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

September 14, 2011

Revisions to the May 24, 2010 Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV-1-Transmission in the United States have been made by the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission

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. Sep. 14, 2011; pp 1-207. Available at http://aidsinfo.nih.gov/contentfiles/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 AIDS*info* Web site (http://aidsinfo.nih.gov).

access AIDS*info* mobile site

What's New in the Guidelines? (Updated September 14, 2011)

Key changes made to update the May 24, 2010, version of the guidelines are summarized below. Throughout the revised guidelines, significant updates are highlighted and discussed.

- **Lessons Learned from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal Transmission and Table 3 (Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV):**
    - This section and Table 3 include updates on recent results from international clinical trials, including HPTN 046 in breastfeeding infants, which demonstrated that extending infant nevirapine prophylaxis from 6 weeks to 6 months improved efficacy in reducing postnatal infections, and NICHD-HPTN 040/PACTG 1043 in formula-feeding infants, which demonstrated that when mothers have not received antepartum antiretroviral (ARV) drugs, combination infant ARV prophylaxis reduces intrapartum transmission more than the standard 6-week infant zidovudine regimen.
- **Preconception Care and Table 4 (Drug Interactions Between Hormonal Contraceptives and Antiretroviral Agents):**
    - This section includes a new subsection on Reproductive Options for HIV Concordant and Serodiscordant Couples. The subsection includes discussion of HPTN 052 trial in discordant couples, which demonstrated that initiating antiretroviral therapy (ART) in infected individuals with CD4 cell counts from 350 to 550 cells/mm^3 reduced the risk of transmission to seronegative partners. The subsection also includes discussion on trials of pre-exposure ARV prophylaxis.
    - The section includes a new Table (Table 4) on drug interactions between hormonal contraceptives and ARV drugs.
- **Recommendations for Use of Antiretroviral Drugs during Pregnancy and Table 5 (Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy):**
    - Table 5 on ARV drugs in pregnancy has been revised to include drug formulation and dosing information in addition to pregnancy-related pharmacokinetic and toxicity data and recommendations for use in pregnancy. Table 5 also includes the newly approved drug rilpivirine.
    - There is expanded discussion on treatment recommendations for adults and postpartum discontinuation of ARV drug regimens.
    - Tenofovir has moved from a nucleoside reverse transcriptase inhibitor (NRTI) for *Use in Special Considerations* to an *Alternative* NRTI choice; it is the *Preferred* NRTI choice for women who are co-infected with HIV and hepatitis B virus.
    - Indinavir and nelfinavir have moved from *Alternative* protease inhibitor (PI) choices to PIs to *Use in Special Circumstances*.
- **HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive):** This section includes expanded discussion of new data suggesting early and sustained control of HIV viral replication is associated with decreased transmission in women who have undetectable viral load at delivery—data which favors initiation of ARV drugs as early in pregnancy as possible for all women.

- **HIV/Hepatitis B Coinfection:** The Panel now recommends combination ARV drug regimens including anti-hepatitis B drugs for all HIV-infected pregnant women with hepatitis B virus (HBV) coinfection:
  - All pregnant women with HIV/HBV coinfection should receive a combination ARV drug regimen, 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 NRTI/NtRTI backbone of a combination antepartum ARV regimen in HIV/HBV-coinfected pregnant women **(AI)**.
- **Acute HIV Infection:** This is a new section discussing diagnosis and management of acute HIV-1 infection in pregnancy.
- **HIV-2 Infection and Pregnancy:** This is a new section discussing diagnosis and management of HIV-2 infection in pregnancy.
- **Combination Antiretroviral Drugs and Pregnancy Outcome:** Data from several new studies on preterm delivery and combination ARV drug regimens are reviewed in this section. The Panel notes the following:
  - Clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving PI-based combination ARV regimens; however, given the clear benefits of such regimens for both the women's health and the prevention of mother-to-child transmission, PIs should not be withheld for fear of altering pregnancy outcome **(AII)**.
- **Intrapartum Antiretroviral Therapy/Prophylaxis:** Based on the results of the NICHD-HPTN 040/P1043 clinical trial, the Panel's no longer recommends intrapartum single-dose nevirapine for HIV-infected women in labor who have not received antepartum drugs. In this circumstance, the Panel recommends the following:
  - Intravenous zidovudine is recommended for HIV-infected women in labor who have not received antepartum ARV drugs, and infant combination ARV prophylaxis is recommended for 6 weeks (see Infant Antiretroviral Prophylaxis) **(AII)**.
- **Postpartum Care:** This section includes expanded discussion of considerations regarding stopping ARVs postpartum, including discussion of results of HPTN 052 and of the importance of counseling on safer sex practices and contraception during the postpartum period.
- **Infant Antiretroviral Prophylaxis and Table 9 (Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs in Special Circumstances Based on NICHD-HPTN 040/PACTG 1043 Regimen):**
  - The Panel now recommends that twice daily dosing can be used for the 6-week zidovudine prophylaxis regimen in full-term infants.
    - The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 4 mg/kg body weight orally twice daily for the first 6 weeks of life, beginning as soon after birth as possible and preferably within 6–12 hours of delivery.
  - The design and results of the NICHD-HPTN 040/PACTG 1043 clinical trial in formula-fed infants are discussed. The trial demonstrated that when mothers have not received antepartum ARV drugs, combination infant ARV prophylaxis reduces intrapartum transmission more than the standard 6-week infant zidovudine regimen. Based on these data, the Panel's recommendation is now:

- Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen, started as soon after birth as possible (AI). A randomized, controlled trial has shown that a 2-drug regimen of zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) is as effective as but less toxic than a 3-drug regimen of zidovudine, nelfinavir and lamivudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States. (see General Considerations for Choice of Infant Prophylaxis and Table 9) **(AI)**.

- Table 9 includes the dosing for the 2-drug regimen used in the NICHD-HPTN 040/PACTG 1043 trial.
- A new subsection is included on management of breastfeeding infants of mothers first diagnosed with HIV infection during the postpartum period.
- Discussion on revised guidance for use of lopinavir/ritonavir in neonates is provided. Lopinavir/ritonavir 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 since birth) of 42 weeks and a postnatal age of at least 14 days.

Members of the Panel 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

Revisions to the May 24, 2010, *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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Introduction (Updated September 14, 2011)

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[1-2]. 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[3-5].

These guidelines update the May 24, 2010, 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 (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), 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 disease in pregnant women are rapidly evolving and will consider new evidence and adjust recommendations accordingly. The updated guidelines are available from the AIDS*info* Web site (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. antiretroviral treatment (ART) 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[2, 6]. After provider counseling and discussion on ARV drug use during pregnancy, a pregnant woman's informed choice on whether to take ARV drugs either for her treatment or for prevention of mother-to-child transmission 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 the 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
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in pregnant women for treatment of HIV infection and for prevention of mother-to-child transmission of HIV in the United States.
Panel members	The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (such as training in either obstetrics/gynecology or women's health) and interventions to prevent mother-to-child transmission (such as specialized training in pediatric HIV infection) as well as community representatives with knowledge of HIV infection in pregnant women and interventions to prevent mother-to-child 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 (HHS) agencies: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. All Panel members are listed on the Panel Roster on Page iv of the guidelines.
Financial disclosures	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Funding source	Office of AIDS Research (OAR), NIH
Evidence collection	The recommendations in these guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	See Table 2.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members 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.
Other guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines outline the use of antiretroviral therapy (ART) in nonpregnant HIV-infected adults and adolescents, HIV-infected children, and people who experience occupational or nonoccupational exposure to HIV. The guidelines described are also available on the AIDS*info* Web site (http://www.aidsinfo.nih.gov). Preconception management for nonpregnant women of reproductive age is briefly discussed in this document. However, for more detailed discussion on issues of treatment of nonpregnant adults, the Working Group defers to the designated expertise offered by Panels that have developed those guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, new dosing formulations, or changes in dosing frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and accompanying recommendations on the AIDS*info* Web site until the guidelines can be updated with appropriate changes. Updated guidelines are available at the AIDS*info* Web site (http://www.aidsinfo.nih.gov).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* Web site. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Basis for Recommendations

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

Table 2. Rating Scheme for Recommendations

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

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Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal Transmission of HIV (Updated September 14, 2011)

Overview

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 the pregnant woman and her infant could reduce the risk of perinatal transmission by nearly 70%[1]. Following the results of PACTG 076, in the United States and in other resource-abundant countries, implementation of the zidovudine regimen coupled with increased antenatal HIV counseling and testing rapidly resulted in significant declines in transmission[2-5]. Subsequent clinical trials and observational studies demonstrated that combination antiretroviral (ARV) prophylaxis (initially dual- and then triple- combination therapy) given to the mother antenatally was associated with further declines in transmission to less than 2%[2, 6-7]. It is currently estimated that fewer than 200 HIV-infected infants are now born each year in the United States[4, 8].

Each individual birth of an infected infant is a sentinel event representing missed opportunities and barriers to prevention[9-10]. Important obstacles to eradication of perinatal transmission in the United States include the continued increase of HIV infection among women of childbearing age; absent or delayed prenatal care, particularly in women using illicit drugs; acute (primary) infection in late pregnancy and in women who are breastfeeding; poor adherence to prescribed ARV regimens among pregnant women; and lack of full implementation of routine, universal prenatal HIV counseling and testing[10].

Following the results of PACTG 076, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. Clinical trials initially focused on shortened zidovudine-alone prophylaxis regimens and moved to evaluating whether combination ARV regimens, such as short-course zidovudine combined with lamivudine, might have improved efficacy over zidovudine alone. Studies also evaluated whether even simpler, less expensive, single-drug regimens, such as single-dose intrapartum/neonatal nevirapine, would be effective and whether combining such regimens with other short-course regimens might result in improved efficacy. These studies have provided important insights into the mechanisms of action of ARV drugs in reducing perinatal transmission and in determining optimal regimens for use in the United States and other resource-rich countries.

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Mechanisms of Action of Antiretroviral Prophylaxis in Reducing Perinatal Transmission of HIV (Updated September 14, 2011)

Panel's Recommendations
• Antiretroviral (ARV) drugs reduce perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and providing infant pre- and post-exposure prophylaxis. Therefore, combined antepartum, intrapartum, and infant ARV prophylaxis is recommended to prevent perinatal transmission of HIV **(AI)**.

Zidovudine and other ARV drugs can reduce perinatal transmission through a number of mechanisms. Antenatal drug administration decreases maternal viral load in blood and genital secretions, which is a particularly important mechanism of action in women with high viral loads. Even among women with HIV RNA levels <1,000 copies/mL, however, ARV drugs have been shown to reduce the risk of transmission[1]. In addition, the level of HIV RNA at delivery and receipt of antenatal ARV drugs are independently associated with risk of transmission, suggesting that reduction in viral load is not solely responsible for the efficacy of ARV prophylaxis[2-3].

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. This mechanism of protection likely is particularly important during passage through the birth canal, a time when infants receive intensive exposure to maternal genital-tract virus. Infant post-exposure prophylaxis is achieved by administering drugs to infants after birth. This intervention provides protection from cell-free or cell-associated virus that may have entered the fetal/infant systemic circulation through maternal-fetal transfusion associated with uterine contractions during labor or systemic dissemination of virus swallowed during infant passage through the birth canal.

The efficacy of ARV drugs in reducing perinatal transmission likely is multifactorial, and each of the mechanisms previously described may make a contribution. 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, discussed in the next section[4-10].

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Lessons from International Clinical Trials of Short-Course Antiretroviral Regimens for Prevention of Perinatal Transmission of HIV (Updated September 14, 2011)

Panel's Recommendations
• All pregnant women who require therapy for their own health should receive a combination antepartum antiretroviral (ARV) drug regimen containing at least three drugs for treatment, which will also reduce the risk of perinatal transmission **(AI)**. • Combination antepartum drug regimens are also recommended for prevention of perinatal transmission in women who do not yet require therapy for their own health **(AII)**. • ARV prophylaxis is more effective when given for a longer than a shorter duration. Therefore, ARV drugs should be started as soon as possible in women who require treatment for their own health **(AI)**, and without delay after the first trimester in women who do not require immediate initiation of therapy for their own health, although earlier initiation can be considered in these women as well **(BIII)** (see Recommendations for Use of Antiretroviral Drugs during Pregnancy). • In the absence of antepartum administration of ARV drugs, ARV drugs should be administered intrapartum in combination with infant ARV prophylaxis to reduce the risk of perinatal transmission (see Intrapartum Care) **(AI)**; if antepartum and intrapartum ARV drugs are not received, infant ARV prophylaxis should be provided (see Infant Antiretroviral Prophylaxis) **(AI)**. • Adding single-dose intrapartum/newborn nevirapine to the standard antepartum combination ARV regimens used for prophylaxis or treatment in pregnant women in the United States is not recommended. This is because the drug does not appear to provide additional efficacy in reducing transmission and it may be associated with development of nevirapine resistance **(AI)**. • Breastfeeding is not recommended for HIV-infected women in the United States—including those receiving combination antiretroviral therapy (ART)—because safe, affordable, and feasible alternatives are available **(AII)**.

A number of simple regimens have been identified that are effective in reducing perinatal transmission in resource-limited countries (see Table 3). Direct comparison of results from trials of these regimens are difficult because the studies involved diverse patient populations residing in different geographic locations, infected with various viral subtypes, and with different infant feeding practices. However, some general conclusions can be drawn from the results, which are relevant to understanding use of ARV drugs for prevention of perinatal transmission in both resource-limited and resource-rich countries.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 1 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
PACTG 076 United States, France[1] Formula feeding	ZDV vs. placebo	Long (from 14 weeks) IV IP	Long (6 weeks), infant only	• MTCT at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).
CDC short-course ZDV trial Thailand[2] Formula feeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	• MTCT at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).
DITRAME (ANRS 049a) trial Ivory Coast, Burkina Faso[3-4] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother only	• MTCT 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). • MTCT was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
CDC short-course ZDV trial Ivory Coast[4-5] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	• MTCT was 16.5% in ZDV arm vs. 26.1% in placebo arm at 3 months (37% efficacy). • MTCT was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
PETRA trial South Africa, Tanzania, and Uganda[6] Breastfeeding and formula feeding	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	• MTCT 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). • MTCT 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).
HIVNET 012 trial Uganda[7] Breastfeeding	sdNVP vs. ZDV	No AP ARV Oral IP: sdNVP vs. oral ZDV	sdNVP within 72 hours of birth (infant only) vs. ZDV (1 week), infant only	• MTCT 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).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 2 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
SAINT trial South Africa[8] Breastfeeding and formula feeding	sdNVP vs. ZDV + 3TC	No AP ARV Oral IP: sdNVP vs. ZDV + 3TC	sdNVP within 48 hours of birth (mother and infant) vs. ZDV + 3TC (1 week), mother and infant	• MTCT was 12.3% in sdNVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, P = 0.11).
Perinatal HIV Prevention Trial (PHPT-1) Thailand[9] Formula feeding	Four ZDV regimens with different durations of AP and infant PP administration, no placebo	Long (from 28 weeks), short (from 36 weeks) Oral IP	Long (6 weeks), short (3 days), infant only	• Short-short arm stopped at interim analysis (10.5%). MTCT was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm at 6 months (no statistical difference). *In utero* transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).
PACTG 316 trial Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States[10] Formula feeding	sdNVP vs. placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)	Nonstudy ARV regimen Oral IP: placebo vs. sdNVP + IV ZDV	Placebo vs. sdNVP 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 due to very low MTCT in both arms: 1.4% in sdNVP arm vs. 1.6% in placebo arm (53% of MTCT was *in utero*).
Perinatal HIV Prevention Trial (PHPT-2) Thailand[11] Formula feeding	ZDV alone vs. ZDV + maternal and infant sdNVP vs. ZDV + maternal sdNVP	ZDV from 28 weeks Oral IP: ZDV alone or ZDV + sdNVP	ZDV for 1 week with or without sdNVP, infant only	• ZDV-alone arm was stopped due to higher MTCT than the NVP-NVP arm (6.3% vs. 1.1%). In arms in which the mother received sdNVP, MTCT rate did not differ significantly between the infant receiving or not receiving sdNVP (2.0% vs. 2.8%).
DITRAME Plus (ANRS 1201.0) trial Ivory Coast[12] Breastfeeding and formula feeding	Open label, ZDV + sdNVP	ZDV from 36 weeks Oral IP: ZDV plus sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 6.5% (95% CI, 3.9%–9.1%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) trial Ivory Coast[12] Breastfeeding and formula feeding	Open label, ZDV + 3TC + sdNVP	ZDV + 3TC from 32 weeks (stopped at 3 days PP) Oral IP: ZDV + 3TC + sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 4.7% (95% CI, 2.4%–7.0%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 3 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
NVAZ trial Malawi[13] Breastfeeding	Neonatal sdNVP vs. sdNVP + ZDV	No AP or IP ARV (latecomers)	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 15.3% in sdNVP + ZDV arm and 20.9% in sdNVP-only arm at 6–8 weeks. MTCT rate at 6–8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP + ZDV trial Malawi[14] Breastfeeding	Neonatal sdNVP vs. sdNVP + ZDV	No AP ARV Oral IP: sdNVP	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 16.3% in NVP + ZDV arm and 14.1% in sdNVP-only arm at 6–8 weeks (difference not statistically significant). MTCT rate at 6–8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.
Post-exposure Infant Prophylaxis South Africa[15] Breastfeeding and formula feeding	Neonatal sdNVP vs. ZDV for 6 weeks	No AP or IP ARV	sdNVP vs. ZDV for 6 weeks	• For formula-fed infants only, MTCT was 14.3% in sdNVP arm vs. 14.1% in ZDV arm at 6 weeks (not significant, $P = 0.30$). For breastfed infants only, MTCT was 12.2% in sdNVP arm and 19.6% in ZDV arm ($P = 0.03$).
Mashi Botswana[16-17] Breastfeeding and formula feeding	**Initial:** short-course ZDV with/without maternal and infant sdNVP and with/without breastfeeding **Revised:** short-course ZDV + infant sdNVP with/without maternal sdNVP and with/without breastfeeding; women with CD4 cell counts <200 cells/mm^3 receive combination therapy	1st randomization ZDV from 34 weeks Oral IP: ZDV + either sdNVP vs. placebo	2nd randomization Breastfeeding + ZDV (infant) 6 months + sdNVP, infant only vs. Formula feeding + ZDV (infant) 4 weeks + sdNVP, infant only	• **Initial design:** In formula-feeding arm, MTCT at 1 month was 2.4% in maternal and infant sdNVP arm and 8.3% in placebo arm (P = 0.05). In breastfeeding + infant ZDV arm, MTCT at 1 month was 8.4% in sdNVP arm and 4.1% in placebo arm (difference not statistically significant). • **Revised design:** MTCT at 1 month was 4.3% in maternal + infant sdNVP arm and 3.7% in maternal placebo + infant sdNVP arm (no significant difference; no interaction with mode of infant feeding). • MTCT 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 vs. 14.2% formula-feeding arm.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 4 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
SWEN Uganda, Ethiopia, India[18] Breastfeeding	sdNVP vs. NVP for 6 weeks	No AP ARV Oral IP: sdNVP	Infant sdNVP vs. NVP for 6 weeks	• Postnatal infection in infants uninfected at birth: - MTCT at 6 weeks was 5.3% in sdNVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, $P = 0.009$). - MTCT at 6 months was 9.0% in sdNVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, $P = 0.16$). • HIV-free survival significantly lower in extended NVP arm at both 6 weeks and 6 months of age.
PEPI-Malawi Trial Malawi[19] Breastfeeding	sdNVP + ZDV for 1 week (control) vs. two extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV Oral IP: sdNVP (if mother presents in time)	Infant sdNVP + ZDV for 1 week (control) vs. control + NVP for 14 weeks vs. control + NVP/ZDV for 14 weeks	• Postnatal infection in infants uninfected at birth: - MTCT 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). - MTCT at age 9 months was 10.6% in control vs. 5.2% in extended NVP (51% efficacy) and 6.4% in extended NVP/ZDV arms (40% efficacy). • No significant difference in MTCT between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV.
MITRA Tanzania[20] Breastfeeding	Infant 3TC for 6 months (observational)	ZDV/3TC from 36 weeks through labor	Maternal ZDV/3TC for 1 week; infant 3TC for 6 months	• MTCT at age 6 months was 4.9% (postnatal MTCT between ages 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study (KiBS) Kenya[21] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 cell count >250 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 cell count >250 cells/mm^3) for 6 months; infant sdNVP	• MTCT at age 6 months was 5.0% (postnatal MTCT between ages 7 days and 6 months was 2.6%).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 5 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
MITRA-PLUS Tanzania[22] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 cell count >200 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 cell count >200 cells/mm^3) for 6 months; infant ZDV/3TC for 1 week	• MTCT at age 6 months was 5.0% (postnatal MTCT between ages 6 weeks and 6 months was 0.9%), not significantly different from 6 months infant prophylaxis in MITRA.
Kesho Bora Multi-African[23] Breastfeeding primarily	Antepartum ZDV/sdNVP with no postnatal prophylaxis vs. maternal triple-drug prophylaxis in women with CD4 cell counts of 200–500 cells/mm^3	**Arm 1:** ZDV/3TC/LPV/r **Arm 2:** ZDV + sdNVP From 28 weeks through labor	**Arm 1:** Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 1 week **Arm 2:** Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis); infant sdNVP + ZDV for 1 week (no further postnatal prophylaxis)	• MTCT at birth was 1.8% with maternal triple-drug prophylaxis Arm 1 and 2.5% with ZDV/sdNVP Arm 2, not significantly different. In women with CD4 cell counts 350–500 cells/mm^3, MTCT at birth was 1.7% in both arms. • MTCT at age 12 months was 5.4% with maternal triple-drug prophylaxis Arm 1 and 9.5% with ZDV/sdNVP (with no further postnatal prophylaxis after 1 week) Arm 2 (P = 0.029).
Mma Bana Botswana[24] Breastfeeding	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 cell counts >200 cells/mm^3	**Arm 1:** ZDV/3TC/ABC **Arm 2:** ZDV/3TC/LPV/r From 26 weeks through labor	**Arm 1:** Maternal ZDV/3TC/ABC for 6 months; infant sdNVP + ZDV for 4 weeks **Arm 2:** Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 4 weeks	• MTCT at age 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 and 0.4% in ZDV/3TC/LPV/r Arm 2 (P = 0.53).
BAN Malawi[25] Breastfeeding	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 cell counts ≥250 cells/mm^3	No AP drugs IP regimens: **Arm 1 (control):** ZDV/3TC + sdNVP **Arm 2:** ZDV/3TC + sdNVP **Arm 3:** ZDV/3TC + sdNVP	**Arm 1 (control):** Maternal ZDV/3TC for 1 week; infant sdNVP + ZDV/3TC for 1 week **Arm 2:** Control as above, then maternal ZDV/3TC/LPV/r for 6 months **Arm 3:** Control as above, then infant NVP for 6 months	• Postnatal infection in infants uninfected at age 2 weeks: - MTCT 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). • No significant difference between maternal triple-drug prophylaxis Arm 2 and infant NVP Arm 3 (P = 0.12).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 6 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intra-partum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
HPTN 046[26] South Africa, Tanzania, Uganda, Zimbabwe Breastfeeding	Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks. **Arm 1:** Daily infant NVP from 6 weeks through 6 months of age **Arm 2:** Daily infant placebo from 6 weeks through age 6 months of age	• 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-ARV regimen for treatment of HIV. • For mothers receiving triple-ARV drugs 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^3 who were not receiving triple ARV drugs, 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).
NICHD-HPTN 040/PACTG 1043 Argentina, Brazil, South Africa, U.S.[27] Formula feeding	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	**Arm 1 (control):** Infant ZDV for 6 weeks **Arm 2:** Control as above plus NVP with first dose within 48 hours of birth, second dose 48 hours later, and third dose 96 hours after the second dose **Arm 3:** Control as above, plus 3TC and NFV from birth through 2 weeks of age	• Intrapartum HIV transmission among infants with negative HIV test at birth: 4.8% (3.2–7.1%) ZDV (Arm 1) vs. 2.2% (1.2–3.9%) in ZDV plus NVP (Arm 2) (P = 0.046 compared with Arm 1) vs. 2.4% (1.4–4.3%) in ZDV plus 3TC/NFV (Arm 3) (P = 0.046 compared with Arm 1). • Overall HIV transmission rates, including in utero infection: 11.0% (8.7–14.0%) ZDV (Arm 1) vs. 7.1% (5.2–9.6%) in ZDV plus NVP (Arm 2) (P = 0.035 compared with Arm 1) vs. 7.4% (5.4–9.9%) in ZDV plus 3TC/NFV (Arm 3) (P = 0.035 compared with Arm 1). • Grade 3 or 4 neutropenia more frequent in ZDV/3TC/NFV Arm 3, 70 infants, compared with ZDV alone Arm 1, 33 infants, or ZDV/NVP Arm 2, 32 infants (P <0.001).

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

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[2, 4-9, 13-15]. In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission. In addition, administration of ARV drugs during the antepartum, intrapartum, and postpartum periods is superior in preventing perinatal transmission than administration of ARV drugs only during the antepartum and intrapartum periods or intrapartum and postpartum periods[6, 12, 28]. Use of ARV drugs to prevent transmission is highly effective, even among HIV-infected women with advanced disease[24, 29].

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[2, 4-5]. However, longer duration antenatal ARV prophylaxis (starting at 28 weeks' gestation) is more effective than shorter duration ARV prophylaxis (starting at 36 weeks' gestation), suggesting that a significant proportion of *in utero* transmission occurs between 28 and 36 weeks' gestation[9]. Analyses from the European National Study of HIV in Pregnancy and Childhood have shown that efficacy is increased with even longer duration antenatal ARV prophylaxis (starting before 28 weeks' gestation), with each additional week of a triple-drug regimen corresponding to a 10% reduction in risk of transmission after adjustment for viral load, mode of delivery, and sex of the infant[30]. More prolonged infant post-exposure prophylaxis does not appear to substitute for longer duration maternal ARV prophylaxis[9].

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 cell counts. In African women with CD4 cell counts ranging from 200 to 500 cells/mm^3, 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. The women in the triple-drug arm continued the drugs until breastfeeding ceased, while 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^3, the rate of infection at birth was 1.7% in each arm[23]. 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[6-8]. However, without continued infant post-exposure prophylaxis, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor (NRTI) drugs (zidovudine/lamivudine) is not effective in reducing transmission[6]. The SAINT trial demonstrated that the two proven effective intrapartum/postpartum regimens (zidovudine/lamivudine or single-dose intrapartum/newborn nevirapine) are similar in efficacy and safety[8].

