosis of HIV infection. Data do not indicate any delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the zidovudine regimen.<sup>1,13</sup> However, the effect of maternal or infant exposure to combination ARV drug regimens on the sensitivity of infant virologic diagnostic testing—particularly using HIV RNA assays—is unknown. Therefore, although HIV RNA assays may be acceptable for diagnosis (particularly in older infants), HIV DNA PCR assays may be optimal for diagnosing infection in the neonatal period. Any newly diagnosed infant should undergo viral resistance testing by genotype and/or phenotype to assess for susceptibility to combination antiretroviral therapy.

HIV can be **presumptively** excluded with two or more negative tests: one at age 14 days or older and the

other at age 1 month or older. **Definitive** exclusion of HIV in non-breastfed infants can be based on two negative virologic tests, with one test performed at age 1 month or older and the other test at age 4 months or older. Many experts confirm HIV-negative status with an HIV antibody test at age 12 to 18 months.

**Persistence of HIV antibodies can occasionally occur at or beyond age 18 months.**<sup>14</sup> Alternative algorithms exist for presumptive and definitive HIV exclusion.<sup>12</sup> This testing algorithm applies mainly to exposure to HIV subtype B, which is the predominant viral subtype found in the United States. Non-subtype B viruses predominate in some other parts of the world. Non-subtype B infection may not be detected by many commercially available nucleic acid tests, particularly HIV DNA PCR. Many of the newer HIV RNA assays have improved detection of non-subtype B HIV, but there are still variants that are either poorly detected or undetectable. If non-subtype B HIV infection is suspected based on maternal origins, then newer HIV RNA assays that have improved ability to detect non-subtype B HIV should be used as part of the initial diagnostic algorithm. Exposed infants also should be closely monitored and undergo definitive HIV serologic testing at age 18 months (see the [Pediatric Antiretroviral Guidelines](#)).

Following birth, HIV-exposed infants should have a detailed physical examination, and a thorough maternal history should be obtained. HIV-infected mothers may be coinfecting with other pathogens that can be transmitted from mother to child, such as cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis. Infants born to mothers with such coinfections should undergo appropriate evaluation, as indicated by maternal CD4 T lymphocyte count and evidence of disease activity, to rule out transmission of additional infectious agents. The routine primary immunization schedule should be followed for HIV-exposed infants born to HIV-infected mothers. Modifications in the schedule for live virus vaccines may be required for infants with known HIV infection (see the [Pediatric Opportunistic Infections Guidelines](#)).

No evidence is available to enable the Panel to assess whether any changes in routine bathing practices, or timing of circumcision, are indicated for HIV-exposed newborns.

### ***Infant Feeding Practices and Risk of HIV Transmission***

In the United States, where safe infant feeding alternatives are available and free for women in need, HIV-infected women should not breastfeed their infants.<sup>15</sup> Maternal receipt of combination ARV regimens is likely to reduce free virus in the breast milk, but the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and, therefore, may continue to pose a transmission risk.<sup>16</sup>

Late HIV transmission events in infancy have been reported in HIV-infected children suspected of acquiring HIV infection as a result of consuming premasticated food given to them by their caregivers. Phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history and investigations identified the practice of feeding premasticated foods to infants as a potential risk factor for HIV transmission. Health care providers should routinely inquire about premastication, instruct HIV-infected caregivers against this feeding practice, and advise on safer feeding options.<sup>17,18</sup>

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## Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants (Last updated March 28, 2014; last reviewed March 28, 2014)

### Panel's Recommendations

- 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).
- Follow-up of children with exposure to ARVs should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of nucleoside analogue ARV drugs (CIII).

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

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

Data remain insufficient to address the effect that exposure to zidovudine or other antiretroviral (ARV) agents *in utero* might have on long-term risk of neoplasia or organ system toxicities in children. Data from follow-up of PACTG 076 infants through age 6 years did not indicate any differences in immunologic, neurologic, and growth parameters between infants who were exposed to the zidovudine regimen and those who received placebo, and no malignancies were noted.<sup>1-3</sup> Data are conflicting regarding whether mitochondrial dysfunction is associated with perinatal exposure to ARV drugs. Children with *in utero* exposure to ARVs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction.<sup>4-6</sup> It is also unclear from laboratory-based and long-term clinical studies of infants and preadolescent children with *in utero* exposure to ARV drugs whether residual effects of these medications result in clinical consequences.<sup>7-11</sup> Studies should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of the nucleoside analogue ARV drugs. Long-term follow-up should include annual physical examinations of all children exposed to ARV drugs. Innovative methods are needed to provide follow-up of infants, children, and youth with *in utero* exposure to ARV drugs. Information regarding such exposure should be part of ongoing permanent medical records for children, particularly those who are uninfected.

Evaluation is ongoing of early and late effects of *in utero* exposure to ARV drugs, including the Pediatric HIV/AIDS Cohort Study, Surveillance Monitoring of Antiretroviral Toxicity Study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and the Centers for Disease Control and Prevention. Because most of the available follow-up data relate to *in utero* exposure to antenatal zidovudine alone and most HIV-infected pregnant women currently receive combination ARV drug regimens, it is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defect and cancer registries to identify potential adverse outcomes.

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## Appendix A: Review of Clinical Trials of Antiretroviral Interventions to Prevent Perinatal HIV Transmission (Last updated March 28, 2014, Last reviewed March 28, 2014)

One of the major achievements in HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group 076 (PACTG 076) clinical trial that administration of zidovudine to pregnant women and their infants could reduce risk of perinatal transmission by nearly 70%.<sup>1</sup> Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. A number of regimens have been identified that are effective in reducing perinatal transmission in resource-limited countries (see [Supplemental Table 1](#)). This Appendix provides a table summarizing results of major studies of antiretroviral (ARV) prophylaxis to prevent perinatal transmission and a brief discussion of lessons learned. In many cases, direct comparison of results from trials of these regimens is not possible because the studies involved diverse patient populations residing in different geographic locations, infected with diverse viral subtypes, and with different infant feeding practices. However, some generalizations are relevant to understanding use of ARV drugs for prevention of perinatal transmission in both resource-limited and resource-rich countries.

### **Combination antenatal prophylaxis taken over a longer duration is more effective than a short-course single-drug regimen in reducing perinatal transmission.**

The use of ARV drugs to prevent transmission is highly effective, even in HIV-infected women with advanced disease.<sup>2,3</sup> 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.<sup>4-13</sup> In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission. In addition, for prevention of perinatal transmission, administration of ARV drugs during the antepartum, intrapartum, and postpartum periods is superior to administration of ARV drugs only during the antepartum and intrapartum periods or intrapartum and postpartum periods.<sup>5,14,15</sup>

Almost all trials in resource-limited countries have included oral intrapartum prophylaxis, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. Perinatal transmission is reduced by regimens with antenatal components starting as late as 36 weeks' gestation and lacking an infant prophylaxis component.<sup>10-12</sup> However, longer-duration antenatal ARV prophylaxis is more effective than shorter-duration ARV prophylaxis.<sup>13</sup> The European National Study of HIV in Pregnancy and Childhood demonstrated that each additional week of a triple-drug regimen corresponded to a 10% reduction in risk of transmission.<sup>16</sup> More prolonged infant post-exposure prophylaxis does not appear to substitute for longer-duration maternal ARV prophylaxis.<sup>13</sup>

No trials have directly compared the efficacy of zidovudine plus single-dose nevirapine with a triple-drug ARV regimen for prevention of *in utero* transmission in women with higher CD4 T lymphocyte (CD4) cell counts. In African women with CD4 cell counts ranging from 200 to 500 cells/mm<sup>3</sup>, the Kesho Bora trial compared a triple-ARV drug prophylaxis regimen with zidovudine plus single-dose nevirapine prophylaxis, both started at 28 weeks' gestation or later, with women in the triple-drug arm continuing the drugs until breastfeeding ceased; those in the zidovudine/single-dose nevirapine arm did not receive postnatal prophylaxis. Although the rate of postnatal transmission was significantly lower in the triple-drug arm than in the zidovudine/single-dose nevirapine arm without postnatal prophylaxis, the rates of transmission at birth were similar in women randomized to a triple-drug regimen (1.8%) and women randomized to antepartum zidovudine/single-dose nevirapine (2.5%); for women with CD4 cell counts from 350 to 500 cells/mm<sup>3</sup>, the rate of infection at birth was 1.7% in each arm.<sup>17</sup> However, the study was not powered to address equivalence between regimens in preventing *in utero* infection in women with higher CD4 cell counts and the drugs in both arms were administered antepartum for only 6 weeks.

Regimens that do not include maternal ARV prophylaxis during pregnancy have been evaluated because some women may lack antenatal care and present for prenatal care for the first time when they go into labor. Regimens that include only intrapartum and postpartum drug administration also have been shown to be effective in reducing perinatal transmission.<sup>4-6</sup> 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.<sup>5</sup> The SAINT trial demonstrated that intrapartum/postpartum zidovudine/lamivudine and single-dose intrapartum/newborn nevirapine are similar in efficacy and safety.<sup>6</sup>

**Combination infant ARV prophylaxis is recommended in the United States for infants whose mothers have not received antenatal ARV drugs.**

In some situations, it may be impossible to administer maternal antepartum and intrapartum therapy and only infant prophylaxis may be an option. In the absence of maternal therapy, the standard infant prophylaxis regimen of 6 weeks of zidovudine was effective in reducing HIV transmission compared with no prophylaxis, based on epidemiologic data in resource-rich countries.<sup>18</sup> 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.<sup>7</sup>

To define the optimal infant prophylaxis regimen in the absence of maternal antepartum ARV drug administration in a formula-fed population of infants such as in the United States, the NICHD-HPTN 040/P1043 (NCT00099359) clinical trial compared 3 infant ARV regimens in formula-fed infants born to mothers who did not receive ARV drugs during the current pregnancy: standard 6 weeks of zidovudine alone versus 6 weeks of zidovudine plus 3 doses of nevirapine given in the first week of life (first dose birth to 48 hours; second dose 48 hours after first dose; third dose 96 hours after second dose) versus 6 weeks of zidovudine plus lamivudine and nelfinavir given from birth through age 2 weeks.<sup>19</sup> The study demonstrated that both the dual and triple combination regimens reduced risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with zidovudine alone, although there was more hematologic toxicity with the triple regimen (see [Supplemental Table 1](#)). Based on these data, combination ARV prophylaxis is now recommended in the United States for infants whose mothers have not received antenatal ARV drugs, with the dual regimen of zidovudine plus 3 doses of nevirapine in the first week of life being preferred due to lower rates of toxicity (see [Infant Antiretroviral Prophylaxis](#)).

**Adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis.**

Several studies in formula-fed and breastfed populations in resource-limited countries have found that adding maternal/infant single-dose nevirapine to a maternal short-course zidovudine or zidovudine/lamivudine regimen increased efficacy compared with the short-course regimen alone.<sup>15,20,21</sup> However, PACTG 316, a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas, demonstrated that for non-breastfeeding women in resource-rich countries, the addition of single-dose nevirapine did not offer significant benefit in the setting of combination ARV prophylaxis throughout pregnancy and very low viral load at the time of delivery.<sup>22</sup> Thus, adding single-dose intrapartum nevirapine is not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis (see [Intrapartum Antiretroviral Therapy/Prophylaxis](#)).

**Breastfeeding by HIV-infected women is not recommended in the United States.**

Breastfeeding by HIV-infected women (including those receiving ARV drugs) is not recommended in the United States where replacement feeding is affordable, feasible, acceptable, sustainable, and safe and the risk of infant mortality due to diarrheal and respiratory infections is low.<sup>23</sup> Clinical trials have demonstrated that both infant prophylaxis (primarily using daily infant nevirapine) during breastfeeding and maternal triple-drug prophylaxis during breastfeeding decrease postnatal infection (see [Supplemental Table 1](#)).<sup>2,17,24-29</sup> However, maternal triple-drug prophylaxis may be less effective than infant prophylaxis if the maternal

regimen is first started postpartum or late in pregnancy because it takes several weeks to months before full viral suppression in breast milk is achieved.<sup>28,30</sup> Importantly, although significantly lowering the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis completely eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for HIV-infected women in the United States (including those receiving combination ARV drug regimens).<sup>23</sup> Finally, both infant nevirapine prophylaxis and maternal triple-drug prophylaxis during breastfeeding may be associated with development of ARV drug resistance in infants who become infected despite prophylaxis; multi-class drug resistance has been described in breastfeeding infants infected despite maternal triple-drug prophylaxis.<sup>31-35</sup>

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

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
<b>PACTG 076; United States, France;<sup>1</sup> Formula feeding</b>	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).
<b>CDC short-course ZDV trial; Thailand;<sup>12</sup> Formula feeding</b>	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).
<b>DITRAME (ANRS 049a) trial; Ivory Coast, Burkina Faso;<sup>11,36</sup> Breastfeeding</b>	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% 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).
<b>CDC short-course ZDV trial; Ivory Coast;<sup>10,11</sup> Breastfeeding</b>	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).
<b>PETRA trial; South Africa, Tanzania, and Uganda;<sup>5</sup> Breastfeeding and formula feeding</b>	AP/IP/PP ZDV + 3TC vs. IP/PP ZDV + 3TC vs. IP-only ZDV + 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 + 3TC, 8.9% for IP/PP ZDV + 3TC, 14.2% for IP-only ZDV + 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively).  Perinatal transmission was 14.9% at 18 months for AP/IP/PP ZDV + 3TC, 18.1% for IP/PP ZDV + 3TC, 20.0% for IP-only ZDV + 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).
<b>HIVNET 012 trial; Uganda;<sup>4</sup> Breastfeeding</b>	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); 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).



**Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission** (page 2 of 6)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
<b>SAINT trial; South Africa;<sup>6</sup> Breastfeeding and formula feeding</b>	SD NVP vs. ZDV + 3TC	No AP ARV <u>Oral IP:</u> SD NVP vs. ZDV + 3TC	SD NVP within 48 hours of birth, mother and infant vs. ZDV + 3TC (1 week); mother and infant	Perinatal transmission was 12.3% in SD NVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, $P = 0.11$ ).
<b>Perinatal HIV Prevention Trial (PHPT-1); Thailand;<sup>13</sup> Formula feeding</b>	Four ZDV regimens with different durations of AP and infant PP administration; no placebo	Long (from 28 weeks), short (from 36 weeks)  Oral IP	Long (6 weeks), short (3 days); infant only	Short-short arm 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%).
<b>PACTG 316 trial; Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States;<sup>22</sup> Formula feeding</b>	SD NVP vs. placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)	Non-study ARV regimen  <u>Oral IP:</u> placebo vs. SD NVP + IV ZDV	Placebo vs. SD NVP within 72 hours of birth + nonstudy 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> ).
<b>Perinatal HIV Prevention Trial (PHPT-2); Thailand;<sup>20</sup> Formula feeding</b>	ZDV alone  vs. ZDV + maternal and infant SD NVP  vs. ZDV + maternal SD NVP	ZDV from 28 weeks  <u>Oral IP:</u> ZDV alone or ZDV + SD NVP	ZDV for 1 week with or without SD NVP; infant only	ZDV-alone arm was stopped because of higher perinatal transmission than the NVP-NVP arm (6.3% vs. 1.1%). In arms in which the mother received SD NVP, perinatal transmission rate did not differ significantly between the infant receiving or not receiving SD NVP (2.0% vs. 2.8%).
<b>DITRAME Plus (ANRS 1201.0) trial; Ivory Coast;<sup>15</sup> Breastfeeding and formula feeding</b>	Open label, ZDV + SD NVP	ZDV from 36 weeks  <u>Oral IP:</u> ZDV plus SD NVP	SD NVP + ZDV for 1 week; infant only	Perinatal transmission was 6.5% (95% CI, 3.9%–9.1%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.
<b>DITRAME Plus (ANRS 1201.1) trial; Ivory Coast;<sup>15</sup> Breastfeeding and formula feeding</b>	Open label, ZDV + 3TC + SD NVP	ZDV + 3TC from 32 weeks (stopped at 3 days PP)  <u>Oral IP:</u> ZDV + 3TC + SD NVP	SD NVP + ZDV for 1 week; infant only	Perinatal transmission was 4.7% (95% CI, 2.4%–7.0%) at 6 weeks; perinatal transmission for historical control group receiving short ZDV (98% breastfed) was 12.8%.
<b>NVAZ trial; Malawi;<sup>7</sup> Breastfeeding</b>	Neonatal SD NVP vs. SD NVP + 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 + ZDV arm and 20.9% in SD NVP-only arm at 6–8 weeks.  Perinatal transmission rate at 6–8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).

**Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 3 of 6)**

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
<b>Postnatal NVP + ZDV trial; Malawi;<sup>8</sup> Breastfeeding</b>	Neonatal SD NVP vs. SD NVP + 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 + ZDV arm and 14.1% in SD NVP-only arm at 6–8 weeks (difference not statistically significant).  Perinatal transmission rate at 6–8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.
<b>Post-Exposure Infant Prophylaxis; South Africa;<sup>9</sup> Breastfeeding and formula feeding</b>	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 ( $P = 0.03$ ).
<b>Mashi; Botswana;<sup>21,37</sup> Breastfeeding and formula feeding</b>	<u>Initial:</u> short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding  <u>Revised:</u> short-course ZDV + infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 cell counts <200 cells/mm <sup>3</sup> receive combination therapy	<u>First Randomization:</u> ZDV from 34 weeks  <u>Oral IP:</u> ZDV + either SD NVP or placebo	<u>Second Randomization:</u> Breastfeeding + ZDV (infant) 6 months + SD NVP; infant only vs.  Formula feeding + ZDV (infant) 4 weeks + 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 + 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 + infant SD NVP arm and 3.7% in maternal placebo + infant SD NVP arm (no significant difference; no interaction with mode of infant feeding).  Perinatal transmission at 7 months was 9.1% in breastfeeding + ZDV arm and 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding + ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% breastfeeding + ZDV arm versus 14.2% formula-feeding arm.
<b>SWEN; Uganda, Ethiopia, India;<sup>25</sup> Breastfeeding</b>	SD NVP vs. NVP for 6 weeks	No AP ARV <u>Oral IP:</u> SD NVP	Infant SD NVP vs. NVP for 6 weeks	Postnatal Infection in Infants Uninfected at Birth: <ul style="list-style-type: none"><li>• Perinatal transmission at 6 weeks was 5.3% in SD NVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, <math>P = 0.009</math>).</li><li>• Perinatal transmission at 6 months was 9.0% in SD NVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, <math>P = 0.16</math>).</li></ul> HIV-free survival was significantly lower in extended NVP arm at both 6 weeks and 6 months of age.

**Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission** (page 4 of 6)

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
<b>PEPI-Malawi Trial; Malawi;<sup>24</sup> Breastfeeding</b>	SD NVP + ZDV for 1 week (control) vs. two 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 + ZDV for 1 week (control) vs. control + NVP for 14 weeks vs. control + NVP/ZDV for 14 weeks	<u>Postnatal Infection in Infants Uninfected at Birth:</u> <ul style="list-style-type: none"> <li>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).</li> <li>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).</li> </ul> No significant difference in perinatal transmission between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV.
<b>MITRA; Tanzania;<sup>27</sup> Breastfeeding</b>	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%).
<b>Kisumu Breastfeeding Study (KiBS); Kenya;<sup>29</sup> Breastfeeding</b>	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 cell count >250 cells/mm <sup>3</sup> ) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4-cell count >250 cells/mm <sup>3</sup> ) 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%).
<b>MITRA-PLUS; Tanzania;<sup>26</sup> Breastfeeding</b>	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 cell count >200 cells/mm <sup>3</sup> ) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4-cell count >200 cells/mm <sup>3</sup> ) 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.
<b>Kesho Bora; Multi-African;<sup>17</sup> Breastfeeding primarily</b>	Antepartum ZDV/SD NVP with no postnatal prophylaxis vs. maternal triple-drug prophylaxis in women with CD4 cell counts of 200–500 cells/mm <sup>3</sup>	<u>Arm 1:</u> ZDV/3TC/LPV/r <u>Arm 2:</u> ZDV + SD NVP From 28 weeks through labor	<u>Arm 1:</u> Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP + ZDV for 1 week <u>Arm 2:</u> Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis), infant SD NVP + ZDV for 1 week (no further postnatal prophylaxis)	Perinatal transmission at birth was 1.8% with maternal triple-drug prophylaxis Arm 1 and 2.5% with ZDV/SD NVP Arm 2, <b>not</b> significantly different. In women with CD4 cell counts 350–500 cells/mm <sup>3</sup> , 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).

**Supplemental Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Perinatal HIV Transmission (page 5 of 6)**

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
<b>Mma Bana; Botswana;<sup>2</sup> Breastfeeding</b>	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 cell counts >200 cells/mm <sup>3</sup>	<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 + ZDV for 4 weeks  <u>Arm 2:</u> Maternal ZDV/3TC/LPV/r for 6 months, infant SD NVP + ZDV for 4 weeks	Perinatal transmission at age 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 and 0.4% in ZDV/3TC/LPV/r Arm 2 ( $P = 0.53$ ).
<b>BAN; Malawi;<sup>28,38</sup> Breastfeeding</b>	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 cell counts $\geq 250$ cells/mm <sup>3</sup>	No AP drugs IP regimens: <u>Arm 1 (control):</u> ZDV/3TC + SD NVP  <u>Arm 2:</u> ZDV/3TC + SD NVP  <u>Arm 3:</u> ZDV/3TC + SD NVP	<u>Arm 1 (Control):</u> Maternal ZDV/3TC for 1 week, infant SD NVP + 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 Uninfected 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 ( $P = 0.009$ vs. control); 1.7% in infant NVP Arm 3 ( $P < 0.001$ vs. control).  • Perinatal transmission at age 48 weeks was 7.0% in control Arm 1; 4% in maternal triple-drug prophylaxis Arm 2 ( $P = 0.0273$ vs. control); 4% in infant NVP Arm 3 ( $P = 0.0027$ vs. control).  No significant difference between maternal triple-drug prophylaxis Arm 2 and infant NVP Arm 3 ( $P = 0.12$ at 28 weeks and $P = 0.426$ at 48 weeks).
<b>HPTN 046; South Africa, Tanzania, Uganda, Zimbabwe;<sup>35</sup> Breastfeeding</b>	Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks.  <u>Arm 1:</u> Daily infant NVP from 6 weeks through 6 months of age  <u>Arm 2:</u> Daily infant placebo from age 6 weeks through age 6 months	In infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3%–1.8%) in the extended NVP Arm 1 and 2.4% (1.3%–3.6%) in the placebo Arm 2 ( $P = 0.048$ ).  At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-drug ARV regimen for treatment of HIV.  For mothers receiving triple-drug ARV regimens at the time of randomization, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.2% and not statistically different between extended NVP Arm 1 (0.5%) and placebo Arm 2 (0%).  For mothers with CD4 cell counts >350 cells/mm <sup>3</sup> who were not receiving triple-drug ARV regimens, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.7% (0%–1.5%) in the extended NVP Arm 1 and 2.8% (1.3%–4.4%) in the placebo Arm 2 ( $P = 0.014$ ).

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

Study; Location(s); Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Perinatal Transmission Rate and Efficacy
<b>NICHD-HPTN 040/PACTG 1043 trial; Argentina, Brazil, South Africa, United States;<sup>19</sup> Formula feeding</b>	Infant prophylaxis with 6 weeks ZDV vs. 6 weeks infant ZDV plus three doses of NVP in first week of life vs. 6 weeks infant ZDV plus 2 weeks of 3TC/NFV	No AP drugs  If mother presented early enough, IV ZDV during labor through delivery	<b>Arm 1 (control):</b> Infant ZDV for 6 weeks  <b>Arm 2:</b> 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  <b>Arm 3:</b> Control as above, plus 3TC and NFV from birth through 2 weeks of age	IP HIV transmission among infants with negative HIV test at birth: 4.8% (3.2%–7.1%) ZDV (Arm 1) vs. 2.2% (1.2%–3.9%) in ZDV plus NVP (Arm 2) ( $P = 0.046$ compared with Arm 1) vs. 2.4% (1.4%–4.3%) in ZDV plus 3TC/NFV (Arm 3) ( $P = 0.046$ compared with Arm 1).  Overall HIV transmission rates, including <i>in utero</i> infection: 11.0% (8.7%–14.0%) ZDV (Arm 1) vs. 7.1% (5.2%–9.6%) in ZDV plus NVP (Arm 2) ( $P = 0.035$ compared with Arm 1) vs. 7.4% (5.4%–9.9%) in ZDV plus 3TC/NFV (Arm 3) ( $P = 0.035$ compared with Arm 1).  Grade 3 or 4 neutropenia more frequent in ZDV/3TC/NFV Arm 3, 70 infants, compared with ZDV alone Arm 1, 33 infants, or ZDV/NVP Arm 2, 32 infants ( $P < 0.001$ ).