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[31]. In a South African study of in-

fants born to mothers who did not receive antenatal or intrapartum ARV drug regimens, overall perinatal transmission rates were not significantly different for administration of single-dose infant nevirapine given within 24 hours of delivery compared with 6 weeks of infant zidovudine therapy[15]. However, a trial in Malawi in breastfeeding infants demonstrated that adding 1 week of zidovudine therapy to infant single-dose nevirapine reduced the risk of transmission by 36% compared with infant single-dose nevirapine alone[13]. To define the optimal infant prophylaxis regimen in the absence of maternal antepartum ARV drug administration in a formula-fed population of infants, the NICHD-HPTN 040/P1043 (NCT00099359) multicountry (Argentina, Brazil, South Africa, and the United States) clinical trial enrolled 1,735 formula-fed infants born to HIV-infected mothers who did not receive ARV drugs during the current pregnancy prior to labor (if women presented early enough, intravenous intrapartum zidovudine was given). The study compared three infant ARV regimens: standard 6 weeks of zidovudine alone versus 6 weeks of zidovudine plus three 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. The study, presented at the 2011 Conference on Retroviruses and Opportunistic Infections, demonstrated that the combination regimens reduced the risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with zidovudine alone (see Table 3). Based on these data, combination ARV prophylaxis is now recommended in the United States for infants whose mothers have not received antenatal ARV drugs (see Infant Antiretroviral 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[11, 12, 16]. Whether single-dose nevirapine provides any additional efficacy when combined with the standard recommended combination ARV prophylaxis regimens used in the United States was evaluated in PACTG 316, a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas. This study demonstrated that for nonbreastfeeding 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[10]. Thus, adding single-dose intrapartum nevirapine is generally not recommended for women in the United States who are receiving standard recommended antenatal ARV prophylaxis (see Intrapartum Care).

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. A number of studies have evaluated the use of maternal or infant ARV prophylaxis during breastfeeding to reduce postnatal transmission (see Table 3). Observational data and randomized clinical trials have demonstrated that infant prophylaxis (primarily using daily infant nevirapine) during breastfeeding significantly decreases the risk of postnatal transmission in breast milk and that maternal triple-drug prophylaxis during breastfeeding likewise decreases postnatal infection[18-25]. Maternal prophylaxis with triple-drug regimens may be less effective than infant prophylaxis if first started in the postpartum period or late in pregnancy, likely because it takes several weeks to months before full viral suppression in breast milk is achieved[25, 32]. Importantly, although significantly lowering the risk of postnatal infection, neither infant nor maternal postpartum ARV prophylaxis completely eliminates the risk of HIV transmission through breast milk. Therefore, breastfeeding is not recommended for HIV-infected women in the United States (including those receiving combination ARV drug regimens). 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[33-36]. Three studies have found multiclass drug resistance in breastfeeding infants who

became infected despite maternal triple-drug prophylaxis[34-36].

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Perinatal Transmission of HIV and Maternal HIV RNA Copy Number (Updated September 14, 2011)

Panel's Recommendations
• All HIV-infected pregnant women should be counseled about and administered antiretroviral (ARV) drugs during pregnancy for prevention of perinatal transmission, regardless of their HIV RNA levels **(AI)**.

Mother-to-child transmission has been observed across the entire range of plasma HIV RNA levels, including in women with undetectable viral loads[1-3]. In PACTG 076, an HIV RNA threshold below which there was no risk of transmission was not identified; zidovudine was effective in reducing transmission regardless of maternal HIV RNA copy number[4-5].

HIV RNA levels correlate with risk of transmission even in women treated with ARV agents[6-9]. Although the risk of perinatal transmission in women with undetectable HIV RNA levels appears to be extremely low, transmission has been reported even among women with very low or undetectable levels of maternal HIV RNA[10]. Additionally, although HIV RNA may be an important risk factor for transmission, other factors also appear to play a role[6, 9, 11].

Although there is a general correlation between viral loads in plasma and in the genital tract, discordance also has been reported, particularly between HIV proviral load in blood and genital secretions, especially in the presence of other genital tract infections[12-15]. Penetration of ARV drugs into the female genital tract has been shown to vary between drugs[16-17]. 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. Long-term changes in one body compartment with ARV drugs may or may not be associated with comparable changes in other compartments. Additional studies are needed to determine the effect of ARV drugs on genital tract viral load and the association between such effects and the risk of perinatal transmission of HIV. In the short-course zidovudine trial in Thailand, plasma and cervicovaginal HIV RNA levels were reduced by zidovudine prophylaxis, and each independently correlated with perinatal transmission[18].

Because transmission can occur even when HIV RNA copy numbers are low or undetectable, all HIV-infected women should be counseled about and administered ARV drugs during pregnancy, regardless of their HIV RNA levels.

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Preconception Counseling and Care for HIV-Infected Women of Childbearing Age (Updated September 14, 2011)

Overview

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 use of alcohol and illicit drugs, and smoking, which are important for the health of all women as well as for fetal/infant health, should pregnancy occur **(AII)**. • When evaluating HIV-infected women, include assessment of HIV disease status and need for antiretroviral therapy (ART) for their own health **(AII)**. • Choose an ART regimen for HIV-infected women of childbearing age based on consideration of effectiveness for treatment of maternal disease, teratogenic potential of the drugs in the regimen should pregnancy occur, and possible adverse outcomes for mother and fetus **(AII)**.

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 the patient's individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes[1]. Preconception care is not a single clinical visit but rather a process of ongoing care and interventions integrated into primary care to address the needs of women during the different stages of reproductive life. Because more than half of all pregnancies in the United States are unintended[2-5] 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[6]. 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[7-8]. Because many women infected with HIV are aware of their HIV status prior to pregnancy, issues that impact pregnancy may be addressed before conception during their routine medical care for HIV disease. In addition to those outlined by the CDC Preconception Care Work Group[9] the following components of preconception counseling and care are specifically recommended for HIV-infected women. Health care providers should:

a. 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[10].

b. Offer all women effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy (see Table 4).

c. Counsel on safe sexual practices that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted infections (STIs), and reduce the potential to acquire more virulent or resistant strains of HIV.

d. Counsel on eliminating alcohol, illicit drug use, and cigarette smoking.

e. Educate and counsel women about risk factors for perinatal transmission of HIV, strategies to reduce those risks, potential effects of HIV or treatment 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 and the availability of safe and sustainable infant feeding alternatives.

f. When prescribing ART to women of childbearing age consider the regimen's effectiveness for treatment of HIV, an individual's hepatitis B disease status, the drugs' potential for teratogenicity should pregnancy occur, and possible adverse outcomes for mother and fetus[11-13].

g. Use the preconception period in women who are contemplating pregnancy to adjust ARV regimens to exclude efavirenz or other drugs with teratogenic potential.

h. For women who are on ART for their own health and who want to get pregnant, make a primary treatment goal the attainment of a stable, maximally suppressed maternal viral load prior to conception to decrease the risk of mother-to-child transmission.

i. Evaluate and appropriately manage therapy-associated side effects such as hyperglycemia, anemia, and hepatoxicity that may adversely impact maternal-fetal health outcomes.

j. Evaluate the need for appropriate prophylaxis or treatment for opportunistic infections (OIs), including safety, tolerability, and potential toxicity of specific agents when used in pregnancy.

k. Administer medical immunizations (e.g., influenza, pneumococcal, or hepatitis A and B vaccines) as indicated.

l. Encourage sexual partners to receive HIV testing and, if infected, counseling and appropriate HIV care.

Table 4: Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (Page 1 of 2)

Antiretroviral (ARV) Drug	Effect on Drug Levels	Dosing Recommendation/ Clinical Comment
Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)		
Efavirenz (EFV)	Oral ethinyl estradiol/norgestimate: No effect on ethinyl estradiol concentrations;↓ active metabolites of norgestimate (levonorgestrel AUC ↓83%; norelgestromin AUC ↓64%)	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. EFV had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on EFV plasma concentrations was observed.
	Implant: ↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and EFV has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in EFV-exposed patients.
	Levonorgestrel AUC ↓58%	Effectiveness of emergency postcoital contraception may be diminished.
Etravirine (ETR)	Ethinyl estradiol AUC ↑22% Norethindrone: no significant effect	No dosage adjustment necessary.
Nevirapine (NVP)	Ethinyl estradiol AUC ↓20% Norethindrone AUC ↓19%	Use alternative or additional methods.
	DMPA: no significant change	No dosage adjustment needed.
Ritonavir (RTV)-boosted Protease Inhibitor (PI)		
Atazanavir/ritonavir (ATV/r)	↓ Ethinyl estradiol ↑ Norgestimate	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
Darunavir/ritonavir (DRV/r)	Ethinyl estradiol AUC ↓44% Norethindrone AUC ↓14%	Use alternative or additional method.
Fosamprenavir/ritonavir (FPV/r)	Ethinyl estradiol AUC ↓37% Norethindrone AUC ↓34%	Use alternative or additional method.
Lopinavir/ritonavir (LPV/r)	Ethinyl estradiol AUC ↓42% Norethindrone AUC ↓17%	Use alternative or additional method.
Saquinavir/ritonavir (SQV/r)	↓Ethinyl estradiol	Use alternative or additional method.
Tipranavir/ritonavir (TPV/r)	Ethinyl estradiol AUC ↓48% Norethindrone: no significant change	Use alternative or additional method.

Table 4: Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (Page 2 of 2)

Antiretroviral (ARV) Drug	Effect on Drug Levels	Dosing Recommendation/ Clinical Comment
PI without RTV		
Atazanavir (ATV)	Ethinyl estradiol AUC↑48% Norethindrone AUC ↑110%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternative method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
Fosamprenavir (FPV)	With APV: ↑ Ethinyl estradiol and ↑ norethindrone; ↓APV 20%	Use alternative method.
Indinavir (IDV)	Ethinyl estradiol AUC ↑25% Norethindrone AUC ↑26%	No dose adjustment.
Nelfinavir (NFV)	Ethinyl estradiol AUC ↓47% Norethindrone AUC ↓18%	Use alternative or additional method.
CCR5 Antagonist		
Maraviroc (MVC)	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination.

Key to Abbreviations: AUC = area under the curve; DMPA = depot medroxyprogesterone acetate

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. January 10, 2011; pp. 1–166; Tables 15a, 15b, and 15d. Accessed August 31, 2011. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

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Reproductive Options for HIV-Concordant and Serodiscordant Couples (Updated September 14, 2011)

Panel's Recommendations
• For 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 **(AIII)**.
• Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
• For an HIV-infected female with an HIV-uninfected male partner, the safest conception option is artificial insemination, including the option of self-insemination with her partner's sperm during the peri-ovulatory period **(AIII)**.
• For HIV-infected men with an HIV-uninfected female partner, the use of sperm preparation techniques coupled with either intrauterine insemination, in vitro fertilization, or intracytoplasmic sperm injection should be considered if using donor sperm from an HIV-uninfected male for insemination is unacceptable **(AII)**.
• In a serodiscordant couple who wishes to conceive, initiation of antiretroviral therapy (ART) for the HIV-infected partner is recommended if the infected partner has a CD4 count ≤550 cells/mm^3 **(AI)**. For HIV-infected individuals with CD4 counts >550 cells/mm^3, initiation of ART could be considered **(BIII)**. If therapy is initiated, maximal viral suppression is recommended before conception is attempted **(AIII)**.
• Data are insufficient at the current time to recommend peri-conception administration of antiretroviral (ARV) pre-exposure prophylaxis for HIV-uninfected partners to reduce the risk of sexual transmission **(AIII)**.

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

Before attempting to conceive, both partners should be screened for genital tract infections. If any such infections are identified, they should be treated because genital tract inflammation is associated with genital tract shedding of HIV[1-2]. Semen analysis is recommended for HIV-infected males before conception is attempted because HIV, and possibly ART, 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[3-6]. 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 even nonexistent.

Observational studies have demonstrated a decreased rate of transmission of HIV among heterosexual serodiscordant couples in which the HIV-infected partner is receiving ART compared with couples in which the HIV-infected partner is not receiving ART[7-9]. HPTN 052 is a randomized clinical trial designed to evaluate whether immediate versus delayed initiation of ART by HIV-infected individuals with CD4 counts of 350–550 cells/mm^3 could prevent sexual transmission of HIV among serodiscordant couples. Preliminary data from this study showed that earlier initiation of ART led to a significant reduction in transmission of HIV to the uninfected partner[10]. Of 28 cases of HIV infection documented to be genetically linked to the infected partner, 27 occurred among the 877 couples in which the HIV-infected partner delayed initiation of ART until the CD4 count fell below 250 cells/mm^3, whereas only 1 case of HIV infection occurred among the 886 couples with an HIV-infected partner who began immediate ART; 17 of the 27 transmissions in the delayed therapy group occurred in individuals with CD4 counts >350 cells/mm^3. These are the first data from a randomized trial to demonstrate that provision of treatment to infected persons can reduce the risk of transmission to their uninfected sexual partners[11]. Based on the

results from HPTN 052, initiation of ART would be recommended for the infected partner in a serodiscordant couple who has a CD4 count of ≤550 cells/mm^3 if the couple wishes to conceive. For HIV-infected individuals with CD4 counts >550 cells/mm^3, initation of therapy could be considered, although the benefit of ART in reducing sexual transmission from individuals with higher CD4 counts has not been determined. Before conception is attempted, maximal viral suppression is recommended if an infected individual is on ART for his/her own health or does not require therapy but opts to start ART to prevent sexual transmission.

It is important to recognize that no single method (including treatment of the infected partner) is fully protective against transmission of HIV. Effective ART that decreases plasma viral load to undetectable levels is also associated with decrease in the concentration of virus in genital secretions. However, discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus[12-13]. Additionally, ARV drugs vary in their ability to penetrate the genital tract[14]. Thus, maximal viral suppression may not completely eliminate risk of heterosexual transmission.

Reducing the risk of perinatal transmission is another potential rationale for starting ART prior to conception in HIV-infected women who do not yet need treatment for their own health. Data suggest that early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission[15-16], but that does not completely eliminate the risk of perinatal transmission[16]. In addition, there are mixed reports on the possible effects of combination ARV drug regimens on prematurity and low birth weight, with some but not all data suggesting that such outcomes may be more frequent in women on ARV drugs at conception[17-18] (see Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants).

The implications of initiating therapy prior to conception solely for prevention of sexual and/or perinatal transmission should be discussed with the patient. These issues include willingness and ability 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 sperm preparation techniques coupled with either intrauterine insemination, in vitro fertilization, or intracytoplasmic sperm injection has been reported to be effective in avoiding seroconversion in uninfected women and offspring in several studies[19-20]. The National Perinatal HIV Hotline (1-888-448-8765) is a resource for a list of institutions offering reproductive services for HIV-serodiscordant couples. 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[20]. Discordant couples who do not have access to assisted reproduction services and who still wish to try to conceive after comprehensive counseling should be advised that timed, peri-ovulatory unprotected intercourse after the infected partner has achieved maximal viral suppression (with use of condoms at all other times) may reduce but not completely eliminate the risk of sexual transmission[20]. Should the uninfected woman become pregnant, she should be regularly counseled regarding consistent condom use to decrease her 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 may offer an additional option in the future to minimize risk of transmission of HIV within discordant couples. Pre-exposure prophylaxis is use of ARV medications by an HIV-uninfected individual to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. An experimental 1% tenofovir gel used intravaginally both before and after sex reduced the incidence of HIV infection among women by up to 54% in a randomized, placebo-controlled trial conducted in South Africa[21]. This product is not available commercially, and additional trials are needed to confirm these findings. Five efficacy trials of pre-exposure prophylaxis with oral ARV agents (primarily tenofovir alone) are currently under way[22]. In 1 study of daily tenofovir/emtricitabine in HIV-seronegative men who have sex with men, there was a 44% reduction in the risk of acquisition of HIV compared with placebo[23-24]. However, the FEM-PrEP clinical trial, designed to study whether HIV-uninfected women at high risk of being exposed to HIV can safely use a daily dose of tenofovir/emtricitabine to prevent infection, was stopped early by its Data and Safety Monitoring Board (DSMB) because it was highly unlikely the study would be able to demonstrate the effectiveness of tenofovir/emtricitabine in preventing HIV infection in the study population. The approximate rate of new HIV infections among trial participants was 5 percent per year. A total of 56 new HIV infections had occurred, with an equal number of infections in participants assigned to tenofovir/emtricitabine and those assigned to a placebo pill[25].

Several studies evaluating the efficacy of pre-exposure prophylaxis among heterosexual discordant couples are ongoing but data are not yet available. Currently data are insufficient to recommend periconception administration of pre-exposure prophylaxis to uninfected partners to reduce the risk of sexual transmission. In addition, the use of pre-exposure prophylaxis during pregnancy and lactation for HIV-uninfected women with HIV-infected partners has not been studied and cannot be recommended at this time. If pre-exposure prophylaxis is proven safe and efficacious in ongoing trials, this approach may offer an option for safer attempts at conception. However, it will be important to have outcome studies that examine adverse events, including risk of congenital abnormalities.

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

Clinicians increasingly may be faced with the situation in which an HIV-uninfected woman presents during pregnancy and relates that she has an HIV-infected partner. As is recommended for all pregnant women, the woman should be notified that HIV screening is recommended and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines. In addition, she should receive a second HIV test during the third trimester, preferably before 36 weeks of gestation, as is recommended for high-risk women. Furthermore, if the pregnant woman presents in labor without results of third-trimester testing, she should be screened with a rapid HIV test on the labor and delivery unit. If at any time during pregnancy the clinician suspects that a pregnant woman may be in the "window" period of seroconversion (i.e., 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.

If results from either conventional or rapid HIV testing are positive, then the woman should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate ARV prophylaxis 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 (e.g., rapid testing during labor), it is still appropriate to initiate interven-

tions to reduce perinatal transmission (see Infant Antiretroviral Prophylaxis).

If HIV test results are negative, HIV-uninfected women with HIV-infected partners 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[26-27].

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Antepartum Care (Updated September 14, 2011)

General Principles Regarding Use of Antiretroviral Drugs During Pregnancy

Panel's Recommendations
• Initial evaluation of infected pregnant women should include assessment of HIV disease status and recommendations regarding initiation of antiretroviral (ARV) drugs or the need for any modification if currently receiving antiretroviral therapy (ART) **(AIII)**. The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.
• Regardless of plasma HIV RNA copy number or CD4 cell count, all pregnant HIV-infected women should receive a combination antepartum ARV drug regimen to prevent perinatal transmission **(AI)**. A combination regimen is recommended both for women who require therapy for their own health **(AI)** and for prevention of perinatal transmission in those who do not yet require therapy **(AII)**.
• The known benefits and potential risks of ARV use during pregnancy should be discussed with all women **(AIII)**.
• 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 (e.g., >500 to 1,000 copies/mL) (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AI)**. When HIV is diagnosed late in pregnancy, ARV therapy or prophylaxis should be initiated pending results of resistance testing **(BIII)**.
• In counseling patients, the importance of adherence to the ARV regimen should be emphasized **(AII)**.
• Considerations regarding continuation of the ARV regimen for maternal therapeutic indications after delivery are the same as for nonpregnant individuals. The pros and cons of continuing versus discontinuing ARV drugs postpartum should be discussed with women so they can make educated decisions about postpartum ARV use before delivery **(AIII)**. Such decisions should be made in consultation with the provider who will assume responsibility for the women's HIV care going forward after delivery.
• 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 **(AIII)**.

In addition to the standard antenatal assessments for all pregnant women, the initial evaluation of an HIV-infected pregnant woman should include an assessment of HIV disease status and recommendations for HIV-related medical care. This initial assessment should include the following:

a. review of prior HIV-related illnesses and past CD4 cell counts and plasma HIV viral loads;

b. current CD4 cell count;

c. current plasma HIV RNA copy number;

d. assessment of the need for prophylaxis against opportunistic infections (OIs) such as *Pneumocystis jirovecii* pneumonia (PCP) or Mycobacterium avium complex (MAC) (see Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents)[1];

e. evaluation of immunization status per guidelines from the American College of Obstetricians and Gynecologists, with particular attention to hepatitis A, hepatitis B, influenza, and pneumococcus immunizations[2];

f. baseline complete blood cell count (CBC) and renal and liver function testing;

g. HLA-B*5701 testing, if abacavir use is anticipated (see Table 5);

h. history of prior and current ARV drug use, including prior ARV use for prevention of perinatal transmission of HIV or for treatment of HIV disease, and history of adherence problems;

i. results of prior and current HIV ARV drug-resistance studies; and

j. assessment of supportive care needs.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 1 of 11)

(See also Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy supplement for additional toxicity data and Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents for detailed guidelines regarding treatment options.)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
NRTIs			NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection.		See text for discussion of potential maternal and infant mitochondrial toxicity.
Preferred Agents					
Lamivudine (3TC) Epivir	**Epivir** 150-, 300-mg tablets or 10-mg/mL oral solution **Combivir** 3TC 150 mg + ZDV 300 mg **Epzicom** 3TC 300 mg + ABC 600 mg **Trizivir**‡ 3TC 150 mg + ZDV 300 mg + ABC 300 mg	**Epivir** 150 mg BID or 300 mg once daily Take without regard to meals. **Combivir** 1 tablet BID **Epzicom** 1 tablet once daily **Trizivir** 1 tablet BID	Because of extensive experience with 3TC in pregnancy in combination with ZDV, 3TC plus ZDV is the recommended dual-NRTI backbone for pregnant women.	PK not significantly altered in pregnancy; no change in dose indicated[3]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)[4]. Well-tolerated, short-term safety demonstrated for mothers and infants. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum, see Special Considerations: Hepatitis B Virus Coinfection.
Zidovudine (AZT, ZDV) Retrovir	**Retrovir** 100-mg capsules, 300-mg tablets, 10-mg/mL IV solution, 10-mg/mL oral solution **Combivir** ZDV 300 mg + 3TC 150 mg **Trizivir**‡ ZDV 300 mg + 3TC 150 mg + ABC 300 mg	**Retrovir** 300 mg BID or 200 mg TID Take without regard to meals. **Combivir** 1 tablet BID **Trizivir** 1 tablet BID	Preferred NRTI for use in combination ARV regimens in pregnancy based on efficacy studies and extensive experience; should be included in the antenatal ARV regimen unless there is severe toxicity, d4T use, documented resistance, or the woman is already on a fully suppressive regimen.	PK not significantly altered in pregnancy; no change in dose indicated[5]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)[4]. Well-tolerated, short-term safety demonstrated for mothers and infants.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 2 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Alternative Agents					
Abacavir (ABC) Ziagen	**Ziagen** 300-mg tablets or 20-mg/mL oral solution **Epzicom** ABC 600 mg + 3TC 300 mg **Trizivir**‡ ABC 300 mg + ZDV 300 mg + 3TC 150 mg	**Ziagen** 300 mg BID or 600 mg once daily Take without regard to meals. **Epzicom** 1 tablet once daily **Trizivir** 1 tablet BID	Alternative NRTI for dual-NRTI backbone of combination regimens. See footnote regarding use in triple-NRTI regimen.‡	PKs not significantly altered in pregnancy; no change in dose indicated[6]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. Testing for HLA-B*5701 identifies patients at risk of reactions[7-8] and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of hypersensitivity reaction.
Didanosine (ddI) Videx EC, generic didanosine enteric coated (EC) (dose same as Videx EC)	**Videx EC** 125-, 200-, 250-, 400-mg capsules Buffered tablets (non-EC) no longer available **Videx** 10-mg/mL oral solution	**Body weight ≥60kg:** 400 mg once daily; with TDF, 250 mg once daily **Body weight <60kg**: 250 mg once daily; with TDF, 200 mg once daily Take 1/2 hour before or 2 hours after a meal Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Alternative NRTI for dual-NRTI backbone of combination regimens. ddI should not be used with d4T.	PKs not significantly altered in pregnancy; no change in dose indicated[9]. Moderate placental transfer to fetus.	Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together[10-11].

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 3 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Emtricitabine (FTC) Emtriva	**Emtriva** 200-mg hard gelatin capsule or 10-mg/mL oral solution **Truvada** FTC 200 mg + TDF 300 mg **Atripla** FTC 200 mg + EFV§ 600 mg + TDF 300 mg	**Emtriva** 200-mg capsule once daily or 240 mg (24 mL) oral solution once daily Take without regard to meals. **Truvada** 1 tablet once daily **Atripla** 1 tablet at or before bedtime. Take on an empty stomach to reduce side effects.	Alternative NRTI for dual-NRTI backbone of combination regimens.	PK study shows slightly lower levels in third trimester, compared with postpartum[12]. No clear need to increase dose. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum, see Special Considerations: Hepatitis B Coinfection.
Stavudine (d4T) Zerit	**Zerit** 15-, 20-, 30-, 40-mg capsules or 1-mg/mL oral solution	**Body weight ≥60 kg:** 40 mg BID **Body weight <60 kg:** 30 mg BID Take without regard to meals. WHO recommends 30-mg BID dosing regardless of body weight.	Alternate NRTI for dual-NRTI backbone of combination regimens. d4T should not be used with ddI or ZDV.	PKs not significantly altered in pregnancy; no change in dose indicated[13]. High placental transfer.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together[10-11].

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 4 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Tenofovir Disoproxil Fumarate (TDF) Viread	**Viread** 300-mg tablet **Truvada** TDF 300 mg + FTC 200 mg **Atripla** TDF 300 mg + EFV§ 600 mg + + FTC 200 mg	**Viread** 1 tablet once daily Take without regard to meals. **Truvada** 1 tablet once daily **Atripla** 1 tablet at or before bedtime Take on an empty stomach to reduce side effects.	Alternative NRTI for dual-NRTI backbone of combination regimens. TDF would be a preferred NRTI in combination with 3TC or FTC in women with chronic HBV infection. Because of potential for renal toxicity, renal function should be monitored.	AUC lower in third trimester than postpartum but trough levels adequate[14]. High placental transfer.[15-18].	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. 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[19]. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown[20-21]. Significant placental passage in humans (cord:maternal blood ratio 0.6–0.99). If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum, see Special Considerations: Hepatitis B Virus Coinfection.
NNRTIs			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.
Preferred Agents					
Nevirapine (NVP) Viramune	200-mg tablets or 50-mg/5-mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID Take without regard to meals. Repeat lead-in period if therapy is discontinued for >7 days. In patients who develop mild-to-moderate rash without constitutional symptoms during lead-in, continue lead-in dosing until rash resolves, but not >28 days total.	NVP should be initiated in pregnant women with CD4 counts >250 cells/mm^3 only if benefit clearly outweighs risk because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 cell counts. Women who enter pregnancy on NVP regimens and are tolerating them well may continue therapy, regardless of CD4 count.	PK not significantly altered in pregnancy; no change in dose indicated [22-24]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts >250/mm^3 when first initiating therapy[25-26]; unclear if pregnancy increases risk.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 5 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Use in Special Circumstances					
Efavirenz§ (EFV) Sustiva	50-, 200-mg capsules or 600- mg tablets **Atripla** EFV§ 600 mg + FTC 200 mg + TDF 300 mg	600 mg once daily at or before bedtime Take on an empty stomach to reduce side effects. **Atripla** 1 tablet once daily at or before bedtime	Use of EFV should be avoided in the first trimester. Use after the first trimester can be considered if, after consideration of other alternatives, this is the best choice for a specific woman. If EFV is to be continued postpartum, adequate contraception must be assured. Women of childbearing age must be counseled regarding the teratogenic potential of EFV and avoidance of pregnancy while on the drug. Because of the known failure rates of contraceptive methods, alternative ARV regimens should be strongly considered in women of childbearing potential.	AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester subjects exceeded target exposure and no change in dose is indicated[27]. Moderate placental transfer to fetus.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 of 20 infants (15%) born to cynomolgus monkeys receiving EFV during the first trimester at a dose resulting in plasma levels comparable to systemic human therapeutic exposure. There are 6 retrospective case reports and 1 prospective case report of neural tube defects in humans with first-trimester exposure and 1 prospective case of anophthalmia with facial clefts[28-30]; relative risk unclear.
Insufficient Data to Recommend Use					
Etravirine (ETR) Intelence	100-, 200-mg tablets	200 mg BID Take following a meal.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	No PK studies in human pregnancy, placental transfer rate unknown.	No experience in human pregnancy.
Rilpivirine (RPV) Endurant	25-mg tablets **Complera** RPV 25 mg + TDF 300 mg + FTC 200 mg	25 mg once daily with a meal. **Complera** 1 tablet once daily	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	No PK studies in human pregnancy, placental transfer rate unknown.	No experience in human pregnancy.
PIs			PIs are recommended for use in combination regimens with 2 NRTI drugs.		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see Protease Inhibitor Therapy and Hyperglycemia).