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; CI = confidence interval; IP = intrapartum; IV = intravenous; LPV/r = ritonavir-boosted lopinavir; NFV = nelfinavir; NVP = nevirapine; PP = postpartum; SD = single-dose; ZDV = zidovudine

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## Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy (Last updated March 28, 2014; last reviewed March 28, 2014)

### Glossary of Terms for Supplement

**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

Six nucleoside analogue reverse transcriptase inhibitors (nucleoside NRTIs) and one nucleotide reverse transcriptase inhibitor (nucleotide NRTI) are currently approved; zalcitabine is no longer available in the United States. Data are available from clinical trials in human pregnancy for the nucleoside NRTIs zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleotide NRTI tenofovir. The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. Tenofovir, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base and, hence, requires only two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnancy and to the infant, see [NRTI Drugs and Mitochondrial Toxicity](#).

#### ***Abacavir (Ziagen, ABC)***

(Last updated March 28, 2014; last reviewed March 28, 2014)

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

#### **Animal Carcinogenicity Studies**

Abacavir is mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.

#### **Reproduction/Fertility**

No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).

#### **Teratogenicity/Developmental Toxicity**

Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve [AUC]). Toxicity to the developing embryo and fetus (increased resorptions and

decreased fetal body weight) occurred with administration of 500 mg/kg/day of abacavir to pregnant rodents. The offspring of female rats were treated with 500 mg/kg of abacavir, beginning at embryo implantation and ending at weaning. In these animals, an increased incidence of stillbirth and lower body weight was seen throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to abacavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with abacavir. Among cases of first-trimester abacavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.1% (26 of 848 births; 95% confidence interval [CI], 2.0%-4.5%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance. <sup>1</sup>

### Placental and Breast Milk Passage

Abacavir crosses the placenta and is excreted into the breast milk of lactating rats. In the Mma Bana study,<sup>2</sup> at 1 month postpartum, the median breast milk-to-plasma ratio for abacavir was 0.85 in the 15 women tested, and the drug was detected in the plasma of 1/9 breastfeeding infants whose mothers were receiving abacavir.

### Human Studies in Pregnancy

A Phase I study of abacavir in pregnant women indicates that the AUC drug concentration during pregnancy was similar to that at 6 to 12 weeks postpartum and in non-pregnant individuals.<sup>3</sup> Thus, no dose adjustment for abacavir is needed during pregnancy. Serious hypersensitivity reactions have been associated with abacavir therapy in non-pregnant adults, but these reactions have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will occur within hours and may include life-threatening hypotension and death.

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## ***Didanosine (Videx, ddI)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

Didanosine is classified as FDA Pregnancy Category B.

### **Animal Carcinogenicity Studies**

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

### **Reproduction/Fertility**

At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.

### **Teratogenicity/Developmental Toxicity**

No evidence of teratogenicity or toxicity was observed with administration of didanosine at 12 and 14 times human exposure, respectively, in pregnant rats and rabbits. Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.8% (20 of 413 births; 95% CI, 3.0%–7.4%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>1</sup> All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be closely monitored.

### **Placental and Breast Milk Passage**

Placental transfer of didanosine was low-moderate in a Phase I/II safety and pharmacokinetic (PK) study.<sup>2</sup> This was confirmed in a study of 100 HIV-infected pregnant women who were receiving nucleoside reverse transcriptase inhibitors (generally as part of a two- or three-drug combination antiretroviral [ARV] regimen). At the time of delivery, cord-to-maternal blood ratio for didanosine (n = 10) was 0.38 (range 0.0–2.0) and in 15 of 24 (62%) samples, cord blood concentrations for didanosine were below the limits of detection.<sup>3</sup> A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. It is not known if didanosine is excreted in human breast milk.

### **Human Studies in Pregnancy**

A Phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum.<sup>2</sup> The drug was well tolerated during pregnancy by the women and the fetuses. PK parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

Lactic acidosis, fatal in some cases, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents;<sup>4-6</sup> the Food and Drug Administration and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination. These two drugs should be prescribed together to pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

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## ***Emtricitabine (Emtriva, FTC)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Emtricitabine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 26 times the human systemic exposure or in rats at doses up to 31 times the human systemic exposure at the therapeutic dose.<sup>1</sup>

### **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 observed with human exposure at the recommended therapeutic dose.<sup>1</sup>

### **Teratogenicity/Developmental Toxicity**

Incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice that resulted in systemic drug exposure 60-fold higher than observed with human exposure at recommended doses or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.<sup>1</sup>

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 2-fold increased risk of overall birth defects. No such increase in birth defects has been observed with emtricitabine. Among cases of first-trimester emtricitabine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (27 of 1,068 births; 95% CI, 1.7%–3.7%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.<sup>2</sup>

### **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.<sup>3</sup> Emtricitabine has been shown to have excellent placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine once daily during pregnancy, mean cord blood concentration was 300 ± 268 ng/mL and the mean ratio of cord blood/maternal emtricitabine concentrations was 1.17 ± 0.6 (n = 9).<sup>4</sup> In a study of 15 women enrolled in IMPAACT P1026s who received emtricitabine during pregnancy, the mean cord to maternal blood ratio was 1.2 (90% CI, 1.0–1.5).<sup>5</sup> In 8 women enrolled in PACTG 394 who were given a single dose of 600 mg emtricitabine with 900 mg of tenofovir, the median cord blood emtricitabine concentration was 717 ng/mL (range 21–1,072), and the median cord blood/maternal ratio was 0.85 (range, 0.46–1.07).<sup>6</sup> Emtricitabine is excreted into human milk. In a study in the Ivory Coast, 5 HIV-infected women who chose to exclusively breastfeed their newborn infants were given 400 mg emtricitabine, 600 mg tenofovir, and 200 mg of nevirapine at onset of labor, followed by 200 mg of emtricitabine and 300 mg of tenofovir once daily for 7 days postpartum. The median minimal and maximal concentrations of emtricitabine in breast milk were 177 and 679 ng/mL, respectively (interquartile ranges 105–254 and 658–743 ng/mL, respectively), well above the estimated emtricitabine IC<sub>50</sub> for HIV-1.<sup>7</sup>

### **Human Studies in Pregnancy**

Emtricitabine pharmacokinetic (PK) parameters have been evaluated in 18 HIV-infected pregnant women receiving antiretroviral therapy including emtricitabine (200 mg once daily) at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum.<sup>4</sup> Emtricitabine exposure was modestly lower during the third trimester (8.6 µg\*h/mL [5.2–15.9]) compared with the postpartum period (9.8 µg\*h/mL [7.4–30.3]). Two-thirds (12 of 18)

of pregnant women versus 100% (14 of 14) of postpartum women met the AUC target (10th percentile in non-pregnant adults). Trough emtricitabine levels were also lower during pregnancy (minimum plasma concentration [ $C_{\min}$ ] 52 ng/mL [14–180]) compared with the postpartum period (86 ng/mL [ $<10$  to 306]). In the IMPAACT P1026s study, 26 women had emtricitabine PKs assessed during the third trimester (median 35 weeks) and 22 postpartum (mean 8 weeks postpartum).<sup>5</sup> The PK parameters during pregnancy were slightly altered with respect to the postpartum period, with higher emtricitabine clearance (25.0 vs. 20.6 L/hour during pregnancy vs. postpartum, respectively) and lower 24-hour post-dose levels (0.058 vs. 0.085 mg/L), but the 24-hour, post-dose levels were well above the inhibitory concentration 50% ( $IC_{50}$ ) in all patients. Similar differences in PK parameters of emtricitabine among women during pregnancy or after delivery were found in the PACTG 394 study,<sup>6</sup> and in a European study.<sup>8</sup> Thus, these changes are not believed to be large enough to warrant dosage adjustment during pregnancy.

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## ***Lamivudine (Epivir, 3TC)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Lamivudine has weak mutagenic activity in one *in vitro* assay but no evidence of *in vivo* genotoxicity in rats at 35 to 45 times human exposure. Long-term animal carcinogenicity screening studies at 10 and 58 times human exposure have been negative in mice and rats, respectively.<sup>1</sup>

### **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.<sup>1</sup>

### **Teratogenicity/Developmental Toxicity Studies**

There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits. Early embryoletality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.<sup>1</sup>

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the most commonly occurring birth defects, such as defects of the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with lamivudine. Among cases of first-trimester lamivudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was **3.2% (133 of 4,185 births; 95% CI, 2.7%–3.8%)** compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>2</sup>

### **Placental and Breast Milk Passage**

Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations.<sup>3</sup> 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.<sup>4</sup> Other studies have also noted accumulation of lamivudine in amniotic fluid.<sup>5</sup> This is likely secondary to renal excretion of lamivudine by the fetus; lamivudine diffuses from maternal to fetal blood through the placenta and the fetal kidney removes lamivudine from fetal blood and concentrates it in urine, with fetal micturition causing a rise in the concentration of lamivudine in amniotic fluid.

Lamivudine is excreted into human breast milk. In a study in Kenya of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56.<sup>6</sup> In infants who received lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (half-maximal IC<sub>50</sub> of wild-type HIV against lamivudine = 0.6–21 ng/mL).

### **Human Studies in Pregnancy**

**Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in two separate studies.<sup>3,5</sup> 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.<sup>4</sup> Pregnant women had a 22% higher apparent clearance than non-pregnant and postpartum women, but this increase did not lead to sub-therapeutic exposure. The level of lamivudine exposure in pregnant women, although lower than exposure in non-pregnant and parturient women, was relatively close to data reported previously for non-**

pregnant adults.<sup>4</sup> Thus, no dose adjustment in pregnancy is necessary.

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## ***Stavudine (Zerit, d4T)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Stavudine is clastogenic in *in vitro* and *in vivo* assays but not mutagenic in *in vitro* assays. In 2-year carcinogenicity studies in mice and rats, stavudine was non-carcinogenic in doses producing exposures 39 (mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.

### **Reproduction/Fertility**

Stavudine has not been shown to have an effect on reproduction or fertility in rodents. A dose-related cytotoxic effect has been observed on pre-implantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100  $\mu\text{M}$  and of post-blastocyst development at 10  $\mu\text{M}$ .<sup>1</sup>

### **Teratogenicity/Developmental Toxicity Studies**

No evidence of teratogenicity was noted in rats or rabbits with exposures (based on  $C_{\text{max}}$ ) up to 399 and 183 times, respectively, that seen at a clinical dosage of 1 mg/kg/day. In rat fetuses, the incidence of a common skeletal variation—unossified or incomplete ossification of sternebra—was increased at 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times human exposure, with no effect noted at approximately 135 times human exposure. An increase in early rat neonatal mortality (birth to Day 4) occurred at 399 times human exposure, although survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to stavudine in humans have been monitored to be able to detect at least a two-fold increased risk of overall birth defects. No such increase in birth defects has been observed with stavudine. Among cases of first-trimester stavudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (20 of 801 births; 95% CI, 1.5% to 3.8%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance.<sup>2</sup>

### **Placental and Breast Milk Passage**

Stavudine crosses the rat placenta *in vivo* and the human placenta *ex vivo*, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pig-tailed macaques), fetal/maternal plasma concentrations were approximately 0.80.<sup>3</sup> Stavudine is excreted into the breast milk of lactating rats. Stavudine also crosses into human breast milk, resulting in breast milk/maternal plasma concentrations of 1.0–1.76. Concentrations in nursing infants were negligible.<sup>4,5</sup>

### **Human Studies in Pregnancy**

A Phase I/II safety and pharmacokinetic (PK) study has been conducted of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332). Both drugs were well tolerated, with stavudine PKs similar to those in non-pregnant adults.<sup>6</sup> Data from primate studies also indicated that pregnancy did not affect the PKs of stavudine.<sup>7</sup>

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.<sup>8-10</sup> The FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of

fatal lactic acidosis when prescribed didanosine and stavudine in combination (see [NRTI Drugs and Mitochondrial Toxicity](#)). These drugs should be prescribed together for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

Although the standard adult dosing in the U.S. is weight-based, the World Health Organization recommends 30 mg, twice-daily dosing regardless of body weight.<sup>11</sup>

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## ***Tenofovir Disoproxil Fumarate (Viread, TDF)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

Tenofovir disoproxil fumarate (hereafter, tenofovir) is classified as Food and Drug Administration Pregnancy Category B.