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 6 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Preferred Agents					
Lopinavir + Ritonavir (LPV/r) Kaletra	**Tablets:** (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) **Oral solution:** Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol	LPV/r 400 mg/100 mg BID **Third trimester:** Some experts recommend increased dose LPV/r 600 mg/150 mg BID in third trimester **With EFV or NVP (PI-naive or PI-experienced patients):** LPV/r 500 mg/125 mg tablets BID (use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.) or LPV/r 533 mg/133 mg oral solution (6.5 mL) BID **Tablets:** Take without regard to meals. **Oral solution:** Take with food. **Not used in pregnancy:** Adult dosage of LPV/r 800 mg/200 mg once daily is not recommended for use in pregnancy.	PK studies suggest dose should be increased to 600 mg/150 mg BID in second and third trimester, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. Once-daily LPV/r dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.	AUC decreased in second and third trimester with standard dosing[31-33]. AUC with dose of LPV/r 600 mg/150 mg twice daily in third trimester in women in the United States resulted in AUC similar to that in nonpregnant adults taking LPV/r 400 mg/100 mg dose twice daily[12]. Low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Well-tolerated, short-term safety demonstrated in Phase I/II studies.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 7 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Alternative Agents					
Atazanavir (ATV) Reyataz (combined with low-dose RTV boosting)	100-, 150-, 200-, 300-mg capsules	**ARV-naive patients:** (ATV 300 mg + RTV 100) mg once daily **With TDF or H2-receptor antagonist (not both) in ARV-experienced non-pregnant patients:** (ATV 300 mg + RTV 100 mg) once daily; **in pregnant patients:** (ATV 400 mg + RTV 100 mg) once daily. **With EFV (after first trimester) in ARV-naive patients:** (ATV 400 mg + RTV 100 mg) once daily (For dosing recommendations with H2 antagonists and PPIs in treatment-naive patients, refer to Adult Guidelines.) Take with food.	Alternative PI for use in combination regimens in pregnancy. Should give as low-dose RTV-boosted regimen, may use once daily dosing. A study of 41 pregnant women described in the package insert for Reyataz concluded that no dose adjustment of ATV was needed for the majority of pregnant women infected with strains of HIV susceptible to ATV. The exception was in ART-experienced pregnant women on either tenofovir or H2-receptor blocker (not both) who should receive increase in ATV dose to 400 mg (with ritonavir 100 mg).	Two of three intensive PK studies of ATV with RTV boosting during pregnancy and the PK study described in the recently approved product label suggest that standard dosing results in decreased plasma concentrations, compared with non-pregnant adults[15, 34-36]. However, for most pregnant women (not on interacting concomitant medications), no dose adjustment was needed. ATV concentrations further reduced ~25% with concomitant TDF use[15, 36]. Low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Transplacental passage is low, with cord blood concentration averaging 10%–19% of the maternal delivery ATV concentration[15, 34, 36]. Theoretical concern regarding increased indirect bilirubin levels causing significant exacerbation in physiologic hyperbilirubinemia in neonates has not been observed in clinical trials to date[15, 34-37].
Ritonavir (RTV) Norvir	100-mg capsules 100-mg tablets 80-mg/mL oral solution Oral solution contains 43% alcohol	**As PK booster for other PIs:** 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations) **Tablets:** Take with food. **Capsule and oral solution:** Take with food if possible, which may improve tolerability.	Given low levels in pregnant women when used alone, should only be used in combination with second PI as low-dose RTV "boost" to increase levels of second PI.	Phase I/II study in pregnancy showed lower levels during pregnancy compared with postpartum[38]. Minimal placental transfer to fetus.	Limited experience at full dose in human pregnancy; has been used as low-dose RTV boosting with other PIs. No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4].

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 8 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Saquinavir (SQV) Invirase (Available as hard gelatin capsules and tablets. SQV must be combined with low-dose RTV boosting.)	500-mg tablets or 200-mg hard gelatin capsules	(SQV 1,000 mg + RTV 100 mg) BID Unboosted SQV is **not** recommended. Take with meals or within 2 hours after a meal.	PK data on SQV hard gelatin capsules and the new tablet formulation in pregnancy are limited. RTV-boosted SQV hard gelatin capsules or SQV tablets are alternative PIs for combination regimens in pregnancy and are alternative initial ARV recommendations for nonpregnant adults. Must give as low-dose RTV-boosted regimen.	Limited PK data on SQV hard gelatin capsules and the new 500-mg tablet formulation suggest that 1,000 mg SQV hard gelatin capsules/100 mg RTV given twice daily achieves adequate SQV drug levels in pregnant women[39]. Minimal placental transfer to fetus.	Well-tolerated, short-term safety demonstrated for mothers and infants for SQV in combination with low-dose RTV. Baseline EKG recommended before starting because PR and/or QT interval prolongations have been observed.
Use in Special Circumstances					
Indinavir (IDV) Crixivan (combined with low-dose RTV boosting)	100-, 200-, 400- mg capsules	**With RTV:** (IDV 800 mg + RTV 100– 200 mg) BID Take without regard to meals. **Not used in pregnancy:** Adult dosage of IDV (without RTV) 800 mg every 8 hours is not recommended for use in pregnancy.	Because of twice-daily dosing, pill burden, and potential for renal stones, IDV should only be used when preferred and alternative agents cannot be used. Must give as low-dose RTV-boosted regimen.	Two studies including 18 women receiving IDV 800 mg three times daily showed markedly lower levels during pregnancy compared with postpartum, although suppression of HIV RNA levels was seen[40-41]. In a study of RTV-boosted IDV (400 mg IDV/100 mg RTV twice daily), 82% of women met the target trough level[42]. Minimal placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[28]. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates, but minimal placental passage. Use of unboosted IDV during pregnancy is not recommended.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 9 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Nelfinavir (NFV) Viracept	250-, 625-mg tablets 50-mg/g oral powder	1,250 mg BID Take with food. **Not used in pregnancy:** Adult dosage of NFV 750 mg TID is not recommended for use in pregnancy.	Given PK data and extensive experience with use in pregnancy, NFV might be considered in special circumstances for prophylaxis of transmission in women in whom therapy would not otherwise be indicated when alternative agents are not tolerated. In clinical trials of initial therapy in non-pregnant adults, NFV-based regimens had a lower rate of viral response compared with LPV/r or EFV-based regimens, but similar viral response to ATVor NVP-based regimens.	Adequate drug levels are achieved in pregnant wome with NFV 1,250 mg given twice daily, although levels are variable in late pregnancy[23, 43-44]. In a study of pregnant women in their second and third trimester dosed at 1,250 mg given twice daily, women in the third trimester had lower concentration of NFV than women in the second trimester[44]. In a study of the new 625-mg tablet formulation dosed at 1,250 mg twice daily, lower AUC and peak levels were observed during the third trimester of pregnancy than postpartum[45]. Minimal to low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[28]. Well-tolerated, short-term safety demonstrated for mothers and infants.
Insufficient Data to Recommend Use					
Darunavir (DRV) Prezista (must be combined with low-dose RTV boosting)	75-, 150-, 400-, 600-mg tablets	**ARV-naive patients:** (DRV 800 mg + RTV 100 mg) once daily **ARV-experienced patients:** (DRV 800 mg + RTV 100 mg) once daily if no DRV resistance mutations (DRV 600 mg + RTV 100 mg) BID if any DRV resistance mutations Unboosted DRV is **not** recommended. Take with food.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients. Must give as low-dose RTV-boosted regimen.	No PK studies in human pregnancy. Minimal to low placental transfer to fetus[46].	No experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 10 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Fosamprenavir (FPV) Lexiva (a prodrug of amprenavir) (recommended to be combined with low-dose RTV boosting)	700-mg tablet or 50-mg/mL oral suspension	**ARV-naive patients:** • FPV 1,400 mg BID or • (FPV 1,400 mg + RTV 100–200 mg) once daily or • (FPV 700 mg + RTV 100 mg) BID **PI-experienced patients (once-daily dosing not recommended):** • (FPV 700 mg + RTV 100 mg) BID **With EFV:** • (FPV 700 mg + RTV 100 mg) BID or • (FPV 1,400 mg + RTV 300 mg) once daily **Tablet:** Take without regard to meals (if not boosted with RTV tablet). **Suspension:** Take without food. **FPV with RTV tablet:** Take with meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients. Recommended to be given as low-dose RTV-boosted regimen.	With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in nonpregnant adults without boosting and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations[47]. Low placental transfer to fetus.	Limited experience in human pregnancy.
Tipranavir (TPV) Aptivus (must be combined with low-dose RTV boosting)	250-mg capsules or 100-mg/mL oral solution	(TPV 500 mg + RTV 200 mg) BID Unboosted TPV is **not** recommended. **TPV taken with RTV tablets:** Take with meals. **TPV taken with RTV capsules or solution:** Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients. Must give as low-dose RTV-boosted regimen.	No PK studies in human pregnancy. Unknown rate of placental transfer to fetus.	No experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 11 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Entry Inhibitors					
Insufficient Data to Recommend Use					
Enfuvirtide (T20) Fuzeon	• Injectable— 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	90 mg (1mL) SQ BID	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients.	No PK studies in human pregnancy. No placental transfer to fetus, based on very limited data.	Minimal data in human pregnancy[48].
Maraviroc (MVC) Selzentry	150-, 300-mg tablets	• 150 mg BID when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • 300 mg BID when given with NRTIs, T-20, TPV/r, NVP, and other drugs that are not strong CYP3A inhibitors or inducers • 600 mg BID when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients.	No PK studies in human pregnancy. Unknown placental transfer rate to fetus.	No experience in human pregnancy
Integrase Inhibitors					
Insufficient Data to Recommend Use					
Raltegravir (RAL) Isentress	400-mg tablets	400 mg BID With rifampin: 800 mg BID Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	During third trimester, RAL PK show extensive variability but RAL exposure was not consistently altered, compared with postpartum and historical data. The standard dose appears appropriate during pregnancy[49]. Variable but high placental transfer to fetus.	No experience in human pregnancy.

Key to Abbreviations: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CYP = cytochrome P; EKG = electrocardiogram; FDA = Food and Drug Administration; IV = intravenous; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; SQ = subcutaneous injection; TID = three times daily; WHO = World Health Organization

* Dosage should be adjusted in renal or hepatic insufficiency (see Adult Guidelines, Appendix B, Table 7).

‡ Triple-NRTI regimens including abacavir have been less potent virologically compared with PI-based combination ARV drug regimens. Triple-NRTI regimens should be used only when an NNRTI- or PI-based combination regimen cannot be used, such as because of significant drug interactions.

§ See section on Teratogenicity for discussion of efavirenz and risks in pregnancy.

† 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

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of whether they have indications for ART for their own health. In general, guidelines for the use of ART for the benefit of maternal health during pregnancy are the same as for women who are not pregnant, with some modifications, based on concerns about specific drugs and limited experience during pregnancy with newer drugs. ARV prophylaxis is recommended for all pregnant women with HIV infection who do not require therapy, regardless of viral load (see HIV-Infected Pregnant Women Not on Antiretroviral Therapy Who Require Antiretroviral Prophylaxis Solely to Prevent Perinatal Transmission of HIV).

Decisions regarding initiation or modification of ARV drug regimens during pregnancy include considerations regarding the benefits and risks of ARV drug use that are common to all HIV-infected adults in addition to considerations unique to pregnancy. In general, the ARV drug combinations now available are more convenient and better tolerated than regimens used previously, resulting in greater efficacy and improved adherence. During pregnancy maternal ARV toxicities must be considered, along with the potential impact of the ARV regimen on pregnancy outcome and on the fetuses and infants. Decisions about ARV drug regimens are further complicated because only limited data exist on the long-term maternal consequences of use of the agents during pregnancy solely for prophylaxis of transmission. Similarly, only limited data are available on the long-term consequences to infants of *in utero* exposure to ARVs.

The known benefits and known and unknown risks of ARV drug use during pregnancy should be considered and discussed with women (see Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-infected Pregnant Women and their Infants). Results from preclinical and animal studies and available clinical information about use of the various agents during pregnancy also should be discussed (see Supplement: Safety and Toxicity of Individual Antireroviral 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 women make informed decisions regarding use of ARV drugs.

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

a. maternal risk of disease progression and the benefits and risks of initiation of therapy for maternal

health;

b. benefit of combination ARV regimens for preventing perinatal transmission of HIV[50];

c. potential adverse effects of ARV drugs for mothers, fetuses, and infants, including potential interactions with other medications the women may already be receiving;

d. the limited long-term outcome data for both women who temporarily use ARV drugs during pregnancy for prophylaxis of transmission and infants who are exposed to ARVs *in utero*; and

e. the possibility of development of ARV resistance, including the need for strict adherence to the prescribed drug regimen to avoid it.

Studies of zidovudine for the prevention of perinatal transmission suggest that pre-exposure prophylaxis of the infant from transplacental passage of drug is an important component of prevention. Thus, when selecting an ARV regimen for a pregnant woman, at least one nucleoside/nucleotide (NRTI) agent with high placental transfer should be included as a component of the dual NRTI backbone (see Table 5)[13, 18, 51-52].

In women with plasma HIV RNA above the threshold for resistance testing (e.g., >500–1,000 copies/mL), ARV drug-resistance studies should be performed before starting ARV drugs for maternal health or prophylaxis. When HIV is diagnosed late in pregnancy, however, ARV drugs should be initiated pending 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. Support services, mental health services, and drug abuse treatment may be required, depending on women'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.

Providers should work with women to develop long-range plans regarding continuity of medical care and decisions about treatment for their own health after giving birth. Considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same following delivery as for nonpregnant individuals. The impact on short- and long-term maternal health is unknown for postpartum discontinuation of combination ARV drug regimens used solely to prevent perinatal transmission. This is particularly important because women may have multiple pregnancies resulting in episodic receipt of ARV drugs. No increase in disease progression has been seen so far, however, in studies of pregnant women with relatively high CD4 counts who stop combination ARV drug regimens after delivery[53-55]. The risks versus benefits of stopping ARV drug regimens postpartum in women with high CD4 cell counts are being evaluated in the ongoing PROMISE study (clinical trial number NCT00955968).

Current adult treatment guidelines strongly recommend ART for all individuals with CD4 cell counts <350 cells/mm^3 based on randomized, controlled clinical trial data demonstrating a clear benefit in reduction of mortality and morbidity. Pregnant women with CD4 counts <350 cells/mm^3 should begin on combination ART as soon as possible during pregnancy and be counseled about the need to continue therapy after delivery and the importance of adherence to the regimen.

Based on observational cohort data, the adult treatment guidelines make a moderate-to-strong recommendation for initiating lifelong ART in individuals with CD4 cell counts between 350 and 500 cells/mm^3. Observational studies suggest a relative decrease in mortality (although the overall number of events was small) and possibly a decrease in complications such as cardiovascular events with initiation of ART in this setting compared with waiting until CD4 cell counts drop below 350 cells/mm^3 [56-57]. Preg-

nant women with CD4 cell counts between 350 and 500 cells/mm^3 should be started on a combination ARV regimen during pregnancy to prevent perinatal transmission of HIV and counseled about the current treatment recommendations, the potential risks versus benefits of stopping versus continuing the regimen after delivery, and the need for strict adherence if the regimen is continued postpartum.

For individuals with CD4 counts >500 cells/mm^3, the adult guidelines note that some experts would recommend initiating lifelong therapy, while other experts would view this as optional, given that data are inconclusive on the clinical benefit of starting treatment at higher CD4 cell counts (>500 cells/mm^3). So far, no increased risk of disease progression has been shown in studies of pregnant women with relatively high CD4 counts who stop ARV drugs after delivery[53-55]. The potential benefits of early therapy must be weighed against possible drug toxicity, cost, and the risk of development of viral resistance with suboptimal adherence, which may be more likely during the postpartum period[58]. Pregnant women with CD4 cell counts >500 cells/mm^3 should be started on a combination ARV regimen during pregnancy to prevent perinatal transmission. They should be assessed for their willingness and ability to commit to ongoing continuous therapy and counseled about the current treatment guidelines, the benefits and risks of therapy, that data on the clinical benefit of starting lifelong treatment at CD4 cell counts >500 cells/mm^3 are inconclusive, and the importance of adherence if the regimen is continued postpartum.

In general, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, as discussed later (see Stopping Antiretroviral Therapy during Pregnancy), in women receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, continuing the dual-NRTI backbone for a period of time after stopping the NNRTI is recommended to reduce the development of NNRTI resistance. An alternative strategy is to replace the NNRTI with a protease inhibitor (PI) drug while continuing the NRTI, then to discontinue all the drugs at the same time[59]. The optimal interval between stopping an NNRTI and stopping the other ARV drugs is unknown, but a minimum of 7 days is recommended. Drug concentrations may be detectable for more than 3 weeks after efavirenz is stopped in patients receiving an efavirenz-based NNRTI regimen. Therefore, for patients receiving efavirenz, some experts recommend continuing the other ARV agents or substituting a PI plus two other agents for up to 30 days.

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[60-64]. 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 (CDC) recommends that HIV-infected women in the United States (including those receiving ART) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk[65].

The National Perinatal HIV Hotline (1-888-448-8765)

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

Recommendations for Use of Antiretroviral Drugs During Pregnancy

The Panel recommends that choice of ARV drug regimens for HIV-infected pregnant women be based on the same principles used to choose regimens for nonpregnant individuals, unless there are compelling

pregnancy-specific maternal or fetal safety issues associated with specific drugs. The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration (FDA) review related to treatment of HIV-infected adult women, both pregnant and nonpregnant. The durability, tolerability, and simplicity of a medication regimen is particularly important for preserving future options for women who will be stopping medications after delivery and women who meet standard criteria for initiation of ART per adult guidelines and will continue the regimen after pregnancy. Regimen selection should be individualized and the following factors should be considered:

- comorbidities;
- patient adherence potential;
- convenience;
- potential adverse maternal drug effects;
- potential drug interactions with other medications;
- results of genotypic resistance testing;
- pharmacokinetic (PK) changes in pregnancy; and
- potential teratogenic effects and other adverse effects on fetuses or newborns.

Information used by the Panel for recommending specific drugs or regimens for pregnant women include:

- Data from randomized prospective clinical trials 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 some drug regimens in reducing mother-to-child transmission of HIV;
- PK data during the prenatal period. (The physiologic changes of pregnancy have the potential to alter drug PKs. ARV dosing during pregnancy should be based on PK data from studies in pregnant women. Physiologic changes are not fixed throughout pregnancy but, rather, reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum period.); and
- Data from animal teratogenicity studies.

Categories of ARV regimens include:

- **Preferred:** Drugs or drug combinations are designated as preferred for use in 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 evidence of teratogenic effects or established association with teratogenic or clinically significant adverse outcomes for mothers, fetuses, or newborn are present.
- **Alternative:** Drugs or drug combinations are designated as alternatives for initial therapy in 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.

- **Use in Special Circumstances:** Drug or drug combinations in this category can be considered for use when intolerance or resistance prohibits use of other drugs with fewer toxicity concerns or in women who have comorbidities or require concomitant medications that may limit drug choice, such as active tuberculosis requiring rifampin therapy.
- **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.
- **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 for pregnancy.

A combination ARV regimen with at least three agents is recommended for use in pregnancy for either treatment or prophylaxis. 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 ART for their own health. In these cases, the choice of active drugs with known safety data in pregnancy may be more limited. In general, women who are already on a fully suppressive regimen should continue their regimens. Use of efavirenz, however, should be avoided in the first trimester.

Other HIV-infected women may not be receiving ART at the time they present for obstetrical care. Some women have never received ARV drugs, while others may have taken ARV drugs for treatment that was stopped or for prophylaxis to prevent perinatal transmission of HIV in prior pregnancies or for pre- or post-exposure prophylaxis. Considerations for initiating therapy in pregnant women differ, depending upon whether ARV drugs are currently indicated for maternal health or solely for fetal protection. The following sections will provide detailed discussions of recommendations based on maternal ARV history and whether there are maternal indications for therapy.

For ARV-naive women, a combination regimen including two NRTIs and either an NNRTI or a PI (generally with low-dose ritonavir) would be preferred.

The preferred NRTI combination for ARV-naive pregnant women is zidovudine/lamivudine, based on efficacy studies in preventing perinatal transmission (see Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission) and large experience with safety of use in pregnancy. Alternate regimens can be used in women who are intolerant of zidovudine because of toxicity such as severe anemia or who have known resistance to the drug.

Tenofovir is a preferred NRTI for nonpregnant women. Data from the Antiretroviral Pregnancy Registry on 1,092 pregnancies with first-trimester exposure to tenofovir have shown no increase in overall birth defects compared with the general population[4]. Animal studies, however, have shown decreased fetal growth and reduction in fetal bone porosity, and studies in infected children on chronic tenofovir-based therapy have shown bone demineralization in some children. Therefore, tenofovir would be considered an alternative NRTI during pregnancy for ARV-naive women. For pregnant women with chronic hepatitis B infection, however, tenofovir in combination with emtricitabine or lamivudine would be the preferred NRTI backbone of a combination ARV regimen. 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 two NRTIs, either an NNRTI or a PI would be preferred for combination regimens in ARV-naive pregnant women. Efavirenz, the preferred NNRTI for nonpregnant adults, is not recom-

mended for use in the first trimester because non-human primate data show risk of anencephaly, microophthalmia, and cleft palate, and there are several concerning case reports of neural tube defects and a single case of anophthalmia with severe facial cleft in humans. Use of efavirenz can be considered after the first trimester, based on clinical indication, but current data are limited in defining the safety of this use. Nevirapine would be the preferred NNRTI for ARV-naive pregnant women with CD4 cell lymphocyte counts <250 cells/mm^3, and it can be continued in ARV-experienced women already receiving a 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^3 because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity (see Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants). Elevated transaminase levels at baseline also may increase the risk of nevirapine toxicity[66]. Safety and PK data on etravirine and rilpivirine in pregnancy are insufficient to recommend use of these NNRTI drugs in ARV-naive women.

Lopinavir/ritonavir is the preferred PI regimen for ARV-naive pregnant women, based on efficacy studies in adults and experience with use in pregnancy (see Table 5 for dosing considerations). Alternative PIs include ritonavir-boosted atazanavir or saquinavir, although experience is more limited with these regimens in pregnancy. Nelfinavir can be considered in special circumstances when used solely for prophylaxis of perinatal transmission in ARV-naive women for whom therapy would not otherwise be indicated and who cannot tolerate alternative agents. 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 lopinavir/ritonavir or efavirenz-based regimens in clinical trials of initial therapy in nonpregnant adults. Indinavir can also be considered in special circumstances for women in whom preferred or alternative drugs cannot be used. Indinavir may be associated with renal stones and has a higher pill burden than many other PI drugs. Data on use in pregnancy are too limited to recommend routine use of darunavir, fosamprenavir, and tipranavir in pregnant women, although they can be considered for women who are intolerant of other agents.

Safety and PK data in pregnancy are insufficient to recommend use of the entry inhibitors enfuvirtide and maraviroc and the integrase inhibitor raltegravir 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.

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 http://www.APRegistry.com.) However, certain drugs are of more concern than others—for example, efavirenz should be avoided during the first trimester of pregnancy (see Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy).

Table 5 provides recommendations for use of specific ARV drugs in pregnancy and data on PKs and toxicity in pregnancy. Table 6 summarizes management recommendations for the mothers and infants in a variety of clinical scenarios.

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 1 of 4)

Clinical Scenario	Recommendations
Nonpregnant HIV-infected women of childbearing potential who have indications for initiating antiretroviral therapy (ART)	Initiate combination antiretroviral (ARV) drug therapy as per adult treatment guidelines. When feasible, include one or more nucleoside reverse transcriptase inhibitors (NRTIs) with good placental passage as a component of the ARV regimen. • Avoid drugs with teratogenic potential (e.g., efavirenz) in women who are trying to conceive or are not using adequate contraception. Exclude pregnancy and ensure access to effective contraception before starting treatment with efavirenz.
HIV-infected women on combination ARV drug therapy who become pregnant	**Women:** • In general, in women who require treatment, ARV drugs should not be stopped during the first trimester or during pregnancy. • Continue current combination ART, if successfully suppressing viremia; however, avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy. • Perform HIV ARV drug-resistance testing in women on therapy who have detectable viremia. • Continue combination ART regimen during the intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infants:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

HIV-infected pregnant women who are ARV naive *and* have indications for ART	**Women:**
	• Perform HIV ARV drug-resistance testing prior to initiating combination ARV drug therapy and repeat after initiating therapy if viral suppression is suboptimal.
	• Initiate combination ARV regimen.
	  • Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy.
	  • When feasible, include one or more NRTIs with good placental passage in the ARV regimen.
	  • Use nevirapine as a component of the ARV regimen only in women who have CD4 counts ≤250 cells/mm^3. Because of the increased risk of severe hepatic toxicity, use nevirapine in women with CD4 counts >250 cells/mm^3 only if the benefit clearly outweighs the risk.
	• In women who require initiation of therapy for their own health, initiate treatment as soon as possible, including in the first trimester.
	• Continue the combination regimen during the intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally) and postpartum.
	• Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery.
	Infants:
	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 2 of 4)

Clinical Scenario	Recommendations

HIV-infected pregnant women who are ARV naive and do *not* require treatment for their own health	**Women:**
	• Perform HIV ARV drug-resistance testing prior to initiating combination ARV drug therapy and repeat after initiation of therapy if viral suppression is suboptimal.
	• Prescribe combination ARV drug prophylaxis (i.e., at least 3 drugs) to prevent perinatal transmission.
	  • Delayed initiation of prophylaxis until after the first trimester of pregnancy can be considered in women who are receiving ARV drugs solely for prevention of perinatal transmission, but earlier initiation of prophylaxis may be more effective in reducing perinatal transmission of HIV.
	  • Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy.
	  • When feasible, use one or more NRTIs with good transplacental passage as a component of the ARV regimen.
	  • Use nevirapine as a component of therapy in women who have CD4 counts >250 cells/mm^3 only if the benefit clearly outweighs the risk because of the drug's association with an increased risk of severe hepatic toxicity.
	• Continue ARV prophylaxis regimen during the intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally).
	• Evaluate need for continuing the combination regimen postpartum. Following delivery, considerations for continuation of the mother's ARV regimen are the same as for other nonpregnant individuals (see General Principles Regarding Use of Antiretroviral Drugs in Pregnancy). If treatment is to be stopped and the regimen includes a drug with a long half-life, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), consider stopping NRTIs at least 7 days after stopping NNRTI. (See Stopping Antiretroviral Therapy Drugs During Pregnancy and Prevention of Antiretroviral Drug Resistance.)
	• Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery.
	Infants:
	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 3 of 4)

Clinical Scenario	Recommendations

HIV-infected pregnant women who are ARV experienced but not currently receiving ARV drugs	**Women:**
	• Obtain full ARV drug history, including prior resistance testing, and evaluate need for ART for maternal health.
	• Test for HIV ARV drug resistance before re-initiating ARV prophylaxis or therapy and retest after initiating combination ARV regimen if viral suppression is suboptimal.
	• Initiate a combination ARV regimen (e.g., at least 3 drugs), with regimen chosen based on results of resistance testing and history of prior therapy.
	  • In women who require initiation of therapy for their own health, initiate treatment as soon as possible, including in the first trimester.
	  • Delayed initiation of prophylaxis until after the first trimester of pregnancy can be considered in women who are receiving ARV drugs solely for prevention of perinatal transmission, but earlier initiation of prophylaxis may be more effective in reducing perinatal transmission of HIV.
	  • Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for the mother (e.g., combination stavudine/didanosine) throughout the pregnancy.
	  • When feasible, include one or more NRTIs with good transplacental passage as a component of the ARV regimen.
	  • Use nevirapine as a component of therapy in women who have CD4 counts >250 cells/mm^3 only if the benefit clearly outweighs the risk because of the drug's association with an increased risk of severe hepatic toxicity.
	• Continue the combination regimen during intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally).
	• Evaluate need for continuing the combination regimen postpartum. Following delivery, considerations for continuation of the mother's ARV regimen are the same as for other nonpregnant adults (see General Principles Regarding Use of Antiretroviral Drugs in Pregnancy). If treatment is to be stopped and the regimen includes a drug with a long half-life, such as NNRTIs, consider stopping NRTIs at least 7 days after stopping NNRTIs. (See Stopping Antiretroviral Therapy and Prevention of Antiretroviral Drug Resistance.)
	• Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery.
	Infants:
	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

HIV-infected women who have received no ART before labor	**Women:** Give zidovudine as continuous infusion[1] during labor. **Infants:** Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen started as close to the time of birth as possible. Zidovudine[b] given for 6 weeks combined with 3 doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) has been shown to be effective in a randomized controlled trial and less toxic than a 3-drug regimen with nelfinavir and laminvudine for 2 weeks and 6 weeks of zidovudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States (see Infant Antiretroviral Prophylaxis and Table 9). • Evaluate need for initiation of maternal therapy postpartum.