### **Animal Carcinogenicity Studies**

Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at 16 times (mice) and 5 times (rats) human exposure. In female mice, liver adenomas were increased at exposures 16 times that observed in humans at therapeutic doses. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

### **Reproduction/Fertility**

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus associated with tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days before mating and to female rats for 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day. **A retrospective analysis of 7,275 women (1,199 receiving tenofovir-based combination antiretroviral therapy) demonstrated a slight reduction in pregnancy rates but the findings were limited by the observational nature of the data and additional studies are needed for confirmation.<sup>1</sup>**

### **Teratogenicity/Developmental Toxicity**

Chronic exposure of fetal monkeys to tenofovir at high doses (i.e., exposure equivalent to 25 times the area under the curve achieved with therapeutic dosing in humans) resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and were associated with lower overall body weights. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment. Significant changes in maternal monkey bone biomarkers were noted but were primarily limited to the treatment period and were reversible.<sup>2</sup> In newborn macaques exposed to tenofovir at high dose over a prolonged period, similar changes have been noted, as well as osteomalacia, bone fracture, hypophosphatemia, and nephrotoxicity.

**These toxicities appear to be dose- and age-related and are reversible. In contrast,** no detectable effects on growth have been seen with administration of tenofovir for shorter durations or at lower doses to newborn or infant macaques.<sup>3,4</sup>

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to tenofovir in humans have been monitored to be able to detect at least a 2-fold increased risk of overall birth defects. No such increase in birth defects has been observed with tenofovir. Among cases of first-trimester tenofovir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (31 of 1,370 births; 95% CI, 1.5% to 3.2%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.<sup>5</sup> **In addition, no association was seen between tenofovir administration and birth defects in two large U.S. cohorts, PACT 219/219C (n = 2,202) and P1025 (n = 1,112).<sup>6,7</sup>**

### **Placental and Breast Milk Passage**

Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir does cross the placenta.<sup>8</sup> In studies of pregnant women on chronic tenofovir dosing, the cord-to-maternal-blood ratio ranged from 0.60 to 1.03, indicating high placental transfer.<sup>9-12</sup> In studies of pregnant women receiving single-dose tenofovir (with and without

emtricitabine) in labor, the drugs were well-tolerated and the median tenofovir cord to maternal-blood ratio at delivery ranged from 0.55 to 0.73.<sup>13,14</sup> In a study evaluating intracellular tenofovir levels in newborns, intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a maternal single dose of 600 mg tenofovir disoproxil fumarate with 400 mg emtricitabine, but intracellular tenofovir diphosphate was detectable in only 2 (5.5%) of 36.<sup>15</sup> Two studies of neonatal dosing of tenofovir disoproxil fumarate resulted in tenofovir and tenofovir diphosphate levels similar to those in adults following either a single neonatal dose of 13 mg/kg or a regimen of 6 mg/kg administered daily for 7 days.<sup>14,15</sup>

Sixteen breast milk samples were obtained from five women who received 600 mg of tenofovir at the start of labor followed by 300 mg daily for 7 days. Tenofovir levels in breast milk ranged from 5.8 to 16.3 ng/mL, and nursing infants received an estimated 0.03% of the proposed oral dose of tenofovir disoproxil fumarate for neonates.<sup>16</sup>

### Human Studies in Pregnancy

A retrospective population pharmacokinetic (PK) study was performed on samples collected for therapeutic drug monitoring from 46 pregnant women and 156 non-pregnant women receiving combination regimens including tenofovir.<sup>17</sup> Pregnant women had a 39% higher apparent clearance compared with non-pregnant women, which decreased slightly but significantly with increasing age. In study P1026s, tenofovir PKs were evaluated in 19 pregnant women receiving tenofovir-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum.<sup>9</sup> The percentage of women with tenofovir area under the curve exceeding the target of 2 µg\*hour/mL (the 10th percentile in non-pregnant adults) was lower in the third trimester (74%, 14 of 19 women) than postpartum (86%, 12 of 14 women) ( $P = .02$ ); however, trough levels were similar in the two groups. A study of 34 women receiving tenofovir plus emtricitabine in the third trimester and postpartum has recently been reported.<sup>11</sup> Although similar decreases in PK parameters were observed during pregnancy, they were not associated with virologic failure. At the present time, standard dosing during pregnancy continues to be recommended.

A case series found tenofovir to be well tolerated in 76 pregnant women, with only 2 stopping therapy, 1 for rash and the other for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV uninfected.<sup>18</sup> A follow-up study of 20 of the tenofovir-exposed infants and 20 controls found no differences between the groups in renal function, including cystatin C levels, through age 2 years.<sup>19</sup> A retrospective review of 16 pregnancy outcomes in 15 heavily antiretroviral-experienced women demonstrated that tenofovir was well tolerated by the women and associated with normal growth and development in the infants.<sup>20</sup> In a cross-sectional study of 68 HIV-exposed uninfected infants who had *in utero* exposure to combination regimens with (N = 33) or without (N = 35) tenofovir, the incidence of low birth weight and length measurements (<10th percentile) was comparable in the 2 groups and evaluation of quantitative bone ultrasound and parameters of bone metabolism gave similar measures between groups.<sup>21</sup> Among 382 pregnancies occurring in 302 women in Uganda and Zimbabwe participating in the DART trial—approximately two-thirds of whom received tenofovir through more than 90% of their pregnancies—there were no differences noted in mortality, birth defects, or growth.<sup>22</sup> The Pediatric HIV/AIDS Cohort Study from the United States reported on the association of tenofovir use during pregnancy with early growth parameters in 449 HIV-exposed but HIV-uninfected infants.<sup>23</sup> Of 2,029 infants, 449 (21%) had *in utero* exposure to tenofovir. There was no difference at birth between those exposed to combination drug regimens with or without tenofovir in low birth weight, small-for-gestational-age, and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively). At age 1 year, infants exposed to combination regimens with tenofovir had a slight but significantly lower adjusted mean LAZ and HCAZ than those without tenofovir exposure (LAZ: -0.17 vs. -0.03,  $P = .04$ ; HCAZ: 0.17 vs. 0.42,  $P = .02$ ), but not lower weight-for-age z-score. However, there were no significant differences between those with and without tenofovir exposure at age 1 year when defining low LAZ or HCAZ as <-1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.



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## **Zalcitabine (HIVID, ddC)**

(Last updated March 28, 2014; last reviewed March 28, 2014)

Zalcitabine is no longer available in the United States.

## **Zidovudine (Retrovir, AZT, ZDV)**

(Last updated March 28, 2014; last reviewed March 28, 2014)

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

### **Animal Carcinogenicity Studies**

Zidovudine was shown to be mutagenic in two *in vitro* assays and clastogenic in one *in vitro* and two *in vivo* assays, but not cytogenic in a single-dose *in vivo* rat study. Long-term carcinogenicity studies have been performed with zidovudine in mice and rats.<sup>1</sup> In mice, 7 late-appearing (>19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of an animal given an intermediate dose. No vaginal tumors were found at the lowest dose. In rats, 2 late-appearing (>20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex in either species. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by area under the curve [AUC]) was approximately three times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours. How predictive the results of rodent carcinogenicity studies may be for humans is unknown.

Two transplacental carcinogenicity studies were conducted in mice.<sup>2,3</sup> In 1 study, zidovudine was administered at doses of 20 mg/kg/day or 40 mg/kg/day from gestation Day 10 through parturition and lactation, with postnatal dosing continuing in offspring for 24 months.<sup>3</sup> The drug doses administered in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. In a second study, zidovudine was administered at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1000 mg/kg non-pregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 to 18 of gestation.<sup>2</sup> There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose of zidovudine.

### **Reproduction/Fertility**

When administered to male and female rats at doses up to seven times the usual adult dose based on body surface area, zidovudine had no effect on fertility, as judged by rates of conception.

Zidovudine has been shown to have no effect on reproduction or fertility in rodents. A dose-related cytotoxic effect on pre-implantation mouse embryos can occur, with inhibition of blastocyst and post-blastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses.<sup>4</sup>

### **Teratogenicity/Developmental Toxicity**

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity, as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times and in rabbits 12 to 87 times mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose

(100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations (estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day). No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Increased fetal resorption occurred in pregnant rats and rabbits treated with zidovudine doses that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100 mg dose of zidovudine. No other developmental anomalies were reported. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen.<sup>5,6</sup> Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts, PACTG 219/219C and P1025.<sup>7,8</sup> 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.<sup>9,10</sup> In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to zidovudine have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased incidence of defects in the more common classes, including the genitourinary system. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.3% (124 of 3,789 births; 95% CI, 2.7% to 3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance.<sup>11</sup>

### 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.<sup>12</sup> Zidovudine is excreted into human breast milk with breast milk-to-maternal-plasma zidovudine concentration ranging from 0.44 to 0.77.<sup>13,14</sup> No zidovudine was detectable in the plasma of the nursing infants, who received zidovudine only via breast milk.

### Human Studies in Pregnancy

Zidovudine is well tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg/kg body weight orally every 6 hours.<sup>5,15</sup> Long-term data on the safety of *in utero* drug exposure in humans are not available for any antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. In PACTG 076, no difference in disease progression was seen between women who received zidovudine and those who received placebo, based on follow-up through 4 years postpartum.<sup>16</sup> Additionally, no differences in immunologic, neurologic, or growth parameters were seen between infants with *in utero* zidovudine exposure and those who received placebo, based on nearly 6 years of follow-up.<sup>6,17</sup>

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## Non-Nucleoside Reverse Transcriptase Inhibitors

### Glossary of Terms for Supplement

**Carcinogenic:** Producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

**Clastogenic:** Causing disruption of or breakages in chromosomes

**Genotoxic:** Damaging to genetic material such as DNA and chromosomes

**Mutagenic:** Inducing or capable of inducing genetic mutation

**Teratogenic:** Interfering with fetal development and resulting in birth defects

Five non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) are currently approved (delavirdine is no longer available in the United States). Nevirapine and efavirenz have been studied in human pregnancy. No adequate and well-controlled studies of etravirine or rilpivirine use in pregnant women have been conducted.

For information about potential interactions between NNRTIs and methergine, see the [Postpartum Hemorrhage](#), [Antiretroviral Drugs](#), and [Methergine Use](#) sections in the perinatal guidelines. For more information regarding nevirapine hepatic/rash toxicity, see the [Nevirapine and Hepatic/Rash Toxicity](#) section in the perinatal guidelines.

### ***Delavirdine (Rescriptor, DLV)***

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Delavirdine is no longer available in the United States.

### ***Efavirenz (Sustiva, EFV)***

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Efavirenz is classified as Food and Drug Administration (FDA) Pregnancy Category D.

### **Animal Carcinogenicity Studies**

Efavirenz was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies with efavirenz have been completed in mice and rats. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice, but in female mice, an increase above background was seen in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas. No increase in tumor incidence above background was observed in male and female rats with systemic drug exposures lower than that in humans receiving therapeutic doses.

### **Reproduction/Fertility Animal Studies**

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

### **Teratogenicity/Developmental Toxicity**

An increase in fetal resorption was observed in rats at efavirenz doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily). Central nervous system (CNS) malformations and cleft palate were observed in 3 of 20 infants born to pregnant cynomolgus



monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 60 mg/kg/day (resulting in plasma concentrations 1.3 times that of systemic human therapeutic exposure, with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values).<sup>1</sup> The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

### Placental and Breast Milk Passage

Efavirenz readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations. In a study of 25 mother-infant pairs, median efavirenz cord blood/maternal blood concentration was 0.49 (range 0.37–0.74).<sup>2</sup> In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery.<sup>3</sup> Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz concentration was significantly higher in maternal plasma than skim breast milk (mean breast milk to mean maternal plasma concentration ratio 0.54) and higher in skim breast milk than in infant plasma (mean skim breast milk to mean newborn plasma concentration ratio 4.08). Mean infant plasma efavirenz concentrations were 13.1% of maternal plasma levels. In a study of plasma and hair drug concentration in 56 mother-infant pairs receiving efavirenz-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested moderate *in utero* transfer during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative with 15% during breastfeeding).<sup>4</sup> All mothers and infants had detectable efavirenz plasma levels at 0, 8, and 12 weeks and mean infant to maternal hair concentration at 12 weeks postpartum was 0.40 for efavirenz.

No data currently are available about the safety and pharmacokinetics of efavirenz in neonates.

### Human Studies in Pregnancy

In a study of 25 pregnant women receiving efavirenz during the third trimester as part of clinical care, efavirenz clearance was slightly increased and trough levels were decreased compared with levels measured postpartum.<sup>2</sup> These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy.

In a pharmacogenomics study, non-pregnant individuals with the CYP2B6 516 TT genotype had more than 3-fold increases in both short-term and long-term efavirenz exposure, as measured by plasma and hair drug levels, suggesting there could be significant variation in drug levels with CYP2B6 polymorphisms.<sup>5</sup> 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.<sup>2</sup>

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry (APR) through July 2013, birth defects were observed in 18 of 766 live births with first-trimester exposure (2.3%, 95% confidence interval [CI], 1.4%–3.7%).<sup>6</sup> Although these data provide sufficient numbers of first-trimester exposures to rule out a two-fold or greater increase in the risk of **overall** birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the APR of defects after first-trimester efavirenz exposure have documented one neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and one case of bilateral facial clefts, anophthalmia, and amniotic band.<sup>6</sup> Among retrospective cases, there are six reports of CNS defects, including three cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester.<sup>7</sup> Retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

In an updated meta-analysis of 19 studies (including the Antiretroviral Pregnancy Registry data) reporting on birth outcomes among women exposed to efavirenz during the first trimester, there were 39 infants with birth defects among live births in 1,437 women receiving first-trimester efavirenz (rate of overall birth defects, 2.0%, 95% CI, 0.8–3.2%).<sup>8</sup> The rate of overall birth defects was similar among women exposed to efavirenz-

containing regimens (1,290 live births) and non-efavirenz containing regimens (8,122 births) during the first trimester (pooled relative risk [RR] 0.85, 95% CI, 0.61–1.20). Across all births (1,437 live births with first-trimester efavirenz exposure), 1 neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.07% (95% CI, 0.002–0.39), within the range reported in the general population. However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a significant increase in low-incidence birth defects (incidence of neural tube defects in the general U.S. population is 0.02%–0.2%).

Although two small studies (Pediatric AIDS Clinical Trials Group [PACTG] protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to efavirenz compared with those without exposure, the number of exposures was small (35 exposures in PACTG 219/219C and 42 in P1025) and there is overlap in defect cases between the 2 studies.<sup>9–11</sup> Thus, additional data are needed on first-trimester efavirenz exposures to more conclusively determine if risk of neural tube defects is elevated.

Efavirenz is classified as FDA Pregnancy Category D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Although the limited data on first-trimester efavirenz exposure cannot rule out a 2- or 3-fold increased incidence of a rare outcome, such as neural tube defects, the available data from the meta-analysis on >1,400 births suggest that there is not a large increase (such as a 10-fold increase to a rate of 1%) in the risk of neural tube defects with first-trimester exposure. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first 8 weeks of pregnancy (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of avoiding pregnancy. Alternate antiretroviral (ARV) regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health. However, given that the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (the neural tube closes at 36–39 days after last menstrual period), pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and ARV drug changes in pregnancy may be associated with loss of viral control and thus increase risk of transmission to the infant,<sup>12</sup> efavirenz can be continued in pregnant women receiving efavirenz-based antiretroviral therapy who present for antenatal care in the first trimester, provided that the regimen produces virologic suppression. In such situations, additional fetal monitoring (e.g., second-trimester ultrasound) should be considered to evaluate fetal anatomy.

Pharmacokinetic (PK) interactions of efavirenz with some hormonal contraceptives have been reported, with the potential for failure of the progesterone component, particularly when used for emergency contraception.<sup>13–16</sup> Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health. Barrier contraception should always be used in combination with other methods of contraception such as hormonal contraceptives and intrauterine devices. A study evaluating the interaction between efavirenz and depot medroxyprogesterone acetate (DMPA) in 17 women found no change in the PK profile of either efavirenz or DMPA with concomitant use.<sup>17</sup> DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

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## ***Etravirine (Intelence, ETV)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.<sup>1</sup> Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200, and 400 mg/kg were administered to mice and doses of 70, 200, and 600 mg/kg were administered to rats in the initial period of approximately 41 to 52 weeks. The high and middle doses were subsequently adjusted because of tolerability and reduced by 50% in mice and by 50% to 66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were observed in either sex. The relevance to humans of these liver tumor findings in mice is unknown. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal versus human area under the curve ratios being 0.6-fold (mice) and 0.2- to 0.7-fold (rats).<sup>1</sup>

### **Reproduction/Fertility**

No effect on fertility and early embryonic development was observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).<sup>1</sup>

### **Teratogenicity/Developmental Toxicity**

Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1000 mg/kg/day). In both species, no treatment-related embryo-fetal effects (including malformations) were observed. In addition, no treatment effects were observed in a separate prenatal and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).<sup>1</sup> In seven reported cases of etravirine use in pregnancy, no maternal, fetal, or neonatal toxicity was noted. One infant was born with a small accessory auricle on the right ear with no other malformations, but no birth defects were noted in the other children.<sup>2</sup> Fewer than 200 first-trimester pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.

### **Placental and Breast Milk Passage**

Etravirine concentrations in cord blood and maternal plasma at delivery were 112 ng/mL and 339 ng/mL, respectively (cord/maternal ratio of 33%), in one mother-infant pair.<sup>3</sup> Placental passage of etravirine was described in a report of the use of etravirine, ritonavir-boosted darunavir, and enfuvirtide in a pregnant woman who gave birth to twins, with cord blood etravirine levels of 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (no maternal delivery etravirine concentration reported).<sup>2</sup> There are no data describing etravirine excretion in human breast milk.

### **Human Studies in Pregnancy**

No adequate and well-controlled studies of etravirine use in pregnant women have been conducted. Very limited case report data are available describing etravirine use in a total of 7 pregnant women.<sup>2</sup> No adverse effects associated with etravirine use were reported. One report described etravirine pharmacokinetics (PK) in four pregnant women whose etravirine PK parameters were similar to those in non-pregnant adults.<sup>3</sup>

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## ***Nevirapine (Viramune, NVP)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. Hepatocellular adenomas and carcinomas were increased at all doses in male mice and rats and at higher doses in female mice and rats. Systemic exposure at all doses studied was lower than systemic exposure in humans receiving therapeutic nevirapine doses. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is unknown.

### **Reproduction/Fertility**

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

### **Teratogenicity/Developmental Toxicity**

Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits at systemic exposures approximately equivalent to or 50% greater than the recommended human dose (based on area under the curve [AUC]). In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to nevirapine in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects **in more commonly seen classes of birth defects in the cardiovascular and genitourinary systems**. No such increase in birth defects has been observed with nevirapine. Among cases of first-trimester nevirapine exposure reported to the APR, the prevalence of birth defects was **3.0% (31 of 1,049 births; 95% CI, 2.0% to 4.2 %)** compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>1</sup>

### **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).<sup>2,3</sup> Nevirapine has also been shown to be excreted into human breast milk. In a study of 57 Malawian women receiving postpartum nevirapine-based therapy, breast milk to maternal serum concentration ratio was approximately 0.6; detectable nevirapine concentrations were found in the breastfeeding infants (intra-quartile range 0.54–1.06 ug/mL).<sup>4</sup> In data from 15 breastfeeding women receiving nevirapine-based therapy in Botswana, median maternal plasma concentration at 1 month postpartum was 6.71 ug/mL and median maternal breast milk concentration was 1.83 ug/mL, for a median maternal breast milk to plasma ratio of 0.27.<sup>5</sup> Infant exposure was measured at 1 month in nine infants; all infants had biologically significant detectable nevirapine concentrations in their blood, with a median level of 0.37 ug/mL (range, 0.24–1.2 ug/mL), representing approximately 6% of median maternal value. Similar data were reported in a study of 67 mothers receiving nevirapine-based therapy in Kenya; the median concentration of nevirapine in breast milk was 4.55 ug/mL, with median concentrations at 2, 6, and 14 weeks postpartum in breastfeeding infants of 0.99 ug/mL, 1.03 ug/mL and 0.73 ug/mL, respectively.<sup>6</sup>**

### **Human Studies in Pregnancy**

The pharmacokinetics (PKs) of nevirapine have been evaluated in pregnant women receiving nevirapine as part of combination antiretroviral therapy (cART) during pregnancy. A study that determined nevirapine PKs in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine PK parameters.<sup>7</sup> 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.<sup>8</sup> A Dutch study reported a non-significant trend toward lower nevirapine exposure during pregnancy, with steady-state nevirapine concentrations of 5.2 ug/mL in 45 pregnant women compared to 5.8 ug/mL in 152 non-pregnant women ( $P = 0.08$ ).<sup>9</sup> No dose adjustment during pregnancy is currently recommended for nevirapine.

Severe, life-threatening, and (in some cases) fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome—has been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of cART for post-exposure prophylaxis of nosocomial or sexual exposure to HIV.<sup>10</sup> In general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5% to 11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, in the range of 0.04% to 0.40%.<sup>11,12</sup> Risk of severe or life-threatening adverse events occurs in approximately 2% of patients receiving nevirapine.<sup>11</sup> 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.<sup>13-15</sup> Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men.<sup>12</sup> Several studies suggest that the degree of risk of hepatic toxicity varies with CD4 T lymphocyte (CD4) cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts  $>250$  cells/mm<sup>3</sup> were 9.8 times more likely than women with lower CD4 cell counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity.<sup>12</sup> Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash.<sup>14</sup> Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of non-pregnant women, although not all have reported an association with CD4 cell counts  $>250$  cells/mm<sup>3</sup>.<sup>16</sup> 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  $\geq 250$  cells/mm<sup>3</sup> was associated with nevirapine-related liver toxicity and drug discontinuation.<sup>17</sup> Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants) and immune human leukocyte antigen loci may be associated with higher risk of nevirapine-associated adverse events and that the relationship between genetic variants and adverse effects may vary by race.<sup>18,19</sup>

Although deaths as a result of hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination ARV regimen, it is uncertain whether pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs.<sup>20</sup> 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%).<sup>21</sup> 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.<sup>22,23</sup>

In the systematic review, there was a non-significant trend toward an increased likelihood of cutaneous events (OR 1.1, 95% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 cell counts  $\geq 250$  cell/mm<sup>3</sup> (OR 1.4, 95% CI 0.8-2.4).<sup>21</sup> 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  $\geq 250$  cells/mm<sup>3</sup>.<sup>24</sup> Nevirapine should be used as a component of a combination regimen in pregnant women with CD4 cell counts  $\geq 250$  cells/mm<sup>3</sup> only if the benefit clearly outweighs the risk. Women with CD4 cell counts  $< 250$  cells/mm<sup>3</sup> can receive nevirapine-based regimens, and women who become pregnant while taking nevirapine and who are tolerating their regimens well can continue therapy, regardless of CD4 cell count.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication. Frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is necessary, particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, and then monthly for the first 18 weeks ([Adult and Adolescent Antiretroviral Guidelines](#)); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.<sup>25</sup> 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.

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## ***Rilpivirine (Edurant, RPV)***

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

### **Animal Carcinogenicity Studies**

Rilpivirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Rilpivirine was not carcinogenic in rats when administered at doses 3 times higher than exposure in humans at the recommended dose of 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses 21 times that of human therapeutic exposure; the observed hepatocellular findings in mice may be rodent-specific.!

### **Reproduction/Fertility**

No effect on fertility was observed when rilpivirine was tested in rats at maternal doses up to 400 mg/kg/day, resulting in systemic drug exposure equivalent to 40 times the recommended human dose.

### **Teratogenicity/Developmental Toxicity**

No evidence of embryonic or fetal toxicity or an effect on reproductive function was observed in rat and rabbit dams treated with rilpivirine during pregnancy and lactation at doses 15 and 70 times higher, respectively, than exposure in humans at the recommended dose of 25 mg once daily.

### **Placental and Breast Milk Passage**

No data exist on whether rilpivirine crosses the placenta or is excreted in breast milk in humans. Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk

### **Human Studies in Pregnancy**

No adequate and well-controlled studies of rilpivirine use in pregnant women have been conducted.

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## Protease Inhibitors

(Last updated March 28, 2014; last reviewed March 28, 2014)

### 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

Ten protease inhibitors (PIs) are currently approved (amprenavir is no longer available in the United States). Data are available from clinical trials in human pregnancy for atazanavir, ritonavir-boosted lopinavir fixed-dose drug formulation, nelfinavir, ritonavir, and saquinavir. Data in pregnancy are limited for darunavir, fosamprenavir, and indinavir. Very limited data in pregnancy are available for tipranavir.

For information regarding the PI class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see [Combination Antiretroviral Drug Regimens and Pregnancy Outcome](#).