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 4 of 4)

Clinical Scenario	Recommendations
Infants born to HIV-infected women who have received no ART before or during labor	• Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen started as close to the time of birth as possible. Zidovudine[b] given for 6 weeks combined with 3 doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) has been shown to be effective in a randomized controlled trial and less toxic than a 3-drug regimen with nelfinavir and laminvudine for 2 weeks and 6 weeks of zidovudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States (see Infant Antiretroviral Prophylaxis and Table 9). • Evaluate need for initiation of maternal therapy postpartum.

[a] Zidovudine continuous infusion: 2 mg/kg zidovudine intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

[b] Zidovudine dosing for infants ≥35 weeks' gestation at birth is 4 mg/kg/dose orally twice daily; for infants <35 weeks of gestation at birth is 1.5 mg/kg/dose intravenously or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if ≥30 weeks of gestation at birth or at 4 weeks of age if <30 weeks' gestation at birth.

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HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Updated September 14, 2011)

Panel's Recommendations

• HIV-infected pregnant women who meet standard criteria for initiation of antiretroviral therapy (ART) per adult antiretroviral (ARV) treatment guidelines should receive standard potent combination ART as recommended for nonpregnant adults, taking into account what is known about the use of specific drugs in pregnancy and the risk of teratogenicity (Table 5) **(AI)**.
  • For women who require immediate initiation of therapy for their own health, treatment should be started as soon as possible, including in the first trimester **(AII)**. (Note that the use of efavirenz should be avoided during the first trimester.)
• A three-drug combination ARV regimen for prophylaxis of perinatal transmission also is recommended for HIV-infected pregnant women who do not require treatment for their own health **(AII)**.
  • Consideration can be given to delaying initiation of prophylaxis until after the first trimester **(BIII)** in women who are receiving ARV drugs solely for prevention of perinatal transmission, but earlier initiation of therapy may be more effective in reducing *in utero* transmission.
• ARV regimens should include a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs with high levels of transplacental passage, if possible, to provide pre-exposure prophylaxis to the infant **(AIII)**.
• If HIV RNA is above the threshold for resistance testing (i.e., >500–1,000 copies/mL), ARV drug-resistance studies should be performed before starting the ARV drug regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AI)**. If HIV is diagnosed late in pregnancy, the ARV drug regimen should be initiated pending results of resistance testing **(BIII)**.
• Nevirapine can be used as a component of the ARV drug regimen for pregnant women with CD4 cell counts ≤250 cells/mm^3. In pregnant women with CD4 cell counts >250 cells/mm^3, however, nevirapine should be used only if the benefit clearly outweighs the risk because the drug is associated with an increased risk of hepatic toxicity **(AII)**.

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation. Decisions about the need for initiation of therapy should be based on the standard guidelines for nonpregnant adults[1].

HIV-Infected Pregnant Women Not on Antiretroviral Therapy and Who Need Antiretroviral Treatment for Their Own Health

Any HIV-infected pregnant woman who meets standard criteria for initiation of ART as per ARV guidelines in nonpregnant adults should receive potent combination ART, generally consisting of NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI), with continuation of therapy postpartum. Treatment should be started as soon as possible—including in the first trimester—for women who require immediate initiation of therapy for their own health because the potential benefit of treatment for the mother outweighs potential risks to the fetus. The regimen generally should be chosen from among those shown to be effective in nonpregnant adults, taking into account what is known about use of the drugs during pregnancy and risk of teratogenicity (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy)[1].

A review of a large database of nevirapine studies indicated that women with CD4 counts >250

cells/mm^3 have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity that can be severe, life threatening, and in some cases fatal[2-3]. A more recent study involving 820 women in Kenya, Zambia, and Thailand, however, did not find an association between CD4 count and development of hepatotoxicity[4]. Rash and liver toxicity were associated with elevated baseline liver transaminases but not with CD4 count; all deaths from hepatic toxicity occurred in women with CD4 counts <100 cells/mm^3 at baseline. In women with CD4 counts >250 cells/mm^3, nevirapine should be used as a component of a combination regimen only when the benefit clearly outweighs the risk. If nevirapine is used, frequent and careful monitoring of transaminase levels is required, particularly during the first 18 weeks of treatment (see Nevirapine and Hepatic/Rash Toxicity). Transaminase levels should be checked in women who develop a rash while receiving nevirapine. Nevirapine should be stopped immediately in women who develop signs or symptoms of hepatitis.

HIV-Infected Pregnant Women Not on Antiretroviral Therapy Who Require Antiretroviral Prophylaxis Solely to Prevent Perinatal Transmission of HIV

HIV-infected pregnant women should be counseled regarding the benefits of ARV drugs for prevention of perinatal transmission even when initiation of ART for maternal health is not recommended or is considered optional on the basis of current guidelines for treatment of nonpregnant persons[1]. Although such women are at low risk of clinical disease progression if ARV treatment is delayed, use of an ARV regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal transmission of HIV and lessens the need for consideration of elective cesarean delivery as an intervention to reduce risk of transmission.

The fetus is 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 of pregnancy who do not require immediate initiation of therapy for their own health may consider delaying initiation of ARV drugs until after 12 weeks of gestation. This decision should be carefully considered by the health care provider and the woman. Their discussion should encompass an assessment of the woman's health status, the benefits and risks to her of delaying initiation of ARV drugs for several weeks, the fact that most perinatal transmission of HIV events occur late in pregnancy or during delivery, and the possibility that early control of viral replication may be important in preventing the smaller proportion of earlier *in utero* transmission. In a recent French study, lack of early and sustained control of maternal viral load appeared strongly associated with residual perinatal transmission of HIV[5]. 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 of gestation. Among women starting ARV drugs during pregnancy, the gestational age at initiation of therapy did not differ between groups (30 weeks), but viral load decreased earlier in the nontransmitters. These data suggest that early and sustained control of HIV viral replication is associated with decreasing residual risk of transmission and favor initiating ARV drugs as early in pregnancy as possible for all women.

ARV prophylaxis is recommended for all pregnant women with HIV infection, 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 assured[6-8]. The mechanism by which ARV drugs reduce perinatal HIV transmission 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[9-13]. Additional mechanisms of protection include pre-exposure prophylaxis and post-exposure prophylaxis of the infant. With pre-exposure prophylaxis, 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. With post-exposure prophylaxis, ARV drugs are administered to the infant after birth. Transplacental passage is excellent with zidovudine but may be variable with many other ARV drugs (Table 4). Therefore, whenever possible, combination ARV drug regimens initiated during pregnancy should include zidovudine or another NRTI with high transplacental passage, such as lamivudine, emtricitabine, stavudine, tenofovir, or abacavir (see Table 5)[14-17].

All pregnant women with HIV infection should be counseled about and offered combination ARV regimens containing at least three drugs for prevention of perinatal transmission of HIV. In an analysis of perinatal transmission in 5,151 HIV-infected women between 2000 and 2006 in the United Kingdom and Ireland, the overall mother-to-child 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[18]. Transmission rates were 0.7% for women receiving a triple-ARV drug regimen combined with a planned cesarean delivery or with planned vaginal delivery and 0.5% in 464 women who received single-drug prophylaxis with zidovudine combined with a planned cesarean delivery (as recommended in the British HIV Association guidelines for women with HIV RNA levels <10,000 copies/mL and wild-type virus who do not require treatment for their own health)[19], not significantly different between groups. 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.

A combination regimen including two NRTIs and either an NNRTI or a PI (the latter with or without low-dose ritonavir) would be the preferred prophylactic regimen for ARV-naive women receiving drugs solely for prevention of transmission, as discussed in Recommendations for Use of Antiretroviral Drugs during Pregnancy. A study in Botswana compared a PI-based triple-drug regimen to a triple-NRTI (zidovudine/lamivudine/abacavir) combination regimen for prevention of transmission in breastfeeding women with CD4 counts ≥200 cells/mm^3 [20]. Both regimens had similar rates of viral suppression by delivery (96% receiving the PI regimen and 93% receiving the triple-NRTI regimen had HIV RNA <400 copies/mL) and perinatal transmission (0.4% and 1.4%, respectively, not significantly different). Thus, for women who plan to discontinue prophylaxis following delivery, a triple-NRTI regimen also can be considered. If using abacavir, testing for HLA-B*5701, which identifies patients at risk of abacavir hypersensitivity reactions[21-22], should be performed and the results documented as negative before abacavir is started.

Some women may wish to restrict fetal exposure to ARV drugs while reducing the risk of HIV transmission to the infant. 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., HIV RNA <1,000 copies/mL) on no ARV drugs. Time-limited administration of zidovudine during the second and third trimesters of pregnancy is less likely to induce the 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[23-24].

Following delivery, considerations regarding continuation of the ARV regimen for treatment of the mother are the same as for other nonpregnant adults (see General Principles for Use of Antiretroviral Drugs during Pregnancy).

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HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment (Updated September 14, 2011)

Panel's Recommendations
• In general, pregnant women receiving and tolerating an antiretroviral therapy (ART) regimen that is currently effective in suppressing viral replication should continue on the regimen; however, the use of efavirenz should be avoided in the first trimester **(AIII)**. • HIV antiretroviral (ARV) drug-resistance testing is recommended for pregnant women who have detectable viremia (e.g., >500–1,000 copies/mL) on therapy (see Failure of Viral Suppression) **(AI)**. • Pregnant women receiving and tolerating nevirapine-containing regimens who are virologically suppressed should continue the regimen, regardless of CD4 count **(AIII)**.

In general, women who have been receiving antiretroviral treatment (ART) for their HIV infection should continue that 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 HIV transmission. Continuation of therapy, therefore, is recommended when pregnancy is identified in HIV-infected women receiving ART.

HIV-infected women receiving ART who present for care during the first trimester should be counseled regarding the benefits and potential risks of administration of ARVs during this period. Clinicians should review the safety and risk/benefit profiles and reproductive considerations for the ARV agents used in the current HIV therapeutic regimen. The use of efavirenz should be avoided during the first trimester of pregnancy. If a first-trimester pregnancy is confirmed in a woman who is receiving efavirenz, an alternative ARV drug should be substituted when possible (see Monitoring of the Woman and Fetus during Pregnancy).

Resistance testing should be performed in women who are on therapy but in whom viral replication is not fully suppressed. The results can be used to select a new regimen with a greater likelihood of suppressing viral replication to undetectable levels. It should be noted that resistance assays vary depending on the HIV RNA level required to detect resistance mutations. Some assays require HIV RNA levels of >500–1,000 copies/mL; other assays can be performed on patients with lower viral loads.

Pregnant women for whom nevirapine-containing regimens are achieving viral suppression and who are tolerating therapy should continue that regimen, regardless of current CD4 count. Although hepatic toxicity is a concern in women starting a nevirapine-containing regimen who have CD4 counts >250 cells/mm^3, an increased risk of hepatic toxicity has not been seen in women receiving nevirapine-based therapy for whom the therapy has produced immune reconstitution.

HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications (Updated September 14, 2011)

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 (e.g., >500–1,000 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 pending results of resistance testing **(BIII)**.
• Choose and initiate a combination ARV drug regimen based on results of resistance testing and prior history of antiretroviral therapy (ART) while avoiding drugs with teratogenic potential (efavirenz in the first trimester of pregnancy) or with known adverse potential for the mother **(AII)**.
• Consult specialists in treatment of HIV infection about the choice of ART in women who previously received ARVs 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 do not achieve virologic suppression on their ARV regimens (see Monitoring of the Woman and Fetus During Pregnancy).

During a previous pregnancy, HIV-infected women may have received ARV drugs solely for prevention of perinatal transmission. At any time in the past, they also may have discontinued ARVs given to them for treatment of their own disease. A small number of clinical trials or observational studies have generated information about how effective ART is in individuals who previously received ARV prophylaxis. The data are limited to outcomes with therapy containing nevirapine initiated after the use of peripartum single-dose nevirapine[1-5].

Initial reports suggested a diminished virologic and clinical response to nevirapine-based ART if therapy was initiated within 6 months of intrapartum single-dose nevirapine exposure[1-3]. Subsequent reports have confirmed that a shorter interval between intrapartum single-dose nevirapine exposure and therapy initiation is associated with decreased efficacy of therapy and suggested that the diminished response may persist 12–24 months following exposure[4-5]. In addition, the subsequent failure of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART after single-dose nevirapine has been associated with lower CD4 count and higher HIV-RNA plasma concentration at the time of single-dose nevirapine exposure, and genotypic resistance to nevirapine. Adding other ARVs to single-dose nevirapine (e.g., use of an ARV "tail") decreases rates of nevirapine resistance[6-7] (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy), but the effect on clinical response to the subsequent initiation of NNRTI-based ART is unknown.

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 the ARV drugs when used for treatment. Rates of resistance appear to be low, based on standard genotyping, after prophylaxis for prevention of perinatal transmission with combination ARVs consisting of zidovudine, lamivudine, and nevirapine[8-9]. However, particularly in women whose virus was inadequately suppressed during the pe-

riod of prophylaxis, minority populations of virus with resistance to nevirapine or lamivudine have been detected using sensitive allele-specific polymerase chain reaction (PCR) techniques[9-11]. Only limited data are available on the impact of these resistance-conferring minority variants on prediction of virologic or clinical failure of subsequent ART, and the PCR-based assays are not widely available. 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[11-12]. However, to date, treatment failure has not been demonstrated with reinitiation of combination ARV regimens (particularly those containing the dual nucleoside reverse transcriptase inhibitor [NRTI] backbone of zidovudine and lamivudine) following prophylactic use in pregnancy for prevention of transmission, although controlled observations are lacking.

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 ARVs was during pregnancy for prophylaxis of perinatal transmission. However, interpretation of resistance testing following 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—as well as the results of resistance testing should be taken into consideration. If the woman presents late in pregnancy, therapy or prophylaxis should be initiated 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 ART 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 as well as her adherence to therapy. The appropriate choice of ARV regimen to be initiated during pregnancy will vary according to a woman's history of ART; 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 ART associated with successful suppression of viral load who then stopped all drugs simultaneously (or staggered discontinuation if 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 ART, 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 suitable ART.

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Special Situations — HIV/Hepatitis B Virus Coinfection (Updated September 14, 2011)

Panel's Recommendations
• Screening for hepatitis B virus (HBV) infection is recommended for all pregnant women who have not been screened during the current pregnancy **(AII)**.
• The HBV vaccine series should be administered to pregnant women who screen negative for hepatitis B (i.e., hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative) **(AII)**.
• Pregnant women with chronic HBV infection should be screened for antibodies to hepatitis A virus (HAV), and those who screen negative should receive the HAV vaccine series **(AII)**.
• Interferon alfa and pegylated interferon alfa are not recommended during pregnancy **(AIII)**.
• The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV is strongly recommended **(AIII)**.
• All pregnant women with HIV/HBV coinfection should receive a combination antiretroviral (ARV) drug regimen, 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 NRTI/NtRTI backbone of a combination antepartum ARV regimen in HIV/HBV-coinfected pregnant women **(AI)**.
• If ARV drugs are discontinued postpartum in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected **(BIII)**.
• Pregnant women with HIV/HBV coinfection receiving ARV drugs should be counseled about the 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 **(BIII)**.
• Within 12 hours of birth, infants born to women with HBV infection should receive hepatitis B immune globulin (HBIG) 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)**.

For additional information on hepatitis B and HIV, see Hepatitis B (HBV)/HIV Coinfection in Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (http://AIDSInfo.nih.gov)[1] and Hepatitis B Virus Infection in the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Recommendations from the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association of the Infectious Diseases Society of America[2].

All HIV-infected pregnant women should be screened for hepatitis A, B, and C. The management of HIV/HBVcoinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended. HIV-infected women who are found to have chronic HBV infection on the basis of persistent hepatitis B surface antigenemia for at least 6 months and who are hepatitis A immunoglobulin G (IgG) negative should receive the HAV vaccine series because of the added risk of acute hepatitis A in persons with chronic viral hepatitis.

HIV-infected pregnant women who test negative for hepatitis B surface antibody and hepatitis B surface antigen should receive the HBV vaccine series. A positive test for hepatitis B core antibody alone can be a false-positive result, or it may signify past exposure with subsequent loss of hepatitis B surface antibody, or "occult" HBV infection, which can be confirmed by detection of HBV DNA[3-4]. The clinical significance of

isolated hepatitis B core antibody is unknown[5-6]. Some experts recommend that HIV-infected persons with hepatitis B core antibody alone should be tested for HBV DNA before vaccination for HBV or before treatment or prophylaxis with ARV drugs is initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS)[2].

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 among women with relatively high 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 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[7-9]. Several small studies 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[10-13]. Although a high HBV viral load clearly is important, it is, however, not the only factor predisposing to failure of prophylaxis[14].

Because lamivudine, tenofovir, and emtricitabine have activity against both HIV and HBV, the recommended dual-NRTI/NtRTI 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 (Table 5). The Antiretroviral Pregnancy Registry includes reports on the outcomes of 3,864 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[15]. Similarly, no increase in birth defects has been noted in 641 cases of first-trimester exposure to emtricitabine, which is an alternative NRTI for use in pregnancy (Table 5). Tenofovir is not teratogenic in animals, but reversible bone changes at high doses have been seen in multiple animal species. A total of 1,092 cases of first-trimester exposure have been reported to the Antiretroviral Pregnancy Registry, with no increase in birth defects noted[15]. Although tenofovir is recommended as an alternative NtRTI during pregnancy for ARV-naive women, it is a preferred NtRTI in women with HIV/HBV coinfection (Table 5).

Several other antivirals with activity against HBV, including entecavir, adefovir, and telbivudine, have had minimal evaluation in pregnancy. Entecavir is associated with skeletal anomalies in rats and rabbits but only at doses high enough to cause toxicity to the mother. No data are available on use of entecavir and adefovir in human pregnancy. Telbivudine was given to 95 HBV-positive, HIV-negative women during the third trimester and was well tolerated[13]. 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 a fully suppressive ARV regimen as well as potential cross resistance to other ARV drugs. (Entecavir, for example, can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine.) These drugs should be used during pregnancy only if the preferred drugs are not appropriate in specific cases. 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[16].

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 (PIs) and nevirapine. Pregnant women with HIV/HBVcoinfection 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 nonpregnant adults.

Following delivery, considerations regarding continuation of the ARV drug regimen are the same as for other nonpregnant individuals (see General Principles Regarding Use of Antiretroviral Drugs During Pregnancy). Discontinuation of 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 reinitiation of treatment for both HIV and HBV if a flare is suspected.

Within 12 hours of birth, all infants born to mothers with chronic HBV infection should receive HBIG and the first dose of the HBV vaccination series. 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.

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Special Situations — HIV/Hepatitis C Virus Coinfection (Updated September 14, 2011)

Panel's Recommendations
• Screening for hepatitis C virus (HCV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy **(AIII)**. • Interferon alfa and pegylated interferon alfa are not recommended and ribavirin is contraindicated during pregnancy **(AIII)**. • Recommendations for antiretroviral (ARV) drug use during pregnancy are the same for women who have chronic HCV as for those without HIV/HCV coinfection **(BIII)**. • Pregnant women with HIV/HCV coinfection receiving ARV drugs should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 1 month following initiation of ARV drugs and then every 3 months thereafter **(BIII)**. • Decisions concerning mode of delivery in HIV/HCV-coinfected 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 with a positive anti-HCV antibody should undergo confirmatory HCV RNA testing. If earlier diagnosis is indicated or desired, HCV RNA virologic testing between ages 3 and 6 months can be performed **(AIII)**. • Women who are found to have chronic HCV infection should also be screened for hepatitis A virus (HAV) and hepatitis B virus (HBV) because they are at increased risk of complications from those two infections. Women with chronic HCV who are negative for hepatitis A immunoglobulin G (IgG) should receive the HAV vaccine series. If they are not infected with HBV (i.e., hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series **(AIII)**.

For additional information on hepatitis C and HIV, see Hepatitis C Virus Infection of the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents, Recommendations from the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association of the Infectious Diseases Society of America at http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf [2].

HIV/HCV coinfection is not uncommon in HIV-infected women, particularly those infected via parenteral use of drugs; among HIV-infected pregnant women, the HCV seroprevalence rate ranges from 17% to 54%[3]. Screening for chronic HCV infection using a sensitive immunoassay for HCV antibody is recommended for all HIV-infected individuals, including pregnant women. False-negative anti-HCV immunoassay results can occur in HIV-infected persons, particularly those with very low 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.

Few data exist on the optimal management of HIV-infected pregnant women with HCV coinfection. Recommendations for ARV drug use during pregnancy for treatment of HIV and/or prevention of mother-to-child transmission are the same for women who have HCV coinfection as for those with HIV alone (see Hepatitis C [HCV]/HIV Coinfection in Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected

Adults and Adolescents, http://AIDSInfo.nih.gov). 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[4], and ribavirin is contraindicated (Food and Drug Administration [FDA] pregnancy category X) due to 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[5]. 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 recently approved by the FDA for treatment of HCV. 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[6].

Because of the added risk of acute HAV and HBV in persons with chronic HCV, women who are found to have chronic HCV infection should also be screened for HAV and HBV. Women with chronic HCV infection who are hepatitis A IgG negative should receive the HAV vaccine series, and if they are not infected with HBV (i.e., hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series.

In a majority of studies, the incidence of HCV transmission from mother to infant increases if the mother is coinfected with HIV, with transmission rates between 10% and 20%[7-10]. These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impact on HCV disease activity[11]. A European study of perinatal transmission of HCV found that use of effective combination therapy for HIV was associated with a strong trend toward reduction in HCV transmission (odds ratio [OR] 0.26, 95% confidence interval [CI], 0.07–1.01)[12]. Maternal HCV/HIV coinfection also may increase the risk of perinatal transmission of HIV[13]. Therefore, potent combination ART with at least three drugs is recommended for all HIV/HCV-coinfected pregnant women, regardless of CD4 cell count or HIV viral load.

As with chronic HBV infection, an elevation in hepatic enzymes following initiation of ART can occur in HIV/HCV-coinfected women—particularly in those with low CD4 cell counts at treatment initiation—as a result of an immune-mediated flare in HCV disease triggered by immune reconstitution with effective ART. 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 mother-to-child transmission of HCV may be increased by use of internal fetal monitoring, amniocentesis, and rupture of membranes for more than 6 hours[9, 14]. 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[12, 15-17]. 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 between ages 3 and 6 months, if earlier diagnosis is indicated or desirable[18-19]. Because HCV viremia can be intermittent, at least two negative tests are needed to exclude HCV infection. Children are considered to be HCV infected if they have two or more positive HCV RNA polymerase chain reaction (PCR) results or are HCV antibody positive beyond age 18 months.

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Special Situations — HIV-2 Infection and Pregnancy (Updated September 14, 2011)

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 and an HIV-1 RNA viral load 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 counts <500 cells/mm^3 **(AIII)**.
  • Based on available data on safety in pregnancy, zidovudine/lamivudine plus lopinavir/ritonavir would be preferred **(AIII)**. Tenofovir plus lamivudine or emtricitabine plus lopinavir/ritonavir can be considered as an alternative **(BIII)**.
• 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 counts ≥500 cells/mm^3 and no significant clinical disease). Experts have recommended the following approaches:
  • A boosted PI-based regimen (two NRTIs plus lopinavir/ritonavir) for prophylaxis, with the drugs stopped postpartum **(BIII)**;
  • Zidovudine prophylaxis alone during pregnancy and intrapartum **(BIII)**.
• Non-nucleoside reverse transcriptase inhibitors (NNRTIs) 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, breastfeeding is not recommended for infants of HIV-2-infected mothers **(AIII)**.

HIV-2 infection is endemic in Angola; Mozambique; West African countries including Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and in parts of India[1-3]. It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions[4]. HIV-2 is rare in the United States. HIV-2 infection should be suspected in pregnant women who are from—or who have partners from—countries in which the disease is endemic, who are HIV-1 antibody positive on an initial enzyme-linked immunoassay screening test, and who have repeatedly indeterminate results on HIV-1 Western blot and HIV-1 RNA viral loads at or below the limit of detection[5-6]. This pattern of HIV testing can also be seen in patients who have a false-positive HIV-1 test.

The majority of commercially available HIV screening tests can detect both HIV-1 and HIV-2 but cannot distinguish between the two viruses. The only Food and Drug Administration (FDA)-approved antibody test that distinguishes between HIV-1 and HIV-2 is the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test. If HIV-2 is suspected, infection can be confirmed using a supplemental test such as an HIV-2 immunoblot or HIV-2-specific Western blot. HIV-2 immunoblots are available through commercial labs; however, none is FDA approved for HIV-2 diagnosis. HIV-2-specific Western blots can be requested through state health departments. HIV-2 viral load assays currently are not commercially available in the United States. The National Perinatal HIV Hotline (1-888-448-8765) can provide a list of sites that perform these tests.

HIV-2 has a longer asymptomatic phase than HIV-1, with a slower progression to AIDS. The most common mode of HIV-2 transmission is through heterosexual sex. HIV-2 is less infectious than HIV-1, with

a 5-fold lower rate of sexual transmission and 20- to 30-fold lower rate of vertical transmission[3, 7-8]. Several studies confirm that rates of mother-to-child 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[9-12]. HIV-2 also can be transmitted through breastfeeding. HIV-2 infection does not protect against HIV-1 and dual infection, which carries the same prognosis as HIV-1 monoinfection, can occur.

Few data exist on which to base treatment decisions or strategies for prevention of mother-to-child transmission in patients infected with HIV-2. NNRTIs and enfuvirtide are not active against HIV-2 and should not be used for treatment or prophylaxis[13-14]. HIV-2 has variable sensitivity to protease inhibitors (PIs), with lopinavir, saquinavir, and darunavir having the most activity against the virus[15]. The integrase inhibitors raltegravir and elvitegravir also appear to be effective against HIV-2[3, 16-17].