### *Amprenavir (Agenerase, APV)*

(Last updated March 28, 2014; last reviewed March 28, 2014)

Amprenavir is no longer available in the United States.

### *Atazanavir (Reyataz, ATV)*

(Last updated March 28, 2014; last reviewed March 28, 2014)

Atazanavir is classified as Food and Drug Administration (FDA) Pregnancy Category B.

### Animal Carcinogenicity Studies

In *in vitro* and *in vivo* assays, atazanavir shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. In female mice, the incidence of benign hepatocellular adenomas was increased at systemic exposures 2.8- to 2.9-fold higher than those in humans at the recommended therapeutic dose (300 mg atazanavir boosted with 100 mg ritonavir once daily). There were no increases in the incidence of tumors in male mice at any dose. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 1.1-fold (males) or 3.9-fold (females) higher than those in humans at the recommended therapeutic dose.<sup>1</sup>

### Reproduction/Fertility

No effect of atazanavir on reproduction or fertility in male and female rodents was seen at systemic drug exposures. The area under the curve (AUC) at this exposure level in rats was 0.9-fold in males and 2.3-fold in females compared with the exposures achieved in humans at the recommended therapeutic dose.<sup>1</sup>

### Teratogenicity/Developmental Toxicity

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg atazanavir boosted with 100 mg ritonavir once daily). In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure 1.3

times the human exposure also resulted in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposure equivalent to that observed in humans at the recommended therapeutic dose.<sup>1</sup>

In a retrospective analysis from London of atazanavir used in 31 women during 33 pregnancies (20 of whom were receiving atazanavir at conception), there were two miscarriages at 12 and 16 weeks, 26 infants born, and five women still pregnant.<sup>2</sup> No infant required phototherapy and no birth defects were seen; none of the infants were HIV-infected. In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to atazanavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.1% (16 of 746 births; 95% confidence interval [CI], 1.2%–3.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.<sup>3</sup>

### Placental and Breast Milk Passage

In studies of women receiving ritonavir-boosted atazanavir-based combination therapy during pregnancy, cord blood atazanavir concentration averaged 13% to 21% of maternal serum levels at delivery.<sup>1,4,5</sup> Atazanavir is excreted in the milk of lactating rats. In a study of three women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.<sup>6</sup>

### Human Studies in Pregnancy

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of ritonavir-boosted atazanavir in pregnancy.<sup>7</sup> Overall, most pregnant patients achieved undetectable HIV RNA at the time of delivery.<sup>1,4,5,8,9</sup> In a retrospective study reporting trough atazanavir concentrations in 19 pregnant women receiving atazanavir 300 mg and ritonavir 100 mg once daily at a median of 30 weeks' gestation (14 in the third trimester), all but 2 women had a trough atazanavir concentration >100 ng/mL.<sup>2</sup> In studies that have evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy, atazanavir AUC was lower during pregnancy than in historic data from HIV-infected non-pregnant patients.<sup>4,5,8,10,11</sup> In one of the studies there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than in non-pregnant HIV-infected historic controls.<sup>4</sup> In the other studies, atazanavir AUC was lower during pregnancy than in the same patients postpartum and in non-pregnant control populations.<sup>5,8-11</sup>

Although use of ritonavir-based atazanavir combined with tenofovir and emtricitabine as a complete once-a-day dosing combination antiretroviral (ARV) regimen is becoming increasingly common in pregnancy, tenofovir reduces atazanavir exposure by 25% in non-pregnant adults.<sup>10</sup> This drug-drug interaction also is present during pregnancy, with a 25% reduction in atazanavir AUC in pregnant women also receiving tenofovir compared with the same women postpartum and a 50% reduction compared with postpartum levels in women who did not receive tenofovir.<sup>5</sup>

Use of an increased dose of atazanavir of 400 mg with 100 mg ritonavir once daily during pregnancy has been investigated in two studies.<sup>8,9</sup> In both studies pregnant women receiving the increased dose without tenofovir had an atazanavir AUC equivalent to that seen in historic non-pregnant HIV-infected controls receiving standard-dose atazanavir without tenofovir. Pregnant women receiving the increased atazanavir dose with tenofovir had an AUC equivalent to that seen in non-pregnant HIV-infected patients receiving standard-dose atazanavir and tenofovir.<sup>8,9</sup> Although some experts recommend increased atazanavir dosing in all women during the second and third trimesters, the package insert recommends increased atazanavir dosing only for ARV-experienced pregnant women in the second and third trimesters also receiving either tenofovir or an H2-receptor antagonist. For additional details about dosing with interacting concomitant medications, please see [Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.](#)

Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir. The effects of elevated maternal indirect bilirubin throughout pregnancy on the fetus are unknown. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received atazanavir during pregnancy.<sup>1,2,4,5,8,12-14</sup> 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.<sup>12,13</sup> Elevated neonatal bilirubin in atazanavir-exposed neonates is not associated with UGT-1 genotypes associated with decreased UGT function.<sup>14</sup>

In an evaluation of neurodevelopment in 374 HIV-exposed uninfected infants aged 9 to 15 months, the adjusted mean on the Language domain of the Bayley-III test was significantly lower for infants with perinatal exposure to atazanavir compared to other drugs.<sup>15</sup> In a study of language assessments among 792 1- and 2-year-old HIV-exposed uninfected children, atazanavir was also associated with increased risk of late language emergence at age 12 months (adjusted odds ratio 1.83, 95% CI, 1.10–3.04) compared with atazanavir-unexposed infants but the association was not significant at 24 months.<sup>16</sup>

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.<sup>1</sup> This finding of infant hypoglycemia is similar to a prior report in which two (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life.<sup>17</sup>

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## ***Darunavir (Prezista, DRV)***

**(Last reviewed March 28, 2014; last updated March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Darunavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in both male and female mice and rats as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on area under the curve) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats) those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg/day).

### **Reproduction/Fertility**

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

### **Teratogenicity/Developmental Toxicity**

No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits. Because of limited bioavailability of darunavir in animals and dosing limitation, the plasma exposures were approximately 50% (mice and rats) and 5% (rabbits) of those obtained in humans. In the rat prenatal and postnatal development study, a reduction in pup weight gain was observed with darunavir alone or with ritonavir exposure via breast milk during lactation. In juvenile rats, single doses of darunavir (20 mg/kg–160 mg/kg at ages 5–11 days) or multiple doses of darunavir (40 mg/kg–1000 mg/kg at age 12 days) caused mortality. The deaths were associated with convulsions in some of the animals. Within this age range, exposures in plasma, liver, and brain were dose- and age-dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the cytochrome P450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or mating performance of offspring was not affected by maternal treatment. Fewer than 200 first-trimester pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.

### **Placental and Breast Milk Passage**

No animal studies of placental passage of darunavir have been reported. Although variable transplacental transfer of darunavir has been observed in some case reports, in a study of 14 mother/infant pairs, the median (range) ratio of darunavir concentration in cord blood to that in maternal delivery plasma was 24% (6%–58%).<sup>1,2,3,4,5</sup> Passage of darunavir into breast milk has been noted in rats; whether breast milk passage of darunavir occurs in humans is unknown.

### **Human Studies in Pregnancy**

Currently, limited data exist about darunavir in pregnancy.<sup>1-5</sup> Three intensive pharmacokinetic studies of darunavir/ritonavir administered as 600 mg/100 mg twice a day or 800 mg/100 mg once a day during pregnancy demonstrate 17% to 35% reductions in darunavir plasma concentration during the third trimester compared with postpartum.<sup>1,5</sup> Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy. A study of use of an increased twice-daily darunavir dose during pregnancy is under way. Darunavir plasma protein binding decreases during pregnancy, which increases the unbound plasma darunavir fraction and may partially mitigate the decrease in total darunavir concentration.<sup>1</sup>



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## ***Fosamprenavir (Lexiva, FPV)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only, there was an increase in interstitial cell hyperplasia at higher doses and an increase in uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus the relevance of the uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 1400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily.

### **Reproduction/Fertility**

No impairment of fertility or mating was seen in rats at doses providing 3 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. **No effect was seen on the development or maturation of sperm in rats at these doses.**

### **Teratogenicity/Developmental Toxicity**

Fosamprenavir was studied in rabbits at 0.8 and in rats at 2 times the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination) the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at 2 times human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls. The number of first-trimester exposures to fosamprenavir that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.<sup>1</sup>

### **Placental and Breast Milk Passage**

In a small study of women receiving fosamprenavir during pregnancy, the median (range) amprenavir concentration in cord blood was 0.27 (0.09–0.60) ug/mL and the median (range) ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery was 0.24 (0.06–0.93).<sup>2</sup> **A second small study in pregnancy yielded a similar mean ratio (95% CI) of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (0.24, 0.30).**<sup>3</sup> Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

### **Human Studies in Pregnancy**

Data on fosamprenavir in pregnant women are very limited. Fosamprenavir pharmacokinetic data have been reported in 26 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700

mg and ritonavir 100 mg, fosamprenavir area under the curve and 12-hour trough concentration were somewhat lower during pregnancy and higher postpartum compared to historical data. Fosamprenavir exposure during pregnancy appeared to be adequate for patients without protease inhibitor resistance mutations.<sup>2</sup> A pediatric liquid formulation is approved for children older than age 2 years, but no dosing information is available for neonates.

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## ***Indinavir (Crixivan, IDV)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Indinavir is neither mutagenic nor clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.

### **Reproduction/Fertility**

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

### **Teratogenicity/Developmental Toxicity**

There has been no evidence of teratogenicity or treatment-related effects on embryonic/fetal survival or fetal weights of indinavir in rats, rabbits, or dogs at exposures comparable to, or slightly greater than, therapeutic human exposure. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related, external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold greater than controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester. In Rhesus monkeys, fetal plasma drug levels were approximately 1% to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to indinavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with indinavir. Among cases of first-trimester indinavir exposure reported to the APR, defects have been seen in 2.4% (7/287, 95% CI: 1.0%–5.0%) compared to total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention surveillance of 2.7%.<sup>1</sup>

### **Placental and Breast Milk Passage**

Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In studies of pregnant women receiving unboosted indinavir and their infants, transplacental passage of indinavir was minimal.<sup>2,3</sup> In a study of Thai pregnant women receiving ritonavir-boosted indinavir, median cord blood indinavir concentration was 0.12 ug/mL, median maternal plasma delivery concentration was 0.96 ug/mL, and the median ratio between indinavir concentrations in cord blood and maternal plasma at delivery was 12%.<sup>4</sup> Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels (milk-to-plasma ratio 1.26 to 1.45); whether indinavir is excreted in human milk is unknown.

### **Human Studies in Pregnancy**

The optimal dosing regimen for use of indinavir in pregnant patients has not been established. Two studies of the pharmacokinetics (PKs) of unboosted indinavir (800 mg 3 times/day) during pregnancy demonstrated significantly lower indinavir plasma concentrations during pregnancy than postpartum.<sup>2,5</sup> Use of unboosted indinavir is not recommended in HIV-infected pregnant patients because of the substantially lower

antepartum exposures observed in these studies and the limited experience in this patient population.

Several reports have investigated use of ritonavir-boosted indinavir during pregnancy. In an intensive PK study of 26 Thai pregnant women receiving 400 mg indinavir/100 mg ritonavir twice a day, indinavir plasma concentrations were significantly lower during pregnancy than postpartum. The median trough indinavir concentration was 0.13 ug/mL; 24% of subjects had trough concentrations below 0.10 ug/mL, the target trough concentration used in therapeutic drug monitoring (TDM) programs; and 81% had RNA viral loads <50 copies/mL at delivery.<sup>4</sup> In a study of pregnant French women receiving 400 mg indinavir/100 mg ritonavir twice a day, the median indinavir trough concentration was 0.16 ug/mL, 18% of subjects had trough concentrations below 0.12 ug/mL, and 93% had HIV RNA level <200 copies/mL at delivery.<sup>6</sup> In a small study of two who received indinavir 800 mg and ritonavir 200 mg twice daily, third-trimester indinavir area under the curve exceeded that for historical non-pregnant control.<sup>7</sup> The available data are insufficient to allow for definitive dosing recommendations for use of ritonavir-boosted indinavir during pregnancy.

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## **Ritonavir-Boosted Lopinavir (Kaletra, LPV/r)**

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

LPV/r is classified as FDA Pregnancy Category C.