The care of HIV-2-infected pregnant women has been based on expert opinion. A regimen with two 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 counts <500 cells/mm^3 [18]. Based on available data on safety in pregnancy, zidovudine/lamivudine plus lopinavir/ritonavir would be preferred. Tenofovir plus lamivudine or emtricitabine plus lopinavir/ritonavir can be considered as an alternative[19-20]. 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 counts ≥500 cells/mm^3 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[10]. Because HIV-2 has a significantly lower risk of mother-to-child transmission than does HIV-1, single-drug prophylaxis with zidovudine alone can be considered for prevention of mother-to-child transmission. All infants born to mothers infected with HIV-2 should receive the standard 6-week zidovudine prophylactic regimen[20]. The possible risks and benefits of antiretroviral (ARV) prophylaxis should be discussed with the mother.

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 the infant 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[10].

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[21]. HIV-2 virologic assays are not commercially available, but the National Perinatal HIV Hotline (1-888-448-8765) can provide a list of sites that perform this testing.

It is also recommended that infants be tested at 18 months of age (e.g., with the Bio-Rad Laboratories Multispot HIV-1/HIV-2 test) to confirm clearance of HIV-2 antibodies[20].

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Special Situations — Acute HIV Infection (Updated September 14, 2011)

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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents) **(AII)**.
• 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 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 reside in jurisdictions with elevated rates of HIV infection (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings) **(AII)**.
• All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) drug regimen as soon as possible to prevent mother-to-child 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 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 (NNRTIs) in ARV-naive individuals in general, a ritonavir-boosted PI-based regimen should be initiated **(AIII)**.

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 mother-to-child 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 (NAAT) of pooled HIV antibody-negative specimens were pregnant at the time of testing[1]. All 5 women received ARV drugs and delivered HIV-uninfected infants.

From 2002 to 2006, 747 (22%) of 3,396 HIV-exposed neonates in New York State 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 [OR] 15.19, 95% confidence interval [CI], 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 mother-to-child transmission cases[2]. 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[3]. This high rate of transmission likely is related to the combination of the high viral load in plasma, breast milk, and the genital tract associated with acute infection[4-5] and the fact that the diagnosis is easy to miss, which results in lost opportunities for implementation of prevention interventions.

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

An estimated 40%–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[4, 6-10]. Providers often do not recognize acute HIV infection, however, because the symptoms are similar to those of other common illnesses and individuals with the condition also can be asymptomatic.

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

Acute 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. A report from the Mother-Infant Rapid Intervention at Delivery (MIRIAD) study found that 6 (11%) of 54 women whose HIV was identified with rapid HIV testing during labor had primary infection[11]. Repeat HIV testing in the third trimester is recommended for pregnant women known to be at risk of HIV who receive care in facilities with an HIV incidence of at least 1 case per 1,000 pregnant women per year, who are incarcerated, or who reside in jurisdictions with elevated HIV incidence (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings)[12].

Whether treatment of acute or recent HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown, and in nonpregnant adults, therapy currently is considered optional[13]. 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%–16% of patients, transmitted virus may be resistant to at least one ARV drug[14-16]. 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 ARV regimen should not be delayed. Because clinically significant resistance to PIs is less common than resistance to NNRTIs 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 5). Following delivery, considerations regarding continuation of the ARV regimen for treatment are the same for the mother as for other nonpregnant individuals.

When acute HIV infection is diagnosed during pregnancy, and particularly if it is documented in late pregnancy, cesarean delivery is more likely to be necessary because there may be insufficient time to fully suppress the 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 HIV acquisition. Several studies suggest that pregnancy may be a time of increased risk of transmission of HIV[17-19], even when controlling for sexual risk behaviors[17]. It is hypothesized that the heightened risk may be attributable to hormonal changes that affect the genital tract mucosa or immune responses[17]. 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[20]. HIV testing of the sexual partners of pregnant women should be encouraged. The importance of using condoms should be reinforced in pregnant women who may be at risk of acquisition of HIV, including

those whose partners are HIV-infected.

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Special Situations — Stopping Antiretroviral Drugs during Pregnancy (Updated September 14, 2011)

Panel's Recommendations
• HIV-infected women receiving antiretroviral treatment (ART) who present for care during the first trimester should continue treatment during pregnancy **(AII)**. Women who present in the first trimester on an efavirenz-containing regimen should continue on therapy without interruption but, when possible, an alternative antiretroviral (ARV) drug should be substituted for efavirenz **(AIII)**.
• If an 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 electively and the patient is receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI) drug, consideration should be given to either: (1) stopping the NNRTI first and continuing the other ARV drugs for a period of time; or (2) 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 more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other ARV agents or substituting a PI plus two other agents for up to 30 days **(CIII)**.
• If nevirapine is stopped and more than 2 weeks have passed before restarting therapy, nevirapine should be restarted with the 2-week dose escalation period **(AII)**.

Discontinuation of 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 ART who present for care during the first trimester of pregnancy 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 transmission of HIV. A recent analysis from a prospective cohort of 937 HIV-infected mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated with perinatal transmission. In the first trimester, the median time at interruption was 6 weeks' gestation and length of time without therapy was 8 weeks (interquartile range [IQR], 7–11 weeks); in the third trimester, the median time at interruption was 32 weeks and length of time without therapy was 6 weeks (IQR, 2–9 weeks). Although the perinatal transmission rate for the entire cohort was only 1.3%, transmission occurred in 4.9% (95% 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[1]. Although the use of efavirenz should be avoided during the first trimester, therapy should not be interrupted in women taking the drug who present in the first trimester but, rather, an alternative ARV should be substituted, if possible.

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 con-

ditions 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 but that does not meet food requirements for certain ARV agents, decisions about the ARV regimen administered during the intrapartum period should be made on an individual basis and in consultation with an HIV treatment expert.

NNRTI drugs such as nevirapine and efavirenz have very long half-lives and can be detected for 21 days or longer after discontinuation; efavirenz has a longer half-life than nevirapine[2-6]. Because other drugs in the ARV regimen have shorter half-lives and are cleared more rapidly, only detectable NNRTI drug levels persist, resulting in subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, certain genetic polymorphisms, which may be more common among racial/ethnic groups such as African Americans and Hispanics, may have potential to result in a slower rate of clearance[4, 6]. To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other ARV drugs for a period of time[3]. However, the optimal interval between stopping an NNRTI and the other ARV drugs is unknown; detectable levels of NNRTIs may be present from less than 1 week to more than 3 weeks after discontinuation, with the longer duration primarily observed with efavirenz[6]. An alternative strategy is to substitute a 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 resuppression after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual-NRTIs[7].

The optimal duration for continuing either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is unknown, but a minimum of 7 days is recommended based on studies to reduce resistance following single-dose nevirapine[8-9].

A pharmacokinetic (PK) 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[10]. Elimination half-life was 39 hours in these subjects, considerably shorter than that observed after peripartum exposure to single doses of nevirapine (average 55–60 hours), likely related to induction of nevirapine metabolism with chronic nevirapine exposure[2, 11-12]. Because efavirenz concentrations have 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 for some reason 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 (CYP3A4) 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 2 weeks, another 2-week dose escalation is recommended when it is reintroduced.

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Special Situations — Failure of Viral Suppression (Updated September 14, 2011)

Panel's Recommendations

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

A three-pronged approach is indicated for management of women on ARV regimens who have suboptimal suppression of HIV RNA (i.e., detectable virus at any time during pregnancy using ultrasensitive assays). They should be: 1) evaluated for resistant virus (if plasma HIV RNA is >500–1,000 copies/mL); 2) assessed for adherence, incorrect dosing, or potential problems with absorption (e.g., with nausea/vomiting or lack of attention to food requirements); and 3) consideration should be given to modifying the ARV regimen. Experts in the care of ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary. Hospitalization may be considered for directly observed drug administration, adherence education, and treatment of comorbidities such as nausea and vomiting.

HIV RNA levels should be assessed 2–4 weeks after an ARV drug regimen is initiated or changed to provide an initial assessment of effectiveness[1]. Baseline HIV RNA levels have been shown to affect the time to response in both pregnant and nonpregnant individuals[2]. Most patients with an adequate viral response at 24 weeks have had at least a one $\log_{10}$ copies/mL HIV RNA decrease within 1–4 weeks after starting therapy[1]. Treatment-naive individuals should have HIV RNA <400 copies/mL after 24 weeks of treatment and <50 copies/mL after 48 weeks of treatment.

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. Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery (see Transmission and Mode of Delivery).

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Monitoring of the Woman and Fetus During Pregnancy (Updated September 14, 2011)

Panel's Recommendations
• CD4 cell count should be monitored at the initial antenatal visit **(AI)** and at least every 3 months during pregnancy **(BIII)**. Monitoring of CD4 count may be performed every 6 months in patients on antiretroviral treatment (ART) for more than 2–3 years who are adherent to therapy, clinically stable, and have sustained viral suppression **(BIII)**.
• Plasma HIV RNA levels should be monitored at the initial visit **(AI)**; 2–4 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 34–36 weeks' gestation to inform decisions about mode of delivery (see Transmission and Mode of Delivery) **(AIII)**.
• Genotypic ARV drug-resistance testing should be performed at baseline in all HIV-infected pregnant women with HIV RNA levels >500–1,000 copies/mL, whether they are ARV-naive or currently on therapy **(AIII)**. Repeat testing is indicated following initiation of an ARV regimen in women who have suboptimal viral suppression or who have persistant 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)**.
• First-trimester 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)**.
• Given the limited data on the effect of combination ARV drugs on the fetus, most experts would recommend second-trimester ultrasound to assess fetal anatomy for women who have received combination ARV regimens during the first trimester, particularly if the regimen included efavirenz **(BIII)**.
• In women on effective combination ARV regimens, 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 combination ARV drug 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.

In HIV-infected pregnant women CD4 cell count should be monitored at the initial visit and at least every 3 months during pregnancy, similar to recommendations in nonpregnant adults. Monitoring of CD4 counts may be performed every 6 months in patients on ART for more than 2–3 years who are adherent to therapy, clinically stable, and have sustained viral suppression. Viral load should be monitored in HIV-infected pregnant women at the initial visit, 2–4 weeks after initiating or changing ARV regimens, monthly until undetectable, and at least every 3 months thereafter. If adherence is a concern, more frequent monitoring is recommended because of the potential increased risk of perinatal HIV infection associated with detectable HIV viremia during pregnancy. More frequent monitoring of viral load is recommended in pregnant versus nonpregnant 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 patients should have a decrease in plasma HIV RNA level by at least one $\log_{10}$ copies/mL within 1 month after initiation of potent therapy[1]. Viral suppression generally is achieved in 16–24 weeks in ARV-naive treatment-adherent individuals who do not harbor resistance mutations to the drugs they are receiving but, in rare cases, it may take longer. Viral load also should be assessed at approximately 34–36 weeks' gestation to inform decisions about mode of delivery (see Transmission and Mode of Delivery).

Because of physiologic changes such as hemodilution that are associated with pregnancy, CD4 percent-

age may be more stable than absolute CD4 count during pregnancy[2-5]. Nevertheless, most clinicians still rely on absolute CD4 count to evaluate immune status during pregnancy because parameters for initiating therapy are based on those values.

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 (e.g., >500–1,000 copies/mL). Testing should also be performed in women with suboptimal viral suppression while receiving an ARV regimen or who have persistant viral rebound to detectable levels after prior viral suppression on an ARV regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Drug-resistance testing in the setting of virologic failure should be performed while patients are receiving ARV drugs or within 4 weeks after discontinuation of drugs. Genotypic testing is preferable to phenotypic testing because it costs less, has a faster turnaround time, and is more sensitive for detection of mixtures of wild-type and resistant virus.

Monitoring for potential complications of ARV drugs during pregnancy should be based on what is known about the adverse effects of the drugs the woman is receiving. For example, routine hematologic monitoring is recommended for women receiving zidovudine-containing regimens. Liver function should be monitored in all women receiving ARV drugs. Hepatic dysfunction has been observed in pregnant women on protease inhibitors (PIs), and hepatic steatosis and lactic acidosis in pregnancy have been related to nucleoside reverse transcriptase inhibitor (NRTI) use. Women with CD4 counts >250 cells/mm^3 are thought to be at particular risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity within the first 18 weeks after initiation of therapy. Data from a 2010 study, however, suggest that abnormal liver transaminase levels at baseline may be more predictive of risk than CD4 cell count[6]. 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.

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)[7-8]. 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.

Because less is known about the effect of combination ARV drug regimens on the fetus during pregnancy, some experts consider more intensive fetal assessment for mothers receiving such therapy. Most experts would recommend second-trimester assessment of fetal anatomy with ultrasound in women who have received combination ARV regimens during the first trimester, particularly if the regimen included efavirenz. Furthermore, in addition to standard clinical monitoring, some experts would also recommend ultrasound assessment of fetal growth and well-being during the third trimester in woman who are receiving a combination drug regimen for which there is limited experience with use in pregnancy. The need for additional assessments such as non-stress testing should be determined based on ultrasound findings, any maternal comorbidities, and standard obstetrical indications.

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 drug regimens resulting in viral suppression. This is in contrast to the pre-combination drug regimen era, during which invasive procedures such as amniocentesis and chorionic villus sampling (CVS) were associated with a two- to fourfold increased risk of perinatal transmission of HIV[9-11]. In an evaluation of

transmission rates of HIV over time among women with or without amniocentesis, the transmission rate among women undergoing the procedure from 1984 to 1996 (pre-combination drug era) was 30% (3 of 10) compared with 16.2% (40 of 247) in those who did not have amniocentesis[12]. In contrast, no transmissions were noted among 18 women undergoing amniocentesis between 1997 and 2000 who received suppressive combination ARV drug regimens[12].

In an Italian multicenter study that included deliveries between 1997 and 2003, 3.3% (2 of 60) of infants were HIV infected after early invasive diagnostic procedures (CVS, amniocentesis, or cordocentesis) during pregnancy, compared with 1.7% (12 of 712) of infants born to women without invasive procedures (P = 0.30)[13]. No transmissions occurred among 45 women on combination ARV drug regimens during the procedure. One mother of an infected infant had not been diagnosed as HIV infected at the time of amniocentesis and was not receiving ARV prophylaxis; the newborn's virologic test at birth was negative. The mother of a second infected infant had been receiving zidovudine prophylaxis for 3 weeks and had an HIV RNA level of 10,000 copies/mL at the time of the procedure; the preterm infant had a positive virologic test at birth. In 2 other single-center series, no transmissions occurred in 6 and 9 live-born infants after amniocentesis in HIV-infected pregnant women on combination ARV drug regimens[14-15]. In the largest series to date, no transmissions were seen among 81 women receiving effective combination ARV drug regimens at the time of amniocentesis[16].

Thus, among 159 cases reported to date of amniocentesis or other invasive diagnostic procedures among women on effective combination ARV drug regimens, no transmissions have occurred, but a small increase in risk cannot be ruled out. HIV-infected women who have indications for invasive testing in pregnancy, such as 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[14], but existing data on transmission risk associated with these procedures are limited. At a minimum, HIV-infected pregnant women should receive an effective combination ARV drug regimen prior to undergoing any invasive prenatal testing and ideally have an undetectable HIV RNA level at the time of the procedure. In women with detectable HIV RNA levels in 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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Special Considerations Regarding the Use of Antiretroviral Drugs By HIV-Infected Pregnant Women and Their Infants (Updated September 14, 2011)

Overview

Recommendations regarding the choice of antiretroviral (ARV) drugs for HIV-infected pregnant women are subject to unique considerations. These include:

a. possible changes in dosing requirements resulting from physiologic changes associated with pregnancy;
b. potential toxicities of ARV drugs that may be exacerbated in pregnant women;
c. the pharmacokinetics (PKs) and toxicity of transplacentally transferred drugs; and
d. the potential short- and long-term effects of the ARV drug on fetuses and newborns, including the potential for preterm birth, teratogenicity, mutagenicity, or carcinogenicity.

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

Although clinical data on ARV drugs in pregnant women are more limited than in nonpregnant individuals, sufficient data exist on which to base recommendations related to drug choice for some of the available ARV drugs. Table 5 provides information on PKs in pregnancy and pregnancy-related concerns for each of the available ARV drugs; drugs are classified for use in pregnancy as preferred, alternative, use in special circumstances, insufficient data to recommend use, or not recommended (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy). This table should be used in conjunction with the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents when developing treatment regimens for pregnant women.

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Pharmacokinetic Changes (Updated September 14, 2011)

Panel's Recommendations
• Altered dosing during pregnancy may be required for some protease inhibitors (PIs), such as lopinavir/ritonavir (see Table 5) **(AII)**.

Physiologic changes that occur during pregnancy can affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering the susceptibility of the pregnant woman to drug toxicity[1-2]. 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 metabolic enzyme pathways in the liver. 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 pharmacokinetics (PKs) in the pregnant woman.

Currently available data on the PKs of antiretroviral (ARV) agents in pregnancy are summarized in Table 5. In general, the PKs of nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and nonpregnant women, although protease inhibitor (PI) PKs are more variable, particularly in later pregnancy. The current data suggest that in many women, exposure to lopinavir/ritonavir, atazanavir, and nelfinavir is decreased during the second and/or third trimester (see Table 5). The need for a dose adjustment depends on the PI, the treatment experience of a particular patient, and use (if any) of concomitant medications with potential for interaction[3-10].

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Teratogenicity (Updated September 14, 2011)

Panel's Recommendations
• All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com) **(AIII)**.
• Efavirenz should not be used in the first trimester and nonpregnant women receiving efavirenz should be counseled to avoid pregnancy **(AIII)**.

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 therapy. Drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of *in vitro* and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans[1]. Limited data exist regarding placental passage, long-term animal carcinogenicity, and animal teratogenicity for the Food and Drug Administration (FDA)-approved ARV drugs. Concerns have been raised about the risk of several ARV agents.

In cynomolgus monkeys receiving efavirenz from gestational days 20–150 at a dose resulting in plasma concentrations comparable to systemic human exposure at therapeutic dosage, significant malformations were observed in 3 of 20 infant monkeys[2]. The malformations included anencephaly and unilateral anophthalmia in 1, microphthalmia in another, and cleft palate in the third. In prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2011, birth defects were observed in 2.7% (17 of 623) live births with first-trimester exposure; this proportion is not significantly different from that observed among U.S. births in the general population (2.7%) as reported by the Registry[3]. Defects reported prospectively included 1 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[3]. In addition, 6 cases of central nervous system (CNS) defects, including myelomeningocele, have been retrospectively detected in infants born to mothers receiving efavirenz during the first trimester[2].

A recent meta-analysis including data from 9 cohorts with prospective reporting on 1,132 first-trimester exposures did not find an increased risk of overall birth defects among infants born to women on efavirenz during the first trimester compared with those on other ARV drugs during the first trimester (relative risk [RR] 0.87; 95% confidence interval [CI], 0.61-1.24)[4]. One neural tube defect occurred among 1,256 live births. Two subsequent smaller studies had conflicting results. A cohort in West Africa found no visible anomalies among 147 infants born after first-trimester exposure to efavirenz, while an analysis of the PACTG 219 database found a significantly increased risk of birth defects among infants born to women after first-trimester exposure to efavirenz (5 of 32; 15.6%), including 1 neural tube defect also included in the retrospective Registry cases[5-6].

Although a causal relationship has not been established between these events and the use of efavirenz, in light of similar findings in primates, efavirenz is classified as FDA Pregnancy Category D and may cause fetal harm when administered to a pregnant woman during the first trimester. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester, which is the primary period of fetal organogenesis. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz and should be counseled about the potential risk to the fetus and need to avoid pregnancy. 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. Use after the first trimester can be considered if, after consideration of other alternatives, it is the best choice for an individual woman. If efavirenz is to be continued postpartum, adequate contraception must be ensured.

Tenofovir has not demonstrated teratogenicity in rodents or monkeys. In infant monkeys with *in utero* exposure to tenfovir 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 1,092 women with first-trimester tenofovir exposure, similar to that in the general population[3]. However, because of the limited data on use in human pregnancy and concern regarding potential fetal bone effects and potential nephrotoxicity, tenofovir is recommended as an alternative rather than a preferred drug for use in pregnancy unless the pregnant woman has HIV/hepatitis B coinfection (see Table 5).

Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 4.7% (19 of 406), compared with a rate of 4.3% (20 of 460) among those with didanosine exposures later in pregnancy[3]. All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. However, these data do suggest a possible higher risk of birth defects with exposure to didanosine in the first trimester compared with the frequency of birth defects observed in the general population and with the use of other ARV agents, and the Registry continues to follow this.

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, nonexperimental data regarding ARV exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting physician.

Referrals should be directed to:

Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405

Telephone: 1–800–258–4263
Fax: 1–800–800–1052
http://www.APRegistry.com

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Combination Antiretroviral Drug Regimens and Pregnancy Outcome (Updated September 14, 2011)

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 (ARV) regimens; however, given the clear benefits of such regimens for both the women's health and the prevention of mother-to-child transmission, PIs should not be withheld for fear of altering pregnancy outcome **(AII)**.

Early data were conflicting as to whether receipt of combination ARV regimens during pregnancy is associated with adverse pregnancy outcomes and, in particular, preterm delivery. The European Collaborative Study and the Swiss Mother + Child HIV Cohort Study investigated the effects of combination ARV regimens in a population of 3,920 mother-child pairs. Adjusting for 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 PIs compared with no drugs; women receiving combination regimens that had been initiated before their pregnancy were twice as likely to deliver prematurely as those who started drugs during the third trimester[1]. 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 mother-child pairs, found a 1.9-fold increased risk of delivery at less than 37 weeks with combination ARV regimens started during pregnancy and a 2.1-fold increased risk with combination ARV regimens started prepregnancy compared with mono- or dual-NRTI prophylaxis[2]. In this report, 767 women received combination ARV regimens 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 combination ARV regimens during pregnancy and 4.4-fold for those entering pregnancy on combination ARV regimens.

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 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 one drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth[3]. Nor were any significant associations between adverse pregnancy outcome and use of ARV drugs by class or by category (including combination ARV regimens) found in an analysis from the Women and Infants Transmission Study (WITS), including 2,543 HIV-infected women (some of whom were included in the previous meta-analysis)[4].

More recent data have continued to be conflicting as to whether preterm delivery is increased with combination ARV regimens. A prospective cohort study including 681 women from Brazil, Argentina, Mexico, and the Bahamas did not find significant associations between use of combination ARV regimens and preterm birth or low birth weight[5]. A single-center study from Miami including 1,337 women did find a 1.8-fold increased chance of preterm birth among the 134 women in the cohort who received PI-containing combination ARV regimens compared with other combination regimens, after adjustment for

possible confounding variables[6]. However, women receiving PI-containing combination ARV regimens uniformly were women with advanced disease or those who had failed other combination drug regimens. The risk of low birth weight and stillbirth were not increased in any drug regimen groups. A recent meta-analysis of 14 European and American clinical studies found no increase in risk of preterm birth with either any ARV drug receipt compared with no drugs or combination ARV regimens including PIs compared with no drugs[7]. However, a significant but modest increased risk of preterm birth (odds ratio [OR] 1.35; 95% confidence interval [CI], 1.08–1.70) was found in women who received combination regimens with PIs compared with combination regimens without PIs.

Other studies have detected small but significant increases (OR of 1.2–1.5 in the largest studies) in preterm birth with PI- or non-PI-based combination ARV regimens as well[8-11]. Another variable that may confound these observational studies is the increased rate of preterm birth if the combination ARV regimen is begun before conception compared with later during pregnancy, which itself may reflect confounding by severity or indication[12]. When data from the IMPAACT P1025 observational cohort were examined by multivariable analysis to correct for HIV disease stage, PI-based combination ARV regimens were no more likely than non-PI-based combination ARV regimens to be associated with spontaneous preterm birth (OR 1.22; 95% CI, 0.70–2.12)[13]. A recent combined analysis of three large studies—two from Europe and one from the United States—found heterogeneity in the association between combination ARV regimens and preterm birth, with significant increases in Europe but not the United States. However, increased rates of preterm birth (adjusted OR [AOR] 1.5) were found in all three cohorts when combination ARV regimens were compared with dual regimens. Additional factors found to be associated with preterm birth in all three cohorts included injection drug use and more advanced HIV disease[14]. A similar increase in preterm birth in women receiving combination ARV regimens compared with dual regimens has been reported in the Swiss Mother and Child Cohort as well[15].

Clinicians should be aware of a possible increased risk of preterm birth with use of combination ARV drug regimens; 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 combination regimens for treatment of their HIV infection should continue their provider-recommended regimens. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

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Nevirapine and Hepatic/Rash Toxicity (Updated September 14, 2011)

Panel's Recommendations
• Nevirapine-based regimens should be initiated in women with CD4 counts >250 cells/mm^3 only if the benefits clearly outweigh the risks because of the drug's potential for causing hepatic toxicity/hypersensitivity reaction **(AII)**.
• Women who become pregnant while receiving nevirapine-containing regimens and who are tolerating the regimen well can continue on the therapy regardless of CD4 count **(AII)**.

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[1]. The development of severe nevirapine-associated skin rash has been reported to be 5.5–7.3 times more common in women than men and has been reported in pregnant women[2-3]. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than in men[4-5]. The degree of risk of rash and hepatic toxicity also appears to vary with CD4 cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4 cell counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity[4]; a single-center study also found higher CD4 cell counts to be associated with increased risk of severe nevirapine-associated skin rash[2]. CD4 cell counts >250 cells/mm^3 predicted rash illness, but not liver enzyme elevation, among pregnant and nonpregnant women initiating nevirapine-based combination antiretroviral (ARV) regimens in three U.S. university clinics[6]. Other international cohorts of nonpregnant 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^3 [7]. In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0%–11.0%) of patients who received nevirapine; severe or life-threatening rash has occurred in approximately 2% of patients receiving nevirapine[8].

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of a combination ARV regimen raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared with other ARV drugs[9-10]. Recent data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy[11]. In an analysis of two multicenter, prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (relative risk [RR] 4.7; 5% confidence interval [CI], 3.4–6.5), but nevirapine use was not, regardless of pregnancy status[11]. Additional data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination ARV regimens versus non-nevirapine-based combination ARV regimens[12]. These data suggest that nevirapine is no more toxic in pregnant women than in nonpregnant women. 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 1–3 months thereafter (see the Hepatotoxicity section of the table on Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating nevirapine and monthly thereafter[1]. 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 five 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[13]. Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well may continue therapy, regardless of CD4 cell count.

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Nucleoside Reverse Transcriptase Inhibitor Drugs and Mitochondrial Toxicity (Updated September 14, 2011)

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

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[1]. 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[2]. In one study, didanosine and didanosine-containing regimens were associated with the greatest degree of mitochondrial suppression[3]. 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[1]. These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to NRTI drugs.

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[4-5]. 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 the development of acute fatty liver of pregnancy and HELLP syndrome[6-9] and possibly contribute to susceptibility to ARV-associated mitochondrial toxicity. HELLP syndrome also can occur postpartum in women with severe preeclampsia[10]. In addition to low platelets and elevated liver enzymes, other laboratory findings reported among HIV-infected pregnant women on ARV drugs include mitochondrial placental depletion but without evidence of ultrastructual damage to placental cells. The clinical significance of reduced mtDNA in placentas exposed to ARV drugs remains unknown[11].