### **Animal Carcinogenicity Studies**

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The ritonavir-boosted lopinavir (LPV/r) combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increased incidence of benign hepatocellular adenomas and increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on  $AUC_{0-24hr}$  measurement). Administration of LPV/r did not cause a statistically significant increase in incidence of any other benign or malignant neoplasm in mice or rats.<sup>1</sup>

### **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.<sup>1</sup>

### **Teratogenicity/Developmental Toxicity**

No evidence exists of teratogenicity with administration of LPV/r to pregnant rats or rabbits. In rats treated with a maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (e.g., early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations, and skeletal ossification delays) were observed. Drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose. In a perinatal and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred with exposure to 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.<sup>1</sup>

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to LPV/r have been monitored for detection of at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with LPV/r. Among cases of first-trimester exposure to LPV/r reported to the APR, the prevalence of birth defects was 2.4% (23 of 969; 95% CI, 1.5% to 3.5%) compared with a total prevalence of 2.7% in the U.S. population, based on CDC surveillance.<sup>2</sup>

### **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  $0.20 \pm 0.13$ . 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.<sup>3</sup> 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.<sup>4-6</sup>

## Human Studies in Pregnancy

The original capsule formulation of LPV/r has been replaced by a new tablet formulation that is heat-stable, has improved bioavailability characteristics, and does not have to be administered with food.<sup>7,8</sup>

Pharmacokinetic studies of standard adult LPV/r doses (400 mg/100 mg twice a day) using either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with that in non-pregnant adults.<sup>9-11</sup> Increasing dose of LPV/r during pregnancy to 600 mg/150 mg (tablets) results in lopinavir plasma concentrations equivalent to those seen in non-pregnant adults receiving standard doses.<sup>12,13</sup> Reports of clinical experience suggest that most, but not all, pregnant women receiving standard LPV/r tablet dosing during pregnancy will have trough lopinavir concentrations that exceed 1.0 mcg/mL, the usual trough concentration target used in therapeutic drug monitoring programs for antiretroviral-naïve subjects, but not the higher trough concentrations recommended for protease inhibitor-experienced subjects.<sup>7,10</sup> Lopinavir plasma protein binding is reduced during pregnancy, but the resulting increase in free (unbound) drug is insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.<sup>14,15</sup>

These PK studies suggest that LPV/r doses should be increased to 600 mg/150 mg twice a day in all HIV-infected pregnant women during the second and third trimesters. If standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations, if available, should be monitored. An alternative strategy for increasing exposure to LPV/r during pregnancy is to add a pediatric LPV/r tablet (100/25 mg) to the standard dose of two adult 200/50 mg tablets.<sup>15</sup> Once-daily dosing of LPV/r is **not** recommended in pregnancy because no data exist to address whether drug levels are adequate with such administration.

LPV/r oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Reduced hepatic metabolic and kidney excretory function in newborns can lead to accumulation of lopinavir as well as alcohol and propylene glycol, resulting in adverse events such as serious cardiac, renal, metabolic, or respiratory problems. Preterm babies may be at increased risk because their metabolism and elimination of lopinavir, propylene glycol, and alcohol are further reduced. Post-marketing surveillance has identified 10 neonates (i.e., babies aged <4 weeks), nine of whom were born prematurely, who received LPV/r and experienced life-threatening events.<sup>16</sup> In a separate report comparing 50 HIV-exposed newborns treated with LPV/r after birth to 108 HIV-exposed neonates treated with zidovudine alone, elevated concentrations of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21 $\alpha$ -hydroxylase activity, were seen only in the lopinavir-exposed infants. All term infants were asymptomatic but three of eight preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.<sup>17</sup> 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.

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## ***Nelfinavir (Viracept, NFV)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Nelfinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. However, incidence of thyroid follicular cell adenomas and carcinomas was increased over baseline in male rats receiving nelfinavir dosages of 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses).

### **Reproduction/Fertility**

No effect of nelfinavir has been seen on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Maternal exposure to nelfinavir also did not affect subsequent reproductive performance of the offspring.

### **Teratogenicity/Developmental Toxicity**

No evidence of teratogenicity has been observed in pregnant rats at exposures comparable to human exposure and in rabbits with exposures significantly less than human exposure.

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased risk of birth defects in the more common classes of birth defects—the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nelfinavir. Among cases of first-trimester nelfinavir exposure reported to the APR, prevalence of birth defects was 3.9% (47 of 1,207 births; 95% CI, 2.9% to 5.2%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>1</sup>

### **Placental and Breast Milk Transfer**

Transplacental passage of nelfinavir has been minimal to low in humans. In a Phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal.<sup>2</sup> 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.<sup>3</sup> Among 20 mother-infant pairs in the Netherlands, the cord to maternal plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.<sup>4</sup>

Nelfinavir also has low breast milk passage. In a pharmacokinetic (PK) study conducted in Kisumu, Kenya, nelfinavir and its active metabolite M8 concentrations were measured in maternal plasma and breast milk from 26 mothers and from their 27 infants at birth, 2, 6, 14, and 24 weeks among women receiving nelfinavir as part of combination antiretroviral therapy.<sup>5</sup> Peak nelfinavir concentrations in maternal plasma and breast milk were at Week 2. Median breast milk to plasma ratio was 0.12 for nelfinavir and 0.03 for its active metabolite (i.e., M8). Nelfinavir and M8 concentrations were below the limit of detection in 20/28 (71%) infant plasma dried blood spots tested from nine infants over time points from delivery 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.



## Human Studies in Pregnancy

A Phase I/II safety and PK study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants.<sup>2</sup> In the first 9 pregnant HIV-infected women enrolled in the study, nelfinavir administered at a dose of 750 mg three times daily produced drug exposures that were variable and generally lower than those reported in non-pregnant adults with both twice- and three-times-daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1250 mg twice daily), which resulted in adequate levels of the drug in pregnancy. However, in two other small studies of women given 1250 mg nelfinavir twice daily in the second and third trimesters, drug concentrations in the second and third trimesters were somewhat lower than in non-pregnant women.<sup>6,7</sup>

In a PK study of combination therapy including the new nelfinavir 625 mg tablet formulation (given as 1250 mg twice daily) in 25 women at 30 to 36 weeks' gestation (and 12 at 6–12 weeks postpartum), peak levels and area under the curve were lower in the third trimester than postpartum.<sup>8</sup> Only 16% (4 of 25) of women during the third trimester and 8% (1/12) women postpartum had trough values greater than the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

Some nelfinavir manufactured before 2008 may have contained low levels of ethyl methane sulfonate (EMS), a process-related impurity. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data exist in humans and no increase in birth defects has been observed in the APR. All nelfinavir manufactured and released since March 31, 2008, meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients.

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## **Ritonavir (Norvir, RTV)**

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

### **Animal Carcinogenicity Studies**

Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of 50, 100, or 200 mg/kg/day; based on area under the curve, exposure in male mice at the highest dose was approximately 0.3-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.

### **Reproduction/Fertility**

No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.

### **Teratogenicity/Developmental Toxicity**

No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).

In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the APR, the prevalence of birth defects was 2.3% (45 of 1,923 births; 95% CI, 1.7%–3.1%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>1</sup>

### **Placental and Breast Milk Transfer**

Transplacental passage of ritonavir has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses. In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.<sup>2</sup> In a Phase I study of pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal.<sup>3</sup> In addition, in a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 83% and was only 0.38 µg/mL in the remaining woman.<sup>4</sup> In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving ritonavir-boosted-lopinavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested *in utero* transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth and mean infant-to-maternal-hair concentrations at 12 weeks postpartum was 0.47 for ritonavir.<sup>5</sup> However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

### **Human Studies in Pregnancy**

A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in

combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants showed lower levels of ritonavir during pregnancy than postpartum.<sup>3</sup> 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.<sup>6,7</sup>

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## ***Saquinavir (Invirase, SQV)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Saquinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years at plasma exposures approximately 60% of those obtained in humans at the recommended therapeutic dose (rats) and at exposures equivalent to those in humans at the recommended therapeutic dose (mice).

### **Reproduction/Fertility**

No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

### **Teratogenicity/Developmental Toxicity**

No evidence of embryotoxicity or teratogenicity of saquinavir has been found in rabbits or rats. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (area under the curve [AUC] values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Too few first-trimester saquinavir exposures have been monitored by the Antiretroviral Pregnancy Registry to be able to accurately calculate the prevalence of birth defects in exposed cases.<sup>1</sup>

### **Placental and Breast Milk Transfer**

Placental transfer of saquinavir in the rat and rabbit was minimal. In a Phase I study in pregnant women and their infants (PACTG 386, see below), transplacental passage of saquinavir was minimal.<sup>2</sup> In addition, in a study of cord blood samples from eight women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was less than the assay limit of detection in samples from all women.<sup>3</sup> Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

### **Human Studies in Pregnancy**

Studies of saquinavir pharmacokinetics (PK) in pregnancy with the original hard-gel capsule formulation demonstrated reduced saquinavir exposures compared to postpartum and dosing recommendations for 800 to 1200 mg saquinavir with 100 mg ritonavir.<sup>4-8</sup> The PK of saquinavir with the current 500 mg tablets boosted with ritonavir at a dose of 1000 mg saquinavir /100 mg ritonavir given twice daily has been studied in pregnant women in two studies.<sup>9,10</sup> One study performed intensive sampling on HIV-infected pregnant women at 20 weeks' gestation (n = 16), 33 weeks' gestation (n = 31), and 6 weeks postpartum (n = 9). PK parameters were comparable during pregnancy and postpartum.<sup>9</sup> 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.<sup>11</sup> In an observational study of saquinavir concentrations collected as part of clinical care between 11 and 13 hours after dosing with the tablet formulation (1000 mg saquinavir/100 mg ritonavir) in HIV-infected pregnant women during the third trimester (n = 20) and at delivery (n = 5), saquinavir plasma concentrations averaged around 1.15 mg/L and exceeded the usual trough drug concentration target for saquinavir of 0.1 mg/L in all but one subject.<sup>10</sup>

One study of a ritonavir-boosted-saquinavir-based combination antiretroviral drug regimen in 42 pregnant

women reported abnormal transaminase levels in 13 women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity Grade 1–2 in most, Grade 3 in 1 woman).<sup>12</sup> In a study of 62 pregnant women on a saquinavir-ritonavir-based regimen, one severe adverse event occurred (maternal grade 3 hepatotoxicity).<sup>10</sup>

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## ***Tipranavir (Aptivus, TPV)***

**(Last reviewed March 28, 2014; last updated March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Tipranavir was neither mutagenic nor clastogenic in a battery of five *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150, or 300 mg/kg/day tipranavir, 150/40 mg/kg/day ritonavir-boosted tipranavir (TPV/r) in combination, or 40 mg/kg/day ritonavir. Incidence of benign hepatocellular adenomas and combined adenomas/carcinomas was increased in females of all groups except females given the low dose of tipranavir. Such tumors also were increased in male mice at the high dose of tipranavir and in the TPV/r combination group. Incidence of hepatocellular carcinoma was increased in female mice given the high dose of tipranavir and in both sexes receiving TPV/r. The combination of tipranavir and ritonavir caused an exposure-related increase in this same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on area under the curve [AUC] or maximum plasma concentration) at all dose levels tested were below those in humans receiving the recommended dose level. Rats were administered 30, 100, or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day TPV/r in combination, or 10 mg/kg/day ritonavir. No drug-related findings were observed in male rats. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the recommended therapeutic dose. This finding is probably not relevant to humans because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.

### **Reproduction/Fertility**

Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels similar to human exposures at the recommended clinical dose (500/200 mg/day of TPV/r).

### **Teratogenicity/Developmental Toxicity**

No teratogenicity was detected in studies of pregnant rats and rabbits at exposure levels approximately 1.1-fold and 0.1-fold human exposure. Fetal toxicity (decreased ossification and body weights) was observed in rats exposed to 400 mg/kg/day or more of tipranavir (~0.8-fold human exposure). Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold human exposures. In rats, no adverse effects on development were seen at levels of 40 mg/kg/day (~0.2-fold human exposure), but at 400 mg/kg/day (~0.8-fold human exposure), growth inhibition in pups and maternal toxicity were seen.

The number of first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.<sup>1</sup>

### **Placental and Breast Milk Passage**

No animal studies of placental or breast milk passage of tipranavir have been reported. It is unknown if placental or breast milk passage of tipranavir occurs in humans.

### **Human Studies in Pregnancy**

No studies of tipranavir have been completed in pregnant women or neonates. A case report with pharmacokinetic measurements of tipranavir used in a single pregnancy showed relatively high levels of tipranavir in the third trimester and relatively high placental transfer (0.41), as measured by cord blood.<sup>2</sup> Whether this finding will be applicable to other pregnancies is unclear.



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## Entry Inhibitors

(Last updated March 28, 2014; last reviewed March 28, 2014)

### 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

Two drugs have been approved in this class of antiretroviral (ARV) drugs aimed at inhibiting viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein (gp)120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor such as CCR5 or CXCR4 on the host cell; binding of gp120 to the co-receptor causes subsequent conformational changes in the viral transmembrane gp41, exposing the fusion peptide of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a zipping together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous (SQ) administration, is a synthetic 36-amino-acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41, and the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other ARV drugs to treat advanced HIV infection in adults and children aged 6 years or older. Maraviroc interferes with viral entry at the chemokine co-receptor level; it is a CCR5 co-receptor antagonist approved for combination therapy for HIV infection in adults infected with CCR5-tropic virus.

### ***Enfuvirtide (Fuzeon, T-20)***

(Last updated March 28, 2014; last reviewed March 28, 2014)

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

#### **Animal Carcinogenicity Studies**

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

#### **Reproduction/Fertility Animal Studies**

Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up to 30 mg/kg/day administered SQ (1.6 times the maximum recommended adult human daily dose on an m<sup>2</sup> body surface area basis).

#### **Teratogenicity/Developmental Toxicity Animal Studies**

Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.2 times, respectively, the adult human daily dose on an m<sup>2</sup> basis.

#### **Placental and Breast Milk Passage**

*In vitro* and *in vivo* studies suggest that enfuvirtide does not readily cross the human placenta. Published reports of a total of 8 peripartum patients and their neonates and data from an *ex vivo* human placental

cotyledon perfusion model demonstrated minimal placental passage of enfuvirtide.<sup>1-5</sup> Studies of radiolabeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not known if this reflected radiolabeled enfuvirtide or metabolites (e.g., amino acid and peptide fragments) of enfuvirtide.

### Human Studies in Pregnancy

Data on the use of enfuvirtide in human pregnancy are limited to case reports of a small number of women treated with the drug.<sup>1,5-10</sup>

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## ***Maraviroc (Selzentry, MVC)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

Maraviroc is classified as Food and Drug Administration (FDA) Pregnancy Category B.

### **Animal Carcinogenicity Studies**

Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of maraviroc showed no drug-related increases in tumor incidence.

### **Reproduction/Fertility Animal Studies**

Reproductive toxicity has been evaluated in rats and rabbits. Maraviroc produced no adverse effects on fertility of male or female rats at doses with exposures (area under the curve [AUC]) up to 20-fold higher than in humans given the recommended 300 mg twice-daily dose.

### **Teratogenicity/Developmental Toxicity Animal Studies**

The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies in rats at AUC approximately 20-fold higher (and in rabbits at approximately 5-fold higher) than human exposures at the recommended 300 mg, twice-daily dose (up to 1000 mg/kg/day in rats and 75 mg/kg/day in rabbits).

### **Placental and Breast Milk Passage**

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.<sup>1</sup> This was also demonstrated in a study of single-dose maraviroc in rhesus macaques that showed poor placental transfer and rapid clearance from infant monkeys' blood.<sup>2</sup> In a study in humans of six mother/infant pairs, the median ratio of cord blood to maternal plasma drug concentrations was 0.33 (0.03–0.56).<sup>3</sup> Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. Whether maraviroc is secreted into human milk is unknown.

### **Human Studies in Pregnancy**

Safety and efficacy of maraviroc have not been established in pregnancy. Data on the use of maraviroc in human pregnancy are limited to a small pharmacokinetic study that found exposure to maraviroc was 21% lower during the third trimester than postpartum.<sup>3</sup> The Antiretroviral Pregnancy Registry lists only 13 pregnancies with first-trimester exposure to entry inhibitors, with no malformations noted.<sup>4</sup>

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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

Three drugs have been approved in this new class of antiretroviral (ARV) drugs aimed at inhibiting integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA and a final “strand transfer” step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step in the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects retrotranscription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

### ***Dolutegravir (Tivicay, DTG)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

#### **Animal Carcinogenicity Studies**

Dolutegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year long-term studies in mice at exposures up to 14-fold higher than that achieved with human systemic exposure at the recommended dose, or in rats at exposures up to 10-fold higher in males and 15-fold higher in females than human exposure at the recommended dose.

#### **Reproduction/Fertility Animal Studies**

Dolutegravir did not affect fertility in male and female rats and rabbits at exposures approximately 27-fold higher than human clinical exposure, based on area under the curve, at the recommended dose.

#### **Teratogenicity/Developmental Toxicity Animal Studies**

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

#### **Placental and Breast Milk Passage**

Studies in rats have demonstrated that dolutegravir crosses the placenta in animal studies and is excreted into breast milk in rats. No human data on placental passage or breast milk excretion are available.

#### **Human Studies in Pregnancy**

No studies of dolutegravir use in human pregnancy have been reported.



***Elvitegravir (Only Available as Stribild [Co-Formulated with Cobicistat/Tenofovir/Emtricitabine], EVG/COBI/TDF/FTC)***

is classified as Food and Drug Administration Pregnancy Category B.

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

**Animal Carcinogenicity Studies**

Elvitegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in long-term studies in mice at exposures up to 14-fold and rats at exposures up to 27-fold that achieved human systemic exposure at the recommended dose. Cobicistat was not genotoxic or mutagenic *in vitro*. Long-term carcinogenicity testing is ongoing for cobicistat.

**Reproduction/Fertility Animal Studies**

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures than in humans at standard dosing. Fertility was normal in offspring. Cobicistat did not affect fertility in male and female rats at exposures approximately 4-fold higher than in humans. Fertility was normal in exposed offspring.

**Teratogenicity/Developmental Toxicity Animal Studies**

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

**Placental and Breast Milk Passage**

Studies in rats have demonstrated that elvitegravir and cobicistat are secreted in milk. No human data are available for either drug. No data on placental passage are available for elvitegravir or cobicistat.

**Human Studies in Pregnancy**

No studies of elvitegravir/cobicistat use in human pregnancy have been reported.

## ***Raltegravir (Isentress, RAL)***

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

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

### **Animal Carcinogenicity Studies**

Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.

Long-term carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential at systemic exposures 1.8-fold (females) or 1.2-fold (males) greater than human exposure at the recommended dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir (exposure 3-fold higher than in humans at the recommended adult dose) for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats receiving doses resulting in systemic exposures that were 1.7-fold (males) to 1.4-fold (females) greater than the human exposure at the recommended dose.

### **Reproduction/Fertility Animal Studies**

Raltegravir produced no adverse effects on fertility of male or female rats at doses up to 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended adult human dose).

### **Teratogenicity/Developmental Toxicity Animal Studies**

Studies in rats and rabbits revealed no evidence of treatment-related effects on embryonic/fetal survival or fetal weights from raltegravir administered in doses producing systemic exposures approximately 3- to 4-fold higher than the exposure at the recommended adult human daily dose. In rabbits, no treatment-related external, visceral, or skeletal changes were observed. However, treatment-related increases in the incidence of supernumerary ribs were seen in rats given raltegravir at 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended human daily dose).

### **Placental and Breast Milk Passage**

Placental transfer of raltegravir was demonstrated in both rats and rabbits. In rats given a maternal dose of 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5- to 2.5-fold higher than in maternal plasma at 1 and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentrations in fetal plasma were approximately 2% of the mean maternal plasma concentration at both 1 and 24 hours following a maternal dose of 1000 mg/kg/day.

In humans, raltegravir appears to readily cross the placenta. In P1026s, maternal and cord blood from six deliveries of mothers receiving raltegravir-based therapy during pregnancy were evaluated; the ratio of cord blood to maternal plasma was 0.98 (95% confidence interval, 0.09–2.26).<sup>1</sup> Other case reports have shown similarly high cord blood/maternal blood drug level ratios of 1.00 to 1.06.<sup>2,3</sup> In a report of three pregnant women with multiresistant HIV-1 who were given raltegravir in late pregnancy to rapidly reduce maternal viral load, raltegravir concentrations within 3 hours of delivery in the neonates of two patients were approximately 7 and 9.5 times higher than in the mother's paired sample; in the third infant, maternal plasma was not available but neonatal concentration was still high 2.5 hours after delivery.<sup>4</sup> However, no adverse reactions were observed in mothers or infants. In a series of three cases with preterm deliveries at 29 to 33 weeks' gestation (in 2 cases raltegravir was added to the maternal antiretroviral regimen shortly before anticipated preterm delivery), cord blood-to-maternal-plasma ratios ranged from 0.44 to 1.88.<sup>5</sup>

Raltegravir is secreted in the milk of lactating rats, with mean drug concentrations in milk about 3-fold higher than in maternal plasma at a maternal dose of 600 mg/kg/day. No effects in rat offspring were attributable to raltegravir exposure through breast milk. Whether raltegravir is secreted in human breast milk is unknown.

## Human Studies in Pregnancy

Only limited data exist on the use of raltegravir in pregnancy. Raltegravir pharmacokinetics (PK) were evaluated in 10 women in the IMPAACT P1026s study. Raltegravir PKs showed extensive variability but did not appear to be consistently altered during the third trimester compared with postpartum and historical data in non-pregnant individuals; thus the standard dose appears appropriate in pregnancy.<sup>1</sup> In multiple case reports and case series of 4, 5, and 14 pregnant women treated with raltegravir in combination with 2 or 3 other antiretroviral drugs because of persistent viremia or late presentation, the drug was well tolerated and led to rapid reduction in HIV RNA levels.<sup>6-10</sup> However, in one case of similar use, 10- to 23-fold increases in liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.<sup>11</sup> Drug levels were not measured in any of those studies.

Because raltegravir is highly protein bound to albumin, there is concern about displacement of bilirubin from albumin in the neonate potentially increasing the risk of neonatal hyperbilirubinemia. In an *in vitro* study of the effect of raltegravir on bilirubin-albumin binding, raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5  $\mu\text{M}$  and 10  $\mu\text{M}$ , caused a small but statistically significant increase in unbound bilirubin at 100  $\mu\text{M}$ , and caused potentially harmful increases at 500 and 1000  $\mu\text{M}$ .<sup>12</sup> These data suggest that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant at typical peak concentrations reached in adults with usual dosing (adult concentrations with standard raltegravir doses were geometric mean  $C_{\text{max}}$  of 4.5  $\mu\text{M}$ , median  $C_{\text{max}}$  of 6.5  $\mu\text{M}$  and maximum observed  $C_{\text{max}}$  of 10.2  $\mu\text{M}$ ).<sup>12</sup> Raltegravir should not be used in neonates until PK and toxicity studies have been completed.

Chewable tablets contain phenylalanine.

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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 March 28, 2014; last reviewed March 28, 2014)

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<b>Acronym/Abbreviation</b>	<b>Full Name</b>
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
AP	antepartum
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
AUC	area under the curve
AZT	zidovudine
BID	twice daily
BMI	body mass index
cART	combination antiretroviral therapy
CBC	complete blood count
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	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	ritonavir-boosted darunavir

DTG	dolutegravir
DSMB	Data and Safety Monitoring Board
EC	enteric coated
ECG	electrocardiogram
EFV	efavirenz
EMS	ethyl methane sulfonate
EPPICC	The European Pregnancy and Paediatric HIV Cohort Collaboration
ETR	etravirine
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed drug combination
FPV	fosamprenavir
FPV/r	ritonavir-boosted fosamprenavir
FTC	emtricitabine
gp	glycoprotein
HAV	hepatitis A virus
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelets
HGC	hard gel capsule
HR	hazard ratio
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
IC <sub>50</sub>	inhibitory concentration 50%
IDV	indinavir
IDV/r	ritonavir-boosted indinavir
IGF	insulin-like growth factor
IP	intrapartum
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
IUD	intrauterine device
IV	intravenous/intravenously
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir
MAC	<i>Mycobacterium avium</i> complex
MACDP	Metropolitan Atlanta Congenital Defects Program
MIRIAD	Mother-Infant Rapid Intervention at Delivery (study)

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
PACTG	Pediatric AIDS Clinical Trials Group
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	ritonavir-boosted saquinavir
STD	sexually transmitted disease
T20	enfuvirtide
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TID	three times daily

TPV	tipranavir
TPV/r	ritonavir-boosted tipranavir
UGT	uridine diphosphate glucuronosyltransferase
WHO	World Health Organization
WITS	Women and Infants Transmission Study
ZDV	zidovudine