Lactic acidosis with microvacuolar 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 persons treated with NRTI drugs for longer than 6 months. In a report from the Food and Drug Administration (FDA) Spontaneous Adverse Event Program, typical initial symptoms included 1–6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness[12]. Metabolic acidosis with elevated serum lactate levels and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight. Although the apparent incidence of this syndrome may increase with better clinical recognition, the actual incidence may decrease as stavudine and didanosine are used less often in combination regimens.

The frequency of this syndrome in pregnant HIV-infected women receiving NRTI drugs is unknown. In 1999, Italian researchers reported a case of severe lactic acidosis in an infected pregnant woman who was receiving stavudine/lamivudine at the time of conception and throughout pregnancy and who experienced symptoms and fetal death at 38 weeks' gestation[13]. Bristol-Myers Squibb has reported three maternal deaths due to lactic acidosis, two with and one without accompanying pancreatitis, among women who were either pregnant or postpartum and whose antepartum regimen during pregnancy included stavudine and didanosine in combination with other ARV agents (either a protease inhibitor [PI] or nevirapine)[14-15]. All women were receiving regimens containing these agents at the time of conception and continued for the duration of pregnancy; all presented late in gestation with symptomatic disease that progressed to death in the immediate postpartum period. Two cases were also associated with fetal death. Nonfatal cases of lactic acidosis also have been reported in pregnant women receiving combination stavudine/didanosine[16].

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for nonpregnant persons 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.

Additionally, because of the reports of several cases 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. Combination stavudine/didanosine also is not recommended for nonpregnant adults.

In Utero *Exposure*

It has been suggested that mitochondrial dysfunction might 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[17]. 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[18]. All children had perinatal exposure to ARVs; risk was higher among infants exposed to combination ARV drugs (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[19-20]. 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%–0.5%)[21].

Other clinical studies from the United States and Europe generally have not duplicated the French reports[22-28]. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring among 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[23]. 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 ARVs[25]. No association was found between clinical manifestations suggestive of mitochondrial abnormalities and perinatal exposure to ARVs. Of the 4 children with seizures in this cohort, none had perinatal exposure to ARVs. 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[27]. 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 NRTI drugs 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[29-30].

Laboratory abnormalities without clinical symptoms have been reported in infants with perinatal exposure to ARVs compared with unexposed infants in a number of studies, most of which are limited by small numbers of subjects. In 1 study, mtDNA quantity was lower in cord and peripheral blood white cells at ages 1 and 2 years among 20 infants born to HIV-infected women compared with 30 infants born to uninfected women and was lowest among 10 HIV-exposed infants with zidovudine exposure compared with 10 without zidovudine exposure[31]. 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[32]. Similar morphologic changes and mtDNA depletion were seen in the human and monkey infants. In the monkeys, 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[33]. One study reported that peripheral blood mononuclear cell (PBMC) mtDNA levels were lower at birth in HIV-exposed, ARV-exposed infants compared with non-HIV, non-ARV-exposed infants[34]. 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 mothers without HIV infection[35].

Transient hyperlactatemia during the first few weeks of life was reported among 17 HIV-exposed infants with perinatal exposure to ARVs; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up[36]. 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[21]. Clinically asymptomatic hematologic findings have been reported by several investigators among uninfected infants with *in utero* exposure to ARV regimens in the United States and Europe[37-39], 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[40].

The clinical significance of these differences in mtDNA, lactate levels, and hematologic laboratory findings is unclear, and further long-term studies are needed to validate the findings and assess the degree to which they affect growth and development of infants exposed to ARV drugs. Thus, data are conflicting on whether mitochondrial dysfunction is associated with perinatal exposure to ARVs, and further studies are needed. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and should be balanced against the clear benefit of ARV prophylaxis in reducing transmission of a fatal infection by 70% or more[25, 41-42]. 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[43]. Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to ARVs who present with severe clinical findings of unknown etiology, particularly neurologic findings. Current recommendations call for long-term clinical follow-up for any child with *in utero* exposure to ARV drugs.

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Protease Inhibitor Therapy and Hyperglycemia (Updated September 14, 2011)

Panel's Recommendations
• HIV-infected women taking antiretroviral (ARV) drug regimens during pregnancy should undergo glucose screening with a standard, 1-hour, 50-g glucose loading test at 24–28 weeks' gestation **(AIII)**. Some experts would perform earlier glucose screening in women receiving ongoing protease inhibitor (PI)-based regimens initiated before pregnancy, similar to recommendations for women with high-risk factors for glucose intolerance **(BIII)**.

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported in HIV-infected patients taking PIs[1-4]. In addition, pregnancy is itself a risk factor for hyperglycemia. To date, however, the majority have not shown an increased risk of glucose intolerance with PI-based regimens during pregnancy. One small retrospective study that included 41 women receiving PI-based combination ARV regimens found an increased risk of glucose intolerance, but not gestational diabetes, among women on combination ARV regimens compared with zidovudine alone[5], while two other retrospective studies did not find an increased risk of glucose intolerance with PIs[6-7]. Secondary analyses of two large cohorts did not find an association between the type of ARV regimen and gestational diabetes, except for an association between initiation of PIs before pregnancy or during the first trimester and gestational diabetes in the PACTG 316 cohort[8-9]. Finally, 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[10]. In both groups, however, the rate of impaired glucose tolerance was high (38%), 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 with a standard, 1-hour, 50-g glucose loading test at 24–28 weeks' gestation. Some experts would perform earlier glucose screening in women with ongoing PI-based ARV regimens initiated before pregnancy (particularly in women 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.

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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy (Updated September 14, 2011)

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

Panel's Recommendations

• HIV drug-resistance testing is recommended for:
  • All pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) not currently receiving antiretroviral (ARV) drugs, before starting treatment or prophylaxis **(AIII)**.
  • All pregnant women receiving antenatal ARV drugs who have suboptimal viral suppression or persistant viral rebound to detectable levels after prior viral suppression on an ARV regimen **(AII)**.
• Empiric initiation of ARV drugs before results of resistance testing are available may be warranted, with adjustment as needed after the test results are available, for optimal prevention of perinatal transmission **(BIII)**.

Resistance testing is recommended for all ARV-naive pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) before initiating treatment or prophylaxis if prior resistance testing has not been done. For details regarding genotypic and phenotypic resistance testing see Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Ideally, resistance testing would have been done at a preconception visit to allow receipt of results and to select an appropriate ARV drug regimen during pregnancy or before pregnancy if maternal therapy was indicated.

Resistance testing should also be performed before initiation of therapy or prophylaxis in pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) who received prophylaxis in previous pregnancies and are now restarting ARV drugs for prevention of perinatal transmission. No data currently are available to address the utility of resistance testing during pregnancy in women who do not require treatment for their own health or in women with multiple pregnancies who have received corresponding courses of ARV prophylaxis for prevention of mother-to-child transmission. The identification of baseline resistance mutations may allow selection of more effective and durable ARV regimens for women who need treatment and help ensure a wider range of future treatment options for women receiving ARV drugs solely for perinatal prophylaxis. There is no evidence, however, that baseline resistance testing in pregnancy is associated with a reduction in rates of perinatal transmission.

Resistance testing should also be performed following initiation of an ARV regimen during pregnancy or in HIV-infected pregnant women who are receiving antiretroviral therapy (ART) when they present for obstetrical care if there is suboptimal viral suppression or persistent viral load rebound to detectable levels after prior viral suppression on the ARV regimen.

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 empiric ARV drug regimen before resistance-testing results are available to optimize prevention of perinatal transmission of HIV. Once resistance test results are obtained, the ARV drug regimen can be modified as needed. Most experts believe that for women in the third trimester, the benefits of immediate initiation of ARV drugs for prevention of mother-to-child transmission, pending results of resistance testing, outweigh the possible risk of short-term use of a regimen that could be suboptimal because of pre-existing resistance.

Significance of Antiretroviral Drug Resistance in Pregnancy

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in HIV-infected individuals. In pregnancy, it is associated with specific concerns that differ from those seen in the nonpregnant population. Pre-existing resistance to a drug in an ARV prophylaxis 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 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 (such as nevirapine or efavirenz combined with two nucleoside analogue drugs) are included in the ARV regimen, simultaneous postpartum discontinuation of all regimen components may result in persistent subtherapeutic drug levels and increase the risk of development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (see Stopping Antiretroviral Therapy during Pregnancy). Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving ARV drugs. Pharmacokinetic (PK) changes during pregnancy, such as increased plasma volume and renal clearance, may lead to subtherapeutic drug levels, increasing the risk that resistance will develop.

Incidence of Antiretroviral Resistance Emerging from the Use of Perinatal Prophylactic Regimens

The presence of mutations conferring resistance to nucleoside analogue drugs appears to be correlated with more advanced maternal disease and longer duration of prior or current exposure to these drugs[1-4]. The development of zidovudine drug resistance when zidovudine is used alone appears uncommon in women with higher CD4 cell counts and lower viral loads[5-6] but is more of a concern in women with advanced disease and lower CD4 cell counts[2].

Development of resistance associated with short-term use of ARV agents for prevention of mother-to-child transmission is most common with nevirapine, particularly single-dose nevirapine. Nevirapine has a low genetic barrier to resistance, with a single point mutation conferring resistance to nevirapine and to other first-generation NNRTI drugs. Furthermore, its long half-life, with blood levels detectable up to 21 days after a single dose in labor, increases selection pressure and the risk of resistance[7]. Factors associated with an increased risk of resistance following single-dose nevirapine exposure include high baseline viral load, low baseline CD4 cell count, viral subtype, and the number of maternal doses. The rate of genotypic resistance after exposure to single-dose nevirapine has varied in studies, ranging from 15% to 75%[8-18]. Studies using more sensitive real-time polymerase chain reaction (PCR) techniques suggest that up to one-half of resistance that develops is not detected by conventional sequence analysis[16, 18-20]. The prevalence of resistance declines rapidly over time and the proportion of resistant virus in those with detectable virus 12 months after exposure is low. In a study of virus from 67 South African women, using a sensitive allele-specific resistance assay, the K103N mutation was seen in 87% of women at 6 weeks but in only 11% at 12 months after single-dose nevirapine exposure, with a median frequency of the mutation of 0.7% (range 0.5%–5.4%) in women with detectable resistance at 12 months[20].

In the PACTG 316 trial, the addition of single-dose nevirapine following antepartum administration of other ARV regimens (primarily combination regimens because 77% of women received antenatal combination ARV regimens still resulted in nevirapine resistance in 14 of 95 (15%; 95% confidence interval [CI], 8%–23%) women with detectable virus postpartum[8]. In this study, adding single-dose nevirapine

did not provide any additional efficacy in prevention of mother-to-child transmission but was associated with development of nevirapine resistance. Therefore, this approach is not recommended.

A recent study examined the presence of resistant mutations in HIV-1-infected women receiving combination ARV drug regimens that were stopped postpartum. All women evaluated received zidovudine and lamivudine, with 76% receiving nelfinavir and 8% receiving nevirapine. Rates of M184V/I mutations postpartum were 65% and 29% in women receiving dual or triple prophylaxis, respectively. NNRTI resistance was identified postpartum among 38% of nevirapine recipients, whereas only 1% of protease inhibitor (PI) recipients developed PI resistance[21].

The Impact of Resistance on Pregnancy and the Risk of Perinatal Transmission of HIV

Perinatal Transmission

Perinatal transmission of resistant virus has been reported, but it appears to be unusual and there is little evidence that the presence of resistance mutations increases the risk of transmission when current recommendations for ARV management in pregnancy are followed. A substudy of the Women and Infants Transmission Study (WITS) followed pregnant women receiving zidovudine alone for treatment of HIV disease in the early 1990s. In this study, the detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count[2]; however, women in this cohort had characteristics that would indicate a need for ART under the current Department of Health and Human Services (HHS) 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 the infant[22], and other studies have suggested that drug-resistance mutations may diminish viral fitness[23], 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[24-25]. Neither resistance to nevirapine 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[26-27].

Maternal Response to Subsequent Treatment Regimens

Because nevirapine resistance mutations can be detected postpartum in a significant proportion of women receiving single-dose intrapartum nevirapine prophylaxis, the response to subsequent NNRTI-based combination therapy given for maternal health has been a concern[12, 20, 26-29]. A study performed in Zambia, Kenya, and Thailand found that prior exposure to single-dose nevirapine was associated with an increased risk of treatment failure in pregnant women receiving NNRTI-based ART, with the greatest risk being in women receiving ART within 12 months of previous nevirapine exposure[30]. The Optimal Combination Therapy After Nevirapine Exposure (OCTANE)/A5208 trial conducted in Africa compared nevirapine with lopinavir/ritonavir-based therapy in women requiring therapy who had prior exposure to single-dose nevirapine prophylaxis. The results suggest that prior exposure to single-dose nevirapine within 24 months of initiating therapy may be associated with a higher risk of viral failure with nevirapine-based therapy compared with lopinavir/ritonavir-based therapy. In this study, significantly more women in the nevirapine arm (29, 24%) failed to achieve a subsequent undetectable viral load (25) or died (4) compared with women in the lopinavir/ritonavir arm (8, 7%; 7 virologic failures and 1 death; $P < 0.0005$). Five of 13 (38%) women with documented nevirapine resistance at the start of therapy either had detectable virus or

died. This study demonstrates that women with documented nevirapine resistance are most likely to benefit from combination therapy that does not contain nevirapine (and because of cross resistance, efavirenz)[29].

Few data evaluate response to subsequent therapy in women who receive current combination drug 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. Issues relating to the discontinuation of nevirapine-based combination therapy are discussed in Prevention of Antiretroviral Drug Resistance.

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Management of Antiretroviral Drug Resistance during Pregnancy (Updated September 14, 2011)

Panel's Recommendations
• 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 whenever possible, along with their established antiretroviral (ARV) regimens **(AII)**. • In women who are receiving a stavudine-containing regimen, the drug should be discontinued during labor while intravenous zidovudine is being administered (see Intrapartum Care) **(AII)**. • The optimal prophylactic regimen for newborns of women with ARV resistance is unknown (see Infant Antiretroviral Prophylaxis). 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 **(AIII)**.

Ideally, ARV regimens used during pregnancy for treatment or prophylaxis should be chosen based upon the results of ARV resistance testing. Although most transmission occurs intrapartum, 30%–35% of transmission may occur *in utero*[1-3]. The majority of the latter infections are believed to occur later in pregnancy[1] and they may be more likely in women with advanced HIV disease and/or high viral load[2-3]. Therefore, a delay in initiation of an ARV drug regimen to await results of resistance testing could result in *in utero* infection of the infant, particularly in women at high risk of transmission or who are late in pregnancy at the time the drugs are initiated. In such circumstances, as noted earlier, empiric initiation of the ARV drug regimen may be warranted, with modification of the regimen once resistance testing results become available.

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, the drug still should be given intravenously during labor whenever possible (see Intrapartum Care). Because stavudine may be antagonistic to zidovudine, it should be stopped during the intrapartum period and restarted after delivery (see Intrapartum Care). Other ARVs should be continued orally during labor to the extent possible. 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).

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[4]. Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility[5]. 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[6-8]. Zidovudine crosses the placenta readily and has one of the highest maternal-to-cord blood ratios among the nucleoside analogue agents. In addition, zidovudine is metabolized to the active triphosphate within the placenta[9-10], which may provide additional protection against transmission. Metabolism to the active triphoshate, 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[11-12]. Thus, intrapartum intravenous administration of zidovudine currently is recommended even in the presence of known resistance because of the unique characteristics of the drug and its proven record in reducing perinatal transmission.

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Prevention of Antiretroviral Drug Resistance (Updated September 14, 2011)

Panel's Recommendations
• HIV-infected pregnant women should be given combination antiretroviral (ARV) drug regimens to maximally suppress viral replication; that is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission **(AII)**. • All pregnant women should be counseled about the importance of adherence to prescribed ARV medications to reduce the potential for development of resistance **(AII)**. • Pregnant women who are receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination ARV therapy solely for prophylaxis of transmission that will be discontinued after delivery should receive nucleoside analogue agents for at least 7 days after the NNRTI is stopped to minimize risk of resistance **(AI)**. An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI prior to the interruption and to continue the PI with dual nucleoside reverse transcriptase inhibitors (NRTIs) for at least 7 days after stopping the NNRTI **(CIII)**. The optimal interval between stopping an NNRTI and the other ARV drugs is not known (see Stopping Antiretroviral Therapy during Pregnancy and Postpartum Follow-Up of HIV-Infected Women). • Adding single-dose maternal/infant nevirapine to an ongoing combination ARV regimen given for treatment or prophylaxis does not increase efficacy in reducing perinatal transmission and may result in nevirapine drug resistance in the mother and/or infant; therefore single-dose maternal/infant nevirapine is not recommended in this situation **(AI)**.

The most effective way to prevent the development of ARV drug resistance in pregnancy is to use and adhere to an effective combination of ARV drugs to achieve maximal viral suppression.

Several studies have shown that development of nevirapine resistance is significantly decreased (but not eliminated) after exposure to single-dose intrapartum nevirapine (given alone or in combination with antenatal ART) when zidovudine/lamivudine is given intrapartum and administered for 3–7 days postpartum in women who have received single-dose nevirapine[1-3]. A variety of other regimens (e.g., tenfovir/emtricitabine, zidovudine/didanosine) given for 7–30 days postpartum following maternal single-dose nevirapine have also been shown to be very effective in reducing the development of nevirapine resistance[4-6]. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time[7]. The optimal duration for continuation of either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is unknown. NNRTI drugs have long half-lives, and drug levels can persist for up to 1–3 weeks after stopping the drug; efavirenz levels persist longer than nevirapine levels[8-9]. 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 NNRTI-based therapy. Many experts will stop the NNRTI drug and continue the other ARV drugs for at least 7 days, although other experts would recommend up to 30 days, particularly if an efavirenz-based regimen is being discontinued.

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Intrapartum Care (Updated September 14, 2011)

Intrapartum Antiretroviral Therapy/Prophylaxis

Panel's Recommendations
• Intrapartum intravenous zidovudine is recommended for all HIV-infected pregnant women, regardless of their antepartum regimen, to reduce perinatal transmission of HIV **(AI)**.
• For women who are receiving a stavudine-containing antepartum regimen, stavudine should be discontinued during labor while intravenous zidovudine is being administered **(AI)**.
• Women who are receiving an antepartum combination antiretroviral (ARV) drug regimen should continue this regimen on schedule as much as possible during labor and before scheduled cesarean delivery **(AIII)**.
• Women receiving fixed-dose combination regimens that include zidovudine should receive intravenous zidovudine during labor while other oral ARV components are continued **(AIII)**.
• For women who have received antepartum ARV drugs but have suboptimal viral suppression near delivery (i.e., HIV RNA >1,000 copies/mL), scheduled cesarean delivery is recommended (see Mode of Delivery) **(AI)**. The addition of single-dose intrapartum/newborn nevirapine is not recommended **(AI)**.
• Women of unknown HIV status 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/infant 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 Neonatal Postnatal Care) **(AI)**; if the test is negative, the infant ARV drugs should be stopped.
• Intravenous zidovudine is recommended for HIV-infected women in labor who have not received antepartum ARV drugs and infant combination ARV prophylaxis is recommended for 6 weeks (see Infant Antiretroviral Prophylaxis) **(AII)**.

Table 8 shows dosing for zidovudine, given intravenously as a continuous infusion during labor and during the neonatal period; Table 9 shows intrapartum and neonatal dosing for additional drugs to be considered in certain situations, as delineated below.

Women Who Have Received Antepartum Antiretroviral Drugs

Use of Intravenous Zidovudine during Labor

Results from PACTG 076 and subsequent epidemiologic studies have proven the efficacy of the three-part zidovudine chemoprophylaxis regimen, alone or in combination with other ARV agents. The PACTG 076 zidovudine regimen includes a continuous intravenous infusion of zidovudine during labor (initial loading dose of 2 mg/kg intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery). Given results from this trial, intravenous zidovudine during the intrapartum period should be discussed with and recommended to all HIV-infected pregnant women. Administration of intravenous zidovudine should begin 3 hours before scheduled cesarean delivery, according to standard dosing recommendations. Women receiving fixed-dose combination regimens that include zidovudine, such as a zidovudine/lamivudine combination, should receive intravenous zidovudine during labor while other oral ARV components are continued. For example, in women who are receiving zidovudine/lamivudine during pregnancy, zidovudine should be given intravenously and lamivudine should be given orally during labor.

If antenatal use of zidovudine was precluded by known or suspected zidovudine resistance, intrapartum use of the drug still should be recommended, except in woman with documented histories of hypersensi-

tivity. 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 Management of Antiretroviral Drug Resistance during Pregnancy). Because there is pharmacologic antagonism between zidovudine and stavudine, those drugs should not be coadministered during labor. Women who are receiving an antepartum stavudine-containing regimen should have the drug temporarily discontinued during labor while intravenous zidovudine is being administered, with other components of the regimen continued orally.

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. 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 (e.g., for less than 24 hours) during the peripartum period, all drugs should be stopped and reinstituted simultaneously to minimize the chance that resistance will develop.

Women Who Have Received Antepartum Antiretroviral Drugs But Have Suboptimal Viral Suppression Near Delivery

Women who have received combination ARV drug regimens may not achieve complete viral suppression by the time of delivery because of factors such as poor adherence, viral resistance, or late entry into care. Regardless of the reason, all women who have HIV RNA levels >1,000 copies/mL near the time of delivery should be offered a scheduled cesarean delivery at 38 weeks, which may significantly reduce the risk of transmission (see Transmission and Mode of Delivery).

The addition of single-dose nevirapine during labor has not been shown to reduce perinatal transmission of HIV in this group of women. The PACTG 316 study, conducted in women in the United States, Europe, Brazil, and the Bahamas who were receiving ARV drugs during pregnancy (primarily combination therapy), showed that the addition of single-dose nevirapine did not reduce the risk of mother-to-child transmission of HIV, even in the setting of maternal viremia. It was, however, associated with the development of nevirapine resistance in 15% of women with detectable HIV RNA levels postpartum[1-2]. Given the risk of development of resistance and the lack of data to suggest added efficacy, addition of single-dose nevirapine is not recommended in women who have received combination antepartum ARV drugs.

Use of additional medications for prophylaxis in infants may be warranted in special circumstances, 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 9). However, no additional intrapartum interventions are indicated for the mothers.

Women Who Have Not Received Antepartum Antiretroviral Drugs

Women Who Present in Labor Without Documentation of HIV Status

All women with undocumented HIV status or 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[3]. Factors that may increase risk of infection include diagnosis of a sexually transmitted infection (STI), illicit drug use or ex-

change 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[3].

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 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. Along with confirmatory HIV antibody testing, these women should receive appropriate assessments as soon as possible to determine their health status and make recommendations for whether antiretroviral therapy (ART) is needed based on that status. Arrangements also should be made for establishing HIV care and providing ongoing psychosocial support after discharge. Intravenous zidovudine should be started immediately in all women with positive rapid HIV tests in labor to prevent perinatal transmission of HIV, as discussed below.

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 intravenous zidovudine started immediately to prevent perinatal transmission of HIV (see Table 8 for dosing information). 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 (NRTI) drugs and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs cross the placenta well, whereas protease inhibitors (PIs) do not (see Table 5).

Epidemiologic data indicate that intravenous maternal intrapartum zidovudine followed by oral zidovudine for 6 weeks for the infant significantly reduces transmission compared with no treatment[4]. In a New York State cohort study, transmission rates were 10% with intrapartum and neonatal zidovudine compared with 27% without zidovudine, a 62% reduction in risk[4]. The PETRA study demonstrated that intrapartum prophylaxis alone, without an infant post-exposure prophylaxis component, is not effective in reducing perinatal transmission[5].

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 mother-to-child 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 only intravenous zidovudine, whereas their infants received zidovudine in combination with other agents, achieving a 50% reduction in transmission. Therefore, no additional intrapartum drugs, including intrapartum maternal single-dose nevirapine, are indicated for the woman in this situation[6].

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Transmission and Mode of Delivery (Updated September 14, 2011)

Panel's Recommendations
• Scheduled cesarean delivery at 38 weeks' gestation is recommended for women with HIV RNA levels >1,000 copies/mL near the time of delivery, irrespective of administration of antepartum antiretroviral (ARV) drugs, and for women with unknown HIV RNA levels near the time of delivery **(AII)**.
• Scheduled cesarean delivery is not routinely recommended for prevention of perinatal transmission in pregnant women receiving combination ARV drugs with plasma HIV RNA levels <1,000 copies/mL near the time of delivery. Data are insufficient to evaluate the potential benefit of cesarean delivery in this group, and given the low rate of transmission in these patients, it is unclear whether scheduled cesarean delivery would confer additional benefit in reducing transmission. This decision should be individualized based on discussion between the obstetrician and the mother **(BII)**.
• 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 based on duration of rupture, progress of labor, plasma HIV RNA level, current ARV regimen, and other clinical factors **(BII)**.
• Women should be informed of the risks associated with cesarean delivery; the risks to the woman should be balanced with potential benefits expected for the neonate **(AIII)**.

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 women with HIV RNA levels >1,000 copies/mL near the time of delivery and for women with unknown HIV RNA levels[1].

This recommendation is based on findings from a multicenter, randomized clinical trial[2] and from a large individual patient data meta-analysis[3]. These two studies were conducted at a time when the majority of HIV-infected women received no 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 <0.001). When adjusted for ARV use in pregnancy (zidovudine alone), scheduled cesarean delivery lowered the 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). When the data were analyzed by the actual mode of delivery, rather than to which group women were allocated, there was still a protective effect of scheduled cesarean delivery (adjusted OR [AOR] 0.3; 95% CI, 0.1–0.8) but not with emergency cesarean delivery (AOR 1.0; 95% CI, 0.3–3.7)[2]. 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[3]. Primarily based on these data, the American College of Obstetricians and Gynecologists has recommended consideration of scheduled cesarean delivery for HIV-infected pregnant women since 1999[4].

HIV RNA Level of 1,000 copies/mL as a Threshold for Recommendation of Scheduled Cesarean Delivery

The original American College of Obstetricians and Gynecologists committee opinion was updated in

2000 to include further refinements based on HIV RNA levels[1]. Currently, the American College of Obstetricians and Gynecologists[1] recommends that women with HIV RNA >1,000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery. Initially, this threshold of 1,000 copies/mL was based largely on data from the Women and Infants Transmission Study (WITS), a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels <1,000 copies/mL[5]. Since that time, newer studies have demonstrated that HIV transmission can occurr among infants born to women with low viral loads.

In an analysis of 957 women with plasma viral loads <1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications, primarily zidovudine alone as prophylaxis (AOR 0.30; $P = 0.022$)[6]. Among infants born to 834 women with HIV RNA <1,000 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 of <50 copies/mL and 50–999 copies/mL, respectively, were HIV infected[7].

The recent studies demonstrate that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission among this group, it is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. Although decisions about mode of delivery for women with HIV RNA levels <1,000 copies/mL should be individualized based on discussion between the obstetrician and the mother, scheduled cesarean delivery is not routinely recommended in this group.

Scheduled Cesarean Delivery in the Highly Active Antiretroviral Therapy Era

In surveillance data from the United Kingdom and Ireland, pregnant women receiving combination ARV regimens (i.e., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery[7]. Given the low transmission rates achievable with use of maternal combination ARV drug regimens, the benefit of scheduled cesarean delivery is difficult to evaluate. Both the randomized clinical trial[2] and meta-analysis[3] documenting the benefits of cesarean delivery included mostly women who were receiving either no ARVs or zidovudine only. 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 among the subset of women on a combination ARV regimen was 11(1.2%) of 918[8]. Among the subset of 560 women with undetectable HIV RNA levels (<50 to ≤200 copies/mL, depending on site), scheduled cesarean delivery was associated with a significant reduction in perinatal transmission in univariate analysis (OR 0.07; 95% CI, 0.02–0.31; $P = 0.0004$). 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; $P = 0.359$). 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) among women on combination ARV drug regimens[7]. The transmission rate among all women who received at least 14 days of ARV medications was 40 (0.8%) of 4,864, regardless of mode of delivery. Therefore, it is not clear whether there is any benefit from scheduled cesarean delivery among women who have been receiving combination ARV medications for several weeks.

Women Presenting Late in Pregnancy

HIV-infected women who present in late pregnancy and are not receiving ARV drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be <1,000 copies/mL at baseline. Even if combination ARV medications were begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the kinetics of

viral decay for the particular drug regimen[9]. 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 prior to 38 weeks.

Timing of Scheduled Cesarean Delivery

In general, for women without HIV infection, American College of Obstetricians and Gynecologists recommends that scheduled cesarean delivery not be performed before 39 weeks' gestation because of the risk of iatrogenic prematurity[10-11]. However, in cases of cesarean delivery performed to prevent transmission of HIV, American College of Obstetricians and Gynecologists recommends scheduling cesarean delivery at 38 weeks' gestation in order to decrease the likelihood of onset of labor or rupture of membranes before delivery[1]. Among 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[11]. Gestational age should be determined by last menstrual period and ultrasonography because amniocentesis to document lung maturity should be avoided, when possible, in HIV-infected women.

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%) of infants born by scheduled cesearean 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[12]. Clinicians should recognize that newborn complications may be increased in planned early term births <39 weeks' gestation. However, for HIV-infected women, the benefits of decreasing HIV transmission by planned delivery at 38 weeks are generally thought to outweigh the risks. When cesarean delivery is performed in HIV-infected women for an indication other than decreasing transmission of HIV, cesarean delivery should be scheduled at 38 weeks gestation based on accepted American College of Obstetricians and Gynecologists guidelines.

Risk of Maternal Complications

Because maternal infectious morbidity is increased with cesarean delivery even among women without HIV infection, the administration of perioperative antimicrobial prophylaxis is recommended for all women undergoing 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 the risk of complications is related to the degree of immunosuppression[13-18]. 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, that scheduled cesarean delivery was intermediate in risk, and that vaginal delivery had the lowest risk of morbidity[19]. Complication rates in most studies[2, 20-24] were within the range reported in populations of HIV-uninfected women with similar risk factors and were not of sufficient frequency or severity to outweigh the potential benefit of reduced transmission. Therefore, HIV-infected women should be counseled regarding the increased risks and potential benefits associated with cesarean delivery based on their HIV RNA levels and current ARV regimen.

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 may decrease the risk of perinatal transmission of HIV. Most studies have shown a similar risk of transmission for cesarean delivery performed after labor and membrane rupture for obstetric indications 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)[7]. A meta-analysis of 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[25]. However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost[26]. Therefore, the management of women originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized based on clinical factors such as duration of rupture, progress of labor, plasma RNA level, and current ARV drug regimen status. When membrane rupture occurs before 37 weeks' gestation, decisions about delivery should be based on gestational age, HIV RNA level, current ARV regimen, and evidence of acute infection such as chorioamnionitis; consultation with an expert is recommended. The ARV drug regimen should be continued and consideration given to initiating intravenous zidovudine if delivery appears imminent. No data exist to suggest that recommendations for administration of steroids to accelerate fetal lung maturity should be altered among HIV-infected women.

Table 7 provides a summary of recommendations regarding mode of delivery for different clinical scenarios.

Table 7. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV

Clinical Scenario	Recommendations
HIV-infected women presenting in late pregnancy (after about 36 weeks' gestation), known to be HIV infected but not receiving antiretroviral (ARV) medications, and who have HIV RNA level and CD4 cell counts pending but unlikely to be available before delivery.	• Start ARV medications as per Table 6. • Provide counseling on the likelihood that scheduled cesarean delivery will reduce the risk of mother-to-child transmission, if viral suppression cannot be documented prior to 38 weeks. Include information on the increased maternal risks of cesarean delivery, including increased rates of postoperative infection, anesthesia, and other surgical risks. • When the delivery method selected is scheduled cesarean, perform the procedure at 38 weeks' gestation, as determined by last menstrual period and ultrasonography. • Administer continuous intravenous zidovudine beginning 3 hours before scheduled cesarean. • Continue other ARV medications on schedule, as much as possible, before and after surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is recommended.
HIV-infected women who began prenatal care early in the third trimester, are receiving combination ARV drug regimens, and have an initial virologic response but have HIV RNA levels that remain substantially >1,000 copies/mL at 36 weeks' gestation.	• Continue the current combination ARV regimen because the drop in HIV RNA level is appropriate. • Provide counseling on the timing of response to ARV medications and the likelihood that maternal HIV RNA levels may not fall below 1,000 copies/mL before delivery. Consider scheduled cesarean delivery if viral load suppression is not achieved by 38 weeks because of the potential additional benefit in preventing intrapartum transmission of HIV. Inform patients about the increased maternal risks associated with cesarean delivery, including risks related to anesthesia and surgery and increased rates of postoperative infection. • When the delivery method selected is scheduled cesarean, perform the procedure at 38 weeks' gestation, as determined by last menstrual period and ultrasonography. • When the delivery method selected is scheduled cesarean delivery, administer continuous intravenous zidovudine beginning 3 hours before scheduled cesarean. • Continue other ARV medications on schedule, as much as possible, before and after surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is recommended.
HIV-infected women on combination ARV drug regimens with undetectable HIV RNA levels at 36 weeks' gestation.	• Provide counseling on the risk of perinatal transmission of HIV with a persistently undetectable HIV RNA level, which is probably 1% or less, even with vaginal delivery. No evidence currently exists to show that this risk can be lowered further by performing scheduled cesarean delivery. • Risk of complications is increased with cesarean delivery, compared with vaginal delivery, even in the HIV-uninfected population, and the risks must be balanced against the uncertain benefits of cesarean delivery in women with undetectable viral load.
HIV-infected women who have elected scheduled cesarean delivery but present after rupture of membranes at >37 weeks' gestation.	• Start intravenous zidovudine immediately. • Individualize the decision regarding mode of delivery, based on clinical factors such as duration of rupture, anticipated progress of labor, plasma RNA level, and current ARV regimen. • When vaginal delivery is chosen, some clinicians may consider administration of oxytocin, if clinically appropriate, in order to expedite delivery. Scalp electrodes and other invasive monitoring and operative delivery should be avoided, if possible, unless there are clear obstetric indications. • When cesarean delivery is chosen, administration of the loading dose of intravenous zidovudine ideally should be completed prior to the procedure. However, decisions regarding timing of delivery should be individualized.

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Other Intrapartum Management Considerations (Updated September 14, 2011)

Panel's Recommendations

• Generally avoid artificial rupture of membranes unless there are clear obstetric indications because of a potential increased risk of transmission **(BIII)**.
• 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 **(BIII)**.
• Operative delivery with forceps or a vacuum extractor and/or episiotomy should be performed only if there are clear obstetric indications **(BIII)**.
• The antiretroviral drug (ARV) 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 (PI), methergine should only be used 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 or efavirenz, additional uterotonic agents may be needed because of the potential for decreased methergine levels and inadequate treatment effect **(BIII)**.

If spontaneous rupture of membranes occurs before or early during the course of labor, interventions to decrease the interval to delivery, such as administration of oxytocin, may be considered in women without 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 load who present in labor and proceed to vaginal delivery. Data are limited on artificial rupture of membranes in women with undetectable viral load and planned vaginal delivery. In general, the procedure should be performed only for clear obstetrical indications because of the potential, albeit small, 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-combination antiretroviral therapy (ART) era[1-4]. Data are limited on routine use of fetal scalp electrodes in labor in women receiving suppressive ARV regimens and undetectable viral load; 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 the pre-combination ART era regarding the potential risk of perinatal transmission of HIV associated with operative vaginal delivery with forceps or the vacuum extractor and/or use of episiotomy[2, 4]. These procedures should be performed only if there are clear obstetric indications. Delayed cord clamping has been associated with improved iron status and benefits such as decreased risk of intraventricular hemorrhage in preterm births to HIV-uninfected mothers[5-7]. 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 CYP3A4 enzyme inhibitors, including 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 as a component of an ARV regimen, methergine should be used in women with excessive postpartum bleeding who are receiving PIs as a component of ART only if alternative treatments such as prostaglandin F 2 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 dosage and for as short a period as possible. In contrast, additional utertonic agents may be needed when other ARV drugs that are CYP3A4 inducers, such as nevirapine and efavirenz, are used because of the potential for decreased methergine levels and inadequate treatment effect.

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Postpartum Management (Updated September 14, 2011)

Postpartum Follow-up of HIV-Infected Women

Panel's Recommendations
• Contraceptive counseling should be included as a critical aspect of postpartum care **(AIII)**.
• Decisions about continuing antiretroviral (ARV) drugs after delivery should take into account current recommendations for initiation of antiretroviral therapy (ART), current and nadir CD4 cell counts and trajectory, HIV RNA levels, adherence issues, whether the woman has an HIV-uninfected sexual partner, and patient preference **(AIII)**.
• For women continuing ARV drugs 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)**.
• Women with a positive rapid HIV antibody test during labor require 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 ART and opportunistic infection (OI) prophylaxis **(AII)**.

The postpartum period provides an opportunity to review and optimize women's health care. Comprehensive care and support services are particularly important for women with HIV infection and their families, who often face multiple medical and social challenges. Components of comprehensive care include the following medical and supportive care 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 the woman, her child(ren), and other family members.

Support services should be tailored to individual women's needs and may 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. It is especially critical to ensure continuity of the antepartum ARV drug regimen when such treatment is required for a woman's health. The decision about whether to continue ARV drugs after delivery should be discussed with a woman and made before delivery.

The postpartum period also is a critical time for addressing the issue of safer sex practices and contraception. Lack of breastfeeding is associated with earlier return of fertility; ovulation returns as early as 6 weeks postpartum, and even earlier in some women, putting them at risk of pregnancy shortly after delivery[1]. Interpregnancy intervals of less than 18 months have been associated with increased risk of poor perinatal and maternal outcomes in HIV-uninfected women[2]. 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[3]. This is an important concern in women who are on an efavirenz-containing regimen because of the potential risk of teratogencity. A "dual-protection" strategy, such as use of condoms plus a second highly effective contraceptive, is ideal for women with HIV infection because it provides simultaneous protection against unintended pregnancy and HIV transmission or sexually transmitted disease (STD) acquisition or transmission[4]. 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 (OCs) and many ARV drugs (see Table 4 in Preconception Counseling). These interactions, however, do not necessarily rule out the use of hormonal contraceptives because there is no clear evidence of an effect on contraceptive or ARV efficacy or toxicity. OCs do significantly lower levels of amprenavir/fosamprenavir and, therefore, coadministration is not recommended; whether low-dose ritonavir boosting raises amprenavir levels sufficiently to allow coadministration is unknown. Depot medroxyprogesterone acetate (Depo-Provera, DMPA) pharmacokinetics (PKs) are not significantly affected by nevirapine, efavirenz, or nelfinavir, and levels of these drugs were not significantly altered by DMPA[5]. Adverse effects of DMPA are no different in HIV-infected women on ARV drugs than in HIV-uninfected women[6]. Other non-oral contraceptives, such as levonorgestrel implants, the combined contraceptive patch, the combined hormonal contraceptive vaginal ring, and the levonorgestrel IUD, are largely unstudied in combination with ARV drugs, but some data do exist on lopinavir/ritonavir interactions with the estrogen patch[7]. ARV drug interactions may be of less concern with contraceptive methods that exert primarily local activity and have minimal systemic absorption, but there is still a potential for interaction if metabolic or elimination pathways are shared[5, 8]. Permanent sterilization is appropriate only for women who are certain they do not desire future childbearing.

Women with nadir CD4 cell counts less than the currently recommended threshold for institution of ART[9] and/or symptomatic HIV infection should be encouraged to continue their ARV regimens postpartum without interruption. Decisions about whether to continue ARV drugs after delivery should be made in consultation with the HIV provider for women who began ARV drugs for prophylaxis of transmission with nadir CD4 cell counts greater than that currently recommended for treatment. Factors to be taken into consideration should include current recommendations for initiation of ART, current and nadir CD4 lymphocyte counts and trajectory, HIV RNA levels, adherence issues, partner HIV status, and patient preference. The risks versus benefits of stopping combination ARV drug regimens postpartum in women with high CD4 cell counts are being evaluated in the ongoing PROMISE study (clinical trial number NCT00955968).

Recent data from the HPTN 052 clinical trial showed that earlier initiation of ARVs led to a significant reduction in sexual transmission of HIV to uninfected partners in serodiscordant couples (see Preconception Counseling). HPTN 052 evaluated immediate versus delayed initiation of ART to HIV-infected individuals with CD4 counts between 350 and 550 cells/mm^3. Based on the results from that trial, continued administration of ARV drugs may be recommended for prevention of sexual transmission of HIV for postpartum women who have CD4 cell counts between 350 and 550 cells/mm^3 and have HIV-uninfected sexual partners, and it may be considered for those with CD4 cell counts greater than 550 cells/mm^3 with HIV-uninfected sexual partners. 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 should be continued.

Concerns have been raised about adherence to ARV regimens during the postpartum period. Women should be counseled that postpartum physical and psychological changes and the stresses and demands

of caring for a new baby may make adherence more difficult and that additional support may be needed during this period[10-12]. Health care providers should be vigilant for signs of depression and illicit drug or alcohol use that may require assessment and treatment and interfere with adherence. Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of ART[13-15]. Simplification of an ARV regimen (for example, to once-daily medications) can be considered. It may be preferable to temporarily interrupt ART in women who are unable to adhere to their regimens while they work with a 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents).

For women whose antepartum regimen included a non-nucleoside reverse transcriptase inhibitor (NNRTI) and who plan to stop ARV prophylaxis 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 Therapy during Pregnancy and Prevention of Antiretroviral Drug Resistance). Women whose antepartum regimen did not include an NNRTI and who plan to stop ARV prophylaxis after delivery should stop all ARV drugs at the same time. Doses of some PIs may be increased during pregnancy. For women continuing therapy, available data suggest that standard doses can be used again, beginning immediately after delivery.

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[16]. 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 ART and prophylaxis for OIs, as indicated. Other children and partner(s) should be referred for HIV testing.

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Infants Born to Mothers with Unknown HIV Infection Status (Updated September 14, 2011)

Panel's Recommendations
• For infants born to mothers with unknown HIV status, rapid HIV antibody testing of the mother and/or infant is recommended as soon as possible after birth, with immediate initiation of infant antiretroviral (ARV) prophylaxis (see Infant Antiretroviral Prophylaxis) if the rapid test is positive **(AII)**. In the setting of a positive test, standard antibody confirmatory testing such as a Western blot also should be performed on mothers (or their infants) as soon as possible. If the confirmatory test is negative, ARV prophylaxis can be discontinued **(AIII)**. • If the HIV antibody confirmatory test is positive, a newborn HIV DNA polymerase chain reaction (PCR) should be obtained **(AIII)**. • If the newborn HIV DNA PCR is positive, ARV prophylaxis should be discontinued and the infant promptly referred to a pediatric HIV specialist for confirmation of the diagnosis and treatment of HIV infection with standard combination antiretroviral therapy (ART) **(AI)**.

Rapid HIV antibody testing of mothers and/or infants is recommended as soon as possible after birth when maternal HIV status is unknown and rapid HIV antibody testing was not performed during labor. If rapid testing is positive, infant ARV prophylaxis should be initiated immediately. Rapid HIV antibody testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care or newborn nursery. A positive test result in mothers or infants should be presumed to indicate maternal HIV infection until standard antibody confirmatory testing clarifies maternal status. A standard confirmatory test (e.g., Western blot) should be performed on mothers (or their infants) as soon as possible after the initial positive rapid test[1]. 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. If the confirmatory test on a mother (or infant) is negative, ARV prophylaxis can be discontinued. If the confirmatory test is positive, an HIV DNA PCR should be obtained urgently from the newborn. If the HIV DNA PCR is positive, ARV prophylaxis should be promptly discontinued and the infant should receive treatment for HIV infection with standard combination ART according to established Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection developed by The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children.

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Infant Antiretroviral Prophylaxis (Updated September 14, 2011)

Panel's Recommendations
• The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV **(AI)**.
• Zidovudine should be initiated as close to the time of birth as possible, preferably within 6–12 hours of delivery **(AII)**.
• The 6-week zidovudine prophylaxis regimen is recommended at gestational age-appropriate doses; zidovudine should be dosed differently for premature infants less than 35 weeks than for infants at least 35 weeks of age (see Zidovudine Dosing and Table 8) **(AII)**.
• In the United States, the use of antiretroviral (ARV) drugs other than zidovudine cannot be recommended in premature infants because of lack of dosing and safety data **(BIII)**.
• The use of intrapartum/neonatal zidovudine is recommended regardless of maternal history of zidovudine resistance **(BIII)**.
• Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen, begun as soon after birth as possible **(AI)**. A randomized, controlled trial has shown that a 2-drug regimen of zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) is as effective as but less toxic than a 3-drug regimen of zidovudine, nelfinavir and lamivudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States (see General Considerations for Choice of Infant Prophylaxis and Table 9) **(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 counseling of the mother on the potential risks and benefits of this approach **(BIII)**.
• The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV, including infant care.

Zidovudine Dosing

All HIV-exposed infants should receive postpartum ARV drugs to reduce perinatal transmission of HIV. The 6-week neonatal zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed infants[1-2]. Table 8 shows zidovudine dosing intrapartum, which is a continuous intravenous infusion during labor, and neonatal dosing. Table 9 shows intrapartum and neonatal dosing for other drugs to be considered in certain situations as delineated below.

The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 4 mg/kg body weight orally twice daily for the first 6 weeks of life, beginning as soon after birth as possible and preferably within 6–12 hours of delivery (Table 8). Although the ACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice-daily oral infant dosing for prophylaxis[3-12]. Most of these studies used a dose of 4 mg/kg twice daily, adjusted for weight gain, but others have used a regimen based on birth weight for the entire 6-week treatment period[13-14]. The current World Health Organization (WHO) guidelines recommend a simplified zidovudine dosing regimen for the 6-week prophylaxis period consisting of 10 mg given twice daily for infants weighing less than 2.5 kg at birth and 15 mg twice daily for infants weighing more than 2.5 kg at birth[15]. The advantages of this simplified regimen are that it avoids the need for dosing calculations and involves administration of either 1.0 or 1.5 mL of zidovudine syrup. The disadvantage is that, compared with mg-per-kg dosing, infants with birth weights greater than 3.75 kg will receive a smaller zidovudine dose and infants less than 3.75 kg will receive a larger zidovudine dose.

Table 8. Recommended Intrapartum Maternal and Neonatal Zidovudine Dosing for Prevention of Mother to Child Transmission of HIV

Maternal Intrapartum		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	**≥35 weeks gestation:** 4 mg per kg body weight per dose given orally twice daily, started as soon after birth as possible and preferably within 6-12 hours of delivery (or, if unable to tolerate oral agents, 1.5 mg per kg body weight per dose intravenously, beginning within 6–12 hours of delivery, then every 6 hours)	Birth through 6 weeks
ZDV	**<35 to ≥30 weeks gestation:** 2 mg per kg body weight per dose given orally (or 1.5 mg per kg body weight per dose intravenously), started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours, advanced to every 8 hours at age 2 weeks	Birth through 6 weeks
ZDV	**<30 weeks gestation:** 2 mg per kg body weight per dose given orally (or 1.5 mg/kg/dose intravenously) started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours, advanced to every 8 hours at 4 weeks of age	Birth through 6 weeks

The zidovudine dosing requirements differ for premature infants and term infants. 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 clearance compared with older infants. Clearance is further prolonged in premature infants because their hepatic metabolic function is even less mature than in term infants[16-17]. The recommended zidovudine dosage for infants less than 35 weeks' gestation is 2 mg/kg body weight per dose orally every 12 hours (or 1.5 mg/kg body weight intravenously per dose every 12 hours), increasing to 2 mg/kg body weight per dose every 8 hours at age 2 weeks for infants born at 30 weeks' gestation or more or at age 4 weeks in those born at less than 30 weeks' gestation. For infants born at more than 35 weeks' gestation or greater who are unable to tolerate oral zidovudine, the drug can be given intravenously at a dose of 1.5 mg/kg body weight every 6 hours.

In the United Kingdom and many other European countries, a 4-week neonatal chemoprophylaxis regimen is recommended for infants born to mothers who have received antenatal combination ARV drug regimens[18-20]. This approach also can be considered in cases where adherence to or toxicity from the 6-week zidovudine prophylaxis regimen is a concern. In an Irish observational study, a transmission rate of 1.1% was observed in 916 infants who received 4 weeks of zidovudine infant prophylaxis following antenatal maternal combination ARV prophylaxis. That is the standard regimen in Ireland and the transmission rate was similar to that observed in the United States, where 6 weeks of infant zidovudine prophylaxis is standard[20]. A recent prospective, observational study reported that the 4-week zidovudine regimen allowed earlier recovery from anemia in otherwise healthy infants compared with the 6-week zidovudine regimen[21]. The optimal duration of neonatal zidovudine chemoprophylaxis, however, has not been established in clinical trials, and in the United States, the standard 6-week infant zidovudine regimen is recommended unless there are concerns about adherence or toxicity. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered.

Table 9. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs in Special Circumstances Based on NICHD-HPTN 040/PACTG 1043 Regimen[1] (See Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants for further discussion.)

Maternal Intrapartum/Postpartum		
Antiretroviral (ARV) Drug	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal (initiated as soon after delivery as possible)		
Antiretroviral (ARV) Drug	**Dosing**	**Duration**
2-drug regimen: ZDV + NVP	• ZDV: 4 mg/kg given orally twice daily[a, b] • NVP: *Birth weight 1.5–2 kg:* 8 mg per dose given orally *Birth weight >2 kg:* 12 mg per dose given orally	Birth through 6 weeks 3 doses in the first week of life • 1st dose within 48 hrs of birth (birth–48 hrs) • 2nd dose 48 hrs after 1st • 3rd dose 96 hrs after 2nd

Key to Abbreviations: 3TC = lamivudine; NFV= nelfinavir; NVP = nevirapine; ZDV = zidovudine

[1] Dosing for the 3 drug regimen is not shown because nelfinavir powder is no longer commercially available in the United States, and the 2-drug regimen is preferred.

[a] NICHD-HPTN 040/PACTG 1043 used ZDV 12 mg given orally twice daily if the birth weight was >2 kg and 8 mg given orally twice daily if the birth weight was 1.5–2.0 kg.

[b] ZDV dosing regimen is for infants ≥35 weeks' gestation. See Table 8 for recommended doses for premature infants.

General Considerations for Choice of Infant Prophylaxis

Infants born to mothers who have received standard antepartum and intrapartum ARV prophylaxis and have undetectable viral loads are at very low risk of HIV transmission. However, the risk of transmission is increased when maternal viral load at delivery is high or maternal antepartum and/or intrapartum prophylaxis was not received. Most experts feel that the potential benefit of combining zidovudine infant prophylaxis with additional ARV drugs may exceed the risk of multiple drug exposure to infants born to:

a. mothers who received antepartum and intrapartum ARV drugs but who had suboptimal viral suppression at delivery, particularly if delivery was vaginal;
b. mothers who received only intrapartum ARV drugs;
c. mothers who received no antepartum or intrapartum ARV drugs; and
d. mothers 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. For example, an infant delivered vaginally to a mother with an HIV RNA level ≥100,000 copies/mL at delivery has a higher risk of acquiring HIV infection than an infant born by cesarean delivery to a mother with an HIV RNA level of approximately 10,000 copies/mL at delivery. Thus, a generic recommendation cannot be made regarding use of combination

drug regimens for infant prophylaxis and 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 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection). Thus, decisions about use of combination ARV prophylaxis in infants should be made in consultation with a pediatric HIV specialist before delivery and should be accompanied by a discussion with the mothers about potential risks and benefits of this approach.

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[22]. Similarly, in a Web-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[23].

Despite widespread use of combination ARV prophylaxis, until recently there were no data evaluating the efficacy of these regimens versus zidovudine alone in the setting of high risk of mother-to-child transmission of HIV. Results from a Phase III randomized trial in 4 countries (including the United States) were presented at the 2011 Conference on Retroviruses and Opportunistic Infections (NICHD-HPTN 040/PACTG 1043)[14]. This study enrolled 1,746 infants born to HIV-infected women who did not receive any ARV drugs during pregnancy and, hence, were at high risk of infection. The study compared infant prophylaxis with the standard 6-week zidovudine regimen and 2 different combination regimens for prevention of intrapartum transmission of HIV: 6 weeks of zidovudine plus 3 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, compared with 6 weeks of zidovudine alone, in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for zidovudine alone; $P = 0.046$ for each experimental arm vs. zidovudine alone). The overall transmission rate of HIV (*in utero* + intrapartum) was also significantly lower in the 2- and 3-drug arms compared with zidovudine alone (7.1%, 7.4%, and 11.1%, respectively, $P = 0.035$ for comparison of each experimental arm with zidovudine alone)[14]. Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the 3-drug regimen than with the 2-drug or zidovudine-alone regimen (27.5% vs. 15%, $P < 0.0001$). In other studies, significantly higher rates of neutropenia and anemia have been reported with coadministration of zidovudine and lamivudine to infants[24].

The NICHD-HPTN 040/PACTG 1043 study provides proof of principle that use of a combination drug regimen for infants is more effective than zidovudine alone in the high-risk setting of no maternal antepartum administration of ARV drugs. The two-drug regimen is less complex and had lower rates of toxicity than the three-drug regimen; additionally, nelfinavir powder is no longer commercially available in the United States, is not a preferred ARV drug for pediatric treatment, and drug levels in neonates are highly variable[25]. Therefore, the two-drug regimen is recommended for prophylaxis in infants born to mothers who have not received antepartum ARV drugs.

Beyond the scenario studied in NICHD-HPTN 040/PACTG 1043, the choice of ARV drug regimens for neonates is limited (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis). Neonatal dosing information is not available for any of the currently available boosted protease inhibitors (PIs). In addition, use of lopinavir/ritonavir in neonates has been associated with severe and

sometimes fatal cardiac, renal, central nervous system (CNS), and metabolic toxicity[26]. Because of the potential for toxicity, lopinavir/ritonavir 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.

The National Perinatal HIV Hotline (1-888-448-8765)

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

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 born by scheduled cesarean section to mothers with low viral loads at delivery. For example, in PACTG 316, the infection rate in infants born to women receiving antepartum PI-based therapy was 0.7% in 269 infants with HIV RNA levels of less than 400 copies/mL at delivery[2]. Such infants should receive the 6-week zidovudine infant prophylaxis regimen. In that situation, combining zidovudine with additional ARV drugs to reduce transmission risk is not recommended because the benefit would be very limited.

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

The risk of perinatal transmission is related to maternal antepartum viral load in women on no ARV drugs as well as women receiving ARVs[27-29]. 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[2]. 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 triple-combination ARV prophylaxis 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[29].

All infants 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. Elective cesarean section is recommended for pregnant women with HIV RNA levels >1,000 copies/mL near delivery. Extrapolation of findings from the previously discussed NICHD-HPTN 040/PACTG 1043 study[14] suggests that combination infant prophylaxis can 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.

Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs

All infants whose mothers have received only intrapartum ARV drugs should be given zidovudine for 6

weeks. This infant prophylaxis regimen 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[3]. A study in Thailand indicated that longer infant prophylaxis with zidovudine (6 weeks vs. 3 days) is required for optimal efficacy when maternal antenatal exposure to zidovudine is <4 weeks[30].

Infant prophylaxis with zidovudine should be initiated as soon after delivery as possible. In the NICHD-HPTN 040/PACTG 043 trial previously discussed, 41% of women received zidovudine during labor. Administration of intrapartum zidovudine did not affect transmission rates. The results of this study support use of a two-drug regimen, involving 6 weeks of zidovudine plus three doses of nevirapine in the first week of life, because combination regimens were found to have increased efficacy in reducing intrapartum transmission compared with use of zidovudine alone and the three-drug regimen was associated with increased toxicity and nelfinavir powder is no longer commercially available in the United States[14].

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

Infants of HIV-infected mothers who have received neither antepartum nor intrapartum ARV drugs should be started on ARV prophylaxis as soon after delivery as possible. Observational and Phase III randomized studies suggest that prophylaxis provided to infants alone may be helpful in preventing transmission of HIV. Epidemiologic data from a New York State study indicated a decline in transmission when infants were given zidovudine for the first 6 weeks of life compared with no prophylaxis[31]. Transmission rates were 9% (95% confidence interval [CI], 4.1%–17.5%) with zidovudine-alone prophylaxis in newborns (initiated within 48 hours after birth) versus 27% (95% CI, 21%–33%) with no zidovudine prophylaxis. For most infants in this study, prophylaxis was initiated within 12 hours of birth[32].

The two-drug regimen of 6 weeks of zidovudine plus three doses of nevirapine in the first week of life is recommended 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[14]. Prophylaxis should be initiated as soon after delivery as possible.

The interval during which infant prophylaxis can be initiated and still be of benefit is undefined. In the New York State study, when prophylaxis was delayed beyond 48 hours after birth, no efficacy could be demonstrated. Data from animal studies indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, ARV prophylaxis initiated 24–36 hours after exposure usually has been ineffective in preventing infection, although a delay in administration has been associated with decreased viremia[33-35]. In the NICHD-HPTN 040/PACTG 1043 study, infant regimens were initiated within 48 hours of life and usually within 12 hours of life[14]. 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[36]. 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 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 the 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[37-38].

Thus, the 6-week infant zidovudine prophylaxis (along with maternal intravenous intrapartum zidovudine prophylaxis) continues to be recommended, even when maternal zidovudine-resistant virus with thymidine-associated mutations (TAMs) is identified.

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility[38]. However, transmission from mother to child of multidrug-resistant virus has been reported[39-41].

For these newborns, use of zidovudine in combination with other ARV drugs, selected on the basis of maternal virus resistance testing, can 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 are incompletely defined. 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. ARV drugs with pharmacokinetic (PK) and safety data in neonates sufficient to support their addition to zidovudine include lamivudine and nevirapine; although there are pharmacokinetic data in neonates for nelfinavir, nelfinavir powder for oral use is no longer commercially available in the United States.

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 at the time of HIV diagnosis or suspected to be HIV infected. Pumping and temporarily discarding 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.

The risk of acquisition of HIV associated with breastfeeding depends on multiple infant and maternal factors, including maternal viral load and CD4 cell count[42]. 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[43] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count[44].

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 4–6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance compared with other nonoccupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure[45].

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[8, 46-47]. The NICHD-HPTN 040/PACTG 043 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[14]. 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.

An alternative approach favored by some experts would be to offer a combination ARV regimen that would be effective for treatment of HIV, should the infant become infected. If this route is chosen, current recommendations for treatment should guide selection of an appropriate combination ARV regimen

(see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection). Regardless of whether post-exposure prophylaxis or "preemptive therapy" is chosen, the duration of the intervention is unknown. A 28-day course seems reasonable based on current recommendations for nonoccupational HIV exposure[45]. 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 4–6 weeks, 3 months, and 6 months after recognition of maternal infection to determine whether they are HIV infected. In infants younger than age 18 months, HIV DNA or RNA polymerase chain reaction (PCR) tests should be used for diagnosis. HIV DNA PCR is preferable for infants who are receiving combination ARV prophylaxis or preemptive treatment. HIV antibody assays can be used in infants older than age 18 months. Post-exposure ARV prophylaxis or preemptive treatment should be discontinued in infants who are found to be HIV infected while receiving one of these regimens. Resistance testing then should be performed and an appropriate combination therapy regimen initiated (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection).

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 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 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 week[3, 14, 48]. 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[24]. 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[49]. In a Phase I study of stavudine in pregnant women, infants received 6 weeks of zidovudine/lamivudine and a single dose of stavudine at ages 1 and 6 weeks; 6 of 14 (43%) infants experienced Grade 3 hematologic toxicity after birth (36% neutropenia and 7% anemia)[50]. Finally, in three Phase I studies of PIs (saquinavir/ritonavir, indinavir, or nelfinavir) in pregnancy, a total of 52 infants received 6 weeks of zidovudine/lamivudine (in 26 infants, zidovudine/lamivudine was combined with nelfinavir); Grade 2 or higher hematologic toxicity was observed in 46%–62% of infants[51-53]. In the NICHD-HPTN 040/PACTG 1043 study, significantly higher rates of Grade 3 or 4 neutropenia were seen with a three-drug regimen including zidovudine and lamivudine than with zidovudine alone or a two-drug regimen with zidovudine and nevirapine (27.5% vs. 16% and 15%, respectively, $P < 0.0001$)[14]. In contrast, Grade 3 or 4 anemia occurred in 23%–27% of infants, with no differences between study arms[14].

Experience with other NRTI drugs for neonatal prophylaxis is more limited[54-55]. Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs[24, 56-59].

Nevirapine is the only non-nucleoside reverse transcriptase inhibitor (NNRTI) drug with a pediatric drug formulation and neonatal dosing information (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection)[60]. In rare cases, chronic multiple-dose nevirapine has been associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding infants receiving nevirapine prophylaxis daily for 6 weeks to 6 months to prevent transmission of HIV via breast milk[8, 14, 46-47, 61]. Resistance to nevirapine can occur, however, with exposure to nevirapine in infants who become infected despite prophylaxis[62-63]. ARV drug-resistance testing is recommended for all HIV-infected infants before initiation of ART (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection).

Of the PIs, nelfinavir, lopinavir/ritonavir, ritonavir, tipranavir, and fosamprenavir have pediatric drug formulations. Dosing information for newborn infants is only available for nelfinavir, which has highly variable levels in neonates and for which high doses are required; however, nelfinavir powder is no longer commercially available in the United States[25, 53, 55]. PK data are available for treatment of HIV-infected infants 2–6 weeks of age with lopinavir/ritonavir. Although the lopinavir area under the curve (AUC) was significantly lower with dosing 300 mg lopinavir/75 mg ritonavir per meter^2 body surface area twice daily than observed for infants >6 weeks of age, treatment was well tolerated and 80% of 10 infants had viral control at 6 months[64]. Studies are ongoing but data are not yet available for infants <2 weeks of age. However, in 4 premature infants (2 sets of twins) started on lopinavir/ritonavir from birth, heart block developed that resolved after drug discontinuation[65-66]. In studies of adults, both ritonavir and lopinavir/ritonavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Based on these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death, predominantly in preterm neonates, the Food and Drug Administration (FDA) now recommends that lopinavir/ritonavir 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.

Dosing for premature infants is available for only zidovudine (see Table 8), making use of other ARV drugs in this group more problematic. In preterm infants immature renal and hepatic metabolism increases the risk of overdosing and toxicity. Because zidovudine is the only ARV drug available in an intravenous formulation, the 6-week zidovudine prophylaxis regimen is recommended for preterm infants at gestational age-appropriate doses. Use of ARV drugs other than zidovudine cannot be recommended in premature infants because data on dosing and safety are lacking.

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Initial Postnatal Management of the HIV-Exposed Neonate (Updated September 14, 2011)

Panel's Recommendations
• A complete blood count (CBC) and differential should be performed on newborns as a baseline evaluation **(BIII)**. • 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 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 (PCR) tests are obtained in infants exposed to combination antiretroviral (ARV) drug regimens *in utero* or during the neonatal period **(CIII)**. • If hematologic abnormalities are identified in infants receiving prophylaxis, decisions on whether to continue infant ARV prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered **(CIII)**. • 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 <18 months of age and should be performed within the first 14–21 days of life, at 1–2 months, and at 4–6 months of age **(AII)**. • To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV infection should begin PCP prophylaxis at age 4–6 weeks, after completing their ARV prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children) **(AII)**.

A CBC and differential should be performed on HIV-exposed newborns before initiation of infant 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 at birth than those in the placebo group, with the maximal difference (1 gm/dL) occurring at age 3 weeks[1]. The lowest mean value for hemoglobin (10 gm/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 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[2-5]. In PACTG 316, where 77% of mothers received antenatal combination therapy, significant Grade 3 or higher anemia was noted in 13% and neutropenia in 12% of infants, respectively. 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 that diagnostic HIV PCR testing is

done; monitoring of bilirubin levels should be considered for infants exposed antenatally to atazanavir[6].

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[7]. A recheck of hemoglobin 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[8].

If hematologic abnormalities are found, decisions on whether to continue infant ARV prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether related symptoms are present, duration of infant prophylaxis, 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[9]. 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[10-11]. 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[10-11]. 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 PCP, all infants born to women with HIV infection should begin trimethoprim-sulfamethoxazole (TMP-SMX) 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 USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children)[12].

HIV infection in infants should be diagnosed using HIV DNA PCR or RNA virologic 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 14–21 days of life, at 1–2 months, and at 4–6 months of age[13]. 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[1,14]. 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 ART.

HIV may 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 nonbreastfed infants may be based on two negative virologic tests at age 1 month or older and at age 4 months or older. Many experts confirm HIV-negative status with an HIV antibody test at age 12–18 months. Alternative algorithms exist for presumptive and definitive HIV exclusion[13]. 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 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, Issues Related to Diagnosis of Non-Subtype B HIV Infection for additional information.)

Following birth, HIV-exposed infants should have a detailed physical examination, and a thorough maternal history should be obtained. HIV-infected mothers may be coinfected with other pathogens that can be transmitted from mother to child, such as cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis (TB). Infants born to mothers with such coinfections should undergo appropriate evaluation, as indicated by maternal CD4 cell 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 USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children).

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. 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[15].

Late HIV transmission events in infancy have recently been reported among three HIV-infected children suspected to have acquired 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 this feeding practice and instruct HIV-infected caregivers on safer feeding options[16].

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Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants (Updated September 14, 2011)

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)**.

Data remain insufficient to address the effect that exposure to zidovudine or other 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 do 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 have been seen[1-3]. As discussed earlier in NRTI Drugs and Mitochondrial Toxicity, data are conflicting regarding whether mitochondrial dysfunction is associated with perinatal exposure to ARVs. Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to ARVs who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Evaluation is ongoing of early and late effects of *in utero* exposure to ARVs, including the Pediatric HIV/AIDS Cohort Study (PHACS), 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 (CDC). Because most of the available follow-up data relate to *in utero* exposure to antenatal zidovudine alone and most pregnant women with HIV infection 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.

Innovative methods are needed to provide follow-up of infants 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. Children with *in utero* exposure to ARVs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction[4-6]. Follow-up of children with exposure to ARVs 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.

HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* exposure to ARVs. 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: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy (Updated September 14, 2011)

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Glossary of Terms for Supplement
Clastogenic = causing disruption of or breakages in chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Genotoxic = damaging to genetic material such as DNA and chromosomes
Carcinogenic = producing or tending to produce cancer
Notes:
• 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.

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 abacavir, didanosine, emtricitabine, lamivudine, stavudine, and zidovudine, 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 in the perinatal guidelines.

Abacavir (Ziagen, ABC) 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 6–32 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 1,000 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 abacavir administration of 500 mg/kg/day 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 3.0% (22 of 744 births; 95% confidence interval [CI], 1.9%–4.5%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance[1].

- **Placental and breast milk passage**

  Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.

- **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 6–12 weeks postpartum and in nonpregnant individuals[2]. Thus, no dose adjustment for abacavir is needed during pregnancy. Serious hypersensitivity reactions have been associated with abacavir therapy in nonpregnant adults and 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) 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 0.7–1.7 and 3 times, respectively, in mice and 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 4.7% (19 of 406 births; 95% CI, 2.8%–7.2%) compared with 2.7% in the U.S. population, based on CDC surveillance[1]. 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 limited in a Phase I/II safety and pharmacokinetic (PK) study[2]. This was confirmed in a study of 100 HIV-infected pregnant women who were receiving NRTIs (generally as part of a two- or three-drug combination antiretroviral [ARV] regimen). At the time of delivery, cord-to-maternal blood ratio for didanosine (n = 10) was 0.38 (range 0.0–2.0) and in 15 of 24 (62%) samples, cord blood concentrations for didanosine were below the limits of detection[3]. 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 26–36 weeks and treated through 6 weeks postpartum[2]. 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, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents[4-6]; 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 in perinatal guidelines). 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) is classified as 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 at a therapeutic dose of 200 mg/day or in rats at doses up to 31 times the human systemic exposure at the therapeutic dose.

- **Reproduction/fertility**

  No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by AUC) approximately 60-fold higher in female mice and 140-fold higher in male mice than observed with human exposure at the recommended therapeutic dose.

- **Teratogenicity/developmental toxicity**

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

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 2-fold increase in 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 2.7% (17 of 641 births; 95% CI, 1.7%–4.8%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance[1].

- **Placental and breast milk passage**

  Emtricitabine has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits[2]. Emtricitabine has been shown to have good placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine daily during pregnancy, mean cord blood concentration was 300 ± 268 ng/mL and mean ratios of cord blood/maternal emtricitabine concentrations were 1.17 ± 0.6 (n = 9)[3]. When 35 women were administered 400 mg of emtricitabine in combination with tenofovir at delivery, median maternal and cord concentrations were 1.02 (0.034–2.04) and 0.74 (0.0005–1.46) mg/L, respectively[4]. It is unknown if emtricitabine is excreted in human milk.

- **Human studies in pregnancy**

  Emtricitabine PKs have been evaluated in 18 HIV-infected pregnant women receiving combination antiretroviral therapy (ART) including emtricitabine (200 mg once daily) at 30–36 weeks gestation and 6–12 weeks postpartum[3]. 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 nonpregnant 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 [<10–306]). In another study of 35 women who received 400 mg of emtricitabine with tenofovir at delivery, median population AUC, maximum plasma concentration (C_{max}), and C_{min} were 14.3 µg*h/mL, 1,680 ng/mL, and 76 ng/mL, respectively[4]. Currently, data are insufficient to recommend a dosage adjustment during pregnancy.

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Lamivudine (Epivir, 3TC) is classified as FDA 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 35–45 times human exposure. Long-term animal carcinogenicity screening studies at 10 and 58 times human exposure have been negative in mice and rats, respectively.

- **Reproduction/fertility**

  Lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47–70 times those in humans, revealed no evidence of impaired fertility and no effect on the offsprings' survival, growth, and development up to the time of weaning.

- **Teratogenicity/developmental toxicity studies**

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

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivu-

dine 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 3.1% (118 of 3,864 births, 95% CI, 2.5%–3.7%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance[1].

- **Placental and breast milk passage**

  Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations[2]. Lamivudine is excreted into human breast milk. In a study in Kenya of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1,214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56[3]. In infants who received lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (half-maximal inhibitory concentration [IC_{50}] of wild-type HIV against lamivudine = 0.6–21 ng/mL).

- **Human studies in pregnancy**

  A small Phase I study in South Africa evaluated the safety and PKs of lamivudine alone or in combination with zidovudine in 20 HIV-infected pregnant women; therapy was started at 38 weeks' gestation, continued through labor, and given to the infants for 1 week following birth[2]. The drug was well tolerated in the women at the recommended adult dose of 150 mg orally twice daily; PKs were similar to those observed in nonpregnant adults, and no PK interaction with zidovudine was observed.

  Intrapartum oral administration of combination zidovudine and lamivudine was well tolerated. Lamivudine was well tolerated in the neonates, but clearance was about 50% that of older children, requiring a reduced dosing regimen (4 mg/kg/day in neonates compared with 8 mg/kg/day for infants older than 3 months). No data currently exist on the PKs of lamivudine in infants 2–6 weeks of age, and the exact age at which lamivudine clearance begins to approximate that in older children is unknown.

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Stavudine (Zerit, d4T) is classified as FDA pregnancy category C.

- **Animal carcinogenicity studies**

  Stavudine is clastogenic in *in vivo* and *in vivo* assays but not mutagenic in *in vitro* assays. In 2-year

carcinogenicity studies in mice and rats, stavudine was noncarcinogenic 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 preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100 μM and of postblastocyst development at 10 μM[1].

- **Teratogenicity/developmental toxicity studies**

  No evidence of teratogenicity was noted in rats or rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of 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 with 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–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 2-fold increase in 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 2.4% (19 of 797 births; 95% CI, 1.4%–3.7%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance[2].

- **Placental and breast milk passage**

  Stavudine crosses the rat placenta *in vivo* and the human placenta *ex vivo*, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pigtailed macaques), fetal/maternal plasma concentrations were approximately 0.80[3]. Stavudine is excreted into the breast milk of lactating rats.

- **Human studies in pregnancy**

  A Phase I/II safety and 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 nonpregnant adults[4]. Data from primate studies also indicated that pregnancy did not affect the PKs of stavudine[5].

  Lactic acidosis, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents[6-8]. 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 in the perinatal guidelines). 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.

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Tenofovir disoproxil fumarate (Viread, TDF) is classified as FDA 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 DF 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 due to tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir DF was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days prior to mating and to female rats for 15 days prior to mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day.

- **Teratogenicity/developmental toxicity**

  Chronic exposure of fetal monkeys to tenofovir at a high dose of 30 mg/kg (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) from Days 20–150 of gestation did not result in gross structural abnormalities[1]. However, significantly lower fetal circulating insulin-like growth factor-1 (a primary regulator of linear growth) and higher insulin-like growth factor binding protein-3 levels were shown and were associated with overall body weights approximately 13% lower than untreated controls. 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.

  Continued administration of tenofovir at 30 mg/kg/day to infant monkeys resulted in significant growth restriction and severe bone toxicity in 2 of 8 (25%) infants and effects on bone biomarkers and defective bone mineralization in all animals. 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. Abnormalities ranged from minimal decrease in bone mineral density and content (with oral dosing in rats and dogs that achieved drug exposures 6–10 times that achieved with therapeutic dosing in humans) to severe, pathologic osteomalacia (with subcutaneous dosing given to monkeys). Juvenile monkeys given chronic subcutaneous tenofovir at 30 mg/kg/day (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) developed osteomalacia, bone fractures, and marked hypophosphatemia. However, no clinical or radiologic bone toxicity was seen when juvenile monkeys received subcutaneous dosing of 10 mg/kg/day (exposure equivalent to 8 times the AUC achieved with therapeutic dosing in humans). Evidence of nephrotoxicity was observed in newborn and juvenile monkeys given tenofovir in doses resulting in exposures 12–50 times higher than the human dose, based on body surface area comparisons.

  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 increase in 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 2.4% (26 of 1,092 births, 95% CI, 1.6%–3.5%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance[2].

- **Placental and breast milk passage**

  Studies in rats have demonstrated that tenofovir is secreted in milk. Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir does cross the placenta[3]. In 3 studies of pregnant women on chronic dosing, the cord-to-maternal blood ratio ranged from 0.60 to 0.99, indicating high placental transfer[4-6]. In 2 studies of single-dose tenofovir (in some cases with emtricitabine) in labor that included 82 mother-infant pairs, the drugs were well tolerated and cord-to-maternal blood ratios were 0.61–0.67[7-9].

  Among women receiving a single 600-mg dose during labor, tenofovir was detectable in only 4 of 25 (16%) breast milk samples during the first week after delivery, with a median concentration of 13 (range 6–18) ng/mL[9]. In another study, 16 breast milk samples were obtained from 5 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 for neonates[10].

- **Human studies in pregnancy**

  In study P1026s, tenofovir PKs were evaluated in 19 pregnant women receiving tenofovir-based combination therapy at 30–36 weeks' gestation and 6–12 weeks postpartum[4]. The percentage of women with tenofovir AUC exceeding the target of 2 µg*hour/mL (the 10th percentile in nonpregnant adults) was lower in the third trimester (74%, 14 of 19 women) than postpartum (86%, 12 of 14 women) (P = 0.02); however, trough levels were similar in the two groups.

  A recent case series found tenofovir to be well tolerated among 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[11]. 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 2 years of age[12]. A retrospective review of 16 pregnancy outcomes among 15 heavily ARV experienced women demonstrated that tenofovir was well tolerated by the women and associated with normal growth and development in the infants[13].

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Zalcitabine (HIVID, ddC) is no longer available in the United States.

Zidovudine (Retrovir, AZT, ZDV) is classified as FDA 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[1]. In mice, seven late-appearing (>19 months) vaginal neoplasms (5 nonmetastasizing 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, two late-appearing (>20 months), nonmetastasizing 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 AUC) was approximately 3 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[2-3]. In one 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[3]. The drug doses administered in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. In a second study, zidovudine was administered at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12–18 of gestation[2]. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

- **Reproduction/fertility**

  When administered to male and female rats at doses up to 7 times the usual adult dose based on body

surface area, zidovudine had no effect on fertility, as judged by rates of conception.

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

- **Teratogenicity/developmental toxicity**

  Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity, as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66–226 times, and in rabbits 12–87 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 the 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 66–226 times (rats) and 12–87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. No other developmental anomalies were reported. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

  In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen[5-6]. A report from the Women and Infants Transmission Study (WITS), a cohort study enrolling women during pregnancy, described an association between first-trimester exposure to zidovudine and a 10-fold increased risk of hypospadias[7]. However, 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 increase in risk of overall birth defects and a 2-fold increase in defects in the more common classes, defects of the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.3% (118 of 3,620 births, 95% CI, 2.7%–3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance[8].

- **Placental and breast milk passage**

  Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal blood ratios of about 0.80. Zidovudine is excreted into human breast milk. In one study in Kenya in 67 mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, zidovudine concentration in the

breast milk of mothers averaged 9 ng/mL and the ratio of breast milk to maternal plasma zidovudine concentration averaged 44%[9]. No zidovudine was detectable in the plasma of the nursing infants, who received zidovudine only via breast milk.

- **Human studies in pregnancy**

  Zidovudine is well tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg/kg body weight orally every 6 hours[5, 10]. Long-term data on the safety of in utero drug exposure in humans are not available for any ARV 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[11]. Additionally, no differences in immunologic, neurologic, or growth parameters were seen between infants with in utero zidovudine exposure and those who received placebo, based on nearly 6 years of follow up[6, 12].

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Non-Nucleoside Reverse Transcriptase Inhibitors (Updated September 14, 2011)

Glossary of Terms for Supplement
Clastogenic = causing disruption of or breakages in chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Genotoxic = damaging to genetic material such as DNA and chromosomes
Carcinogenic = producing or tending to produce cancer
Notes:
• 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.

Five non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) currently are 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 Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use in the perinatal guidelines. For more information regarding nevirapine hepatic/rash toxicity, see Nevirapine and Hepatic/Rash Toxicity in the perinatal guidelines.

Delavirdine (Rescriptor, DLV) is no longer available in the United States.

Efavirenz (Sustiva, EFV) is classified as 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 con-

centrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily). Central nervous system (CNS) malformations were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational Days 20–150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure)[1]. The malformations included anencephaly and unilateral anophthalmia in 1 fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

In pregnancies with prospectively reported exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2011, birth defects were observed in 17 of 623 live births with first-trimester exposure (2.7%, 95% confidence interval [CI], 1.6%–4.3%). Although these data provide sufficient numbers of first-trimester exposures to rule out a 2-fold or greater increase in the risk of overall birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the Antiretroviral Pregnancy Registry of defects after first-trimester efavirenz exposure have documented 1 neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and 1 case of bilateral facial clefts, anophthalmia, and amniotic band[2]. Among retrospective cases, there are 6 reports of CNS defects, including 3 cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester[3]. Although a causal relationship has not been established between these events and the use of efavirenz, similar defects have been observed in preclinical studies of the drug.

- **Placental and breast milk passage**

  Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery[4]. Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz passed into breast milk with a ratio of 0.54 (mean breast milk to mean maternal plasma concentration) and 4.08 (mean skim milk to mean newborn plasma concentration). Mean infant plasma efavirenz concentrations were 13.1% of maternal plasma levels. No data currently are available about efavirenz in neonates.

- **Human studies in pregnancy**

  In a meta-analysis of 16 observational cohorts reporting birth outcomes among women exposed to efavirenz during the first trimester, the rate of overall birth defects was similar among women exposed to efavirenz-containing regimens (1,132 live births) and non-efavirenz containing regimens (7,163 births) during the first trimester (pooled relative risk [RR] 0.87, 95% CI, 0.61–1.24, P = 0.45)[5]. Across all studies (1,256 live births with first-trimester efavirenz exposure), 1 neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.08% (95% CI, 0.002–0.44), within the range reported in the general population. In a separate study from the Ivory Coast, no congenital malformations were observed in 344 HIV-infected pregnant women who conceived while receiving NNRTI-based antiretroviral therapy (ART) (213 on efavirenz and 131 on nevirapine)[6]. In a South African study, the prevalence of overall birth defects was not significantly different between 184 women receiving efavirenz-based ART at conception and 623 receiving efavirenz-based ART in the second or third trimester (3.3% vs. 2.6%, respectively, prevalence ratio 1.27, 95% CI, 0.5–3.2)[7]. However, the number of reported first-trimester efavirenz exposures still remains insufficient to rule out a significant increase in low-incidence birth defects (0.1–0.4% incidence of neural tube defect in the general population).

Efavirenz is classified as FDA Pregnancy Category D and may cause fetal harm when administered to a pregnant woman during the first trimester. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester, which is the primary period of fetal organogenesis. Women of childbearing age should undergo pregnancy testing prior to initiation of efavirenz and should be counseled about the potential risk to the fetus and the need to avoid pregnancy. Higher rates of failure for hormonal contraceptives containing estrogen and progesterone may be associated with antiretroviral (ARV) drugs such as efavirenz. 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. 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 medroxyprogesetrone (DMPA) in 17 women found no change in the pharmacokinetic (PK) profile of either efavirenz or DMPA with concomitant use[8]. DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

Limited PK data exist for efavirenz in pregnancy. In a study of 25 pregnant women receiving efavirenz during the third trimester as part of clinical care, efavirenz clearance was increased and C24h was decreased compared with postpartum. These differences are not of sufficient magnitude to warrant dose adjustment during pregnancy[9].

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Etravirine (Intelence, ETR) is classified as FDA pregnancy category B.

- **Animal carcinogenicity studies**

  Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of etravirine in rodents are ongoing.

- **Reproduction/fertility**

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

- **Teratogenicity/developmental toxicity**

  Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1,000 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 pre- 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).

- **Placental and breast milk passage**

  There are no data on whether etravirine crosses the placenta or is excreted in breast milk in humans.

- **Human studies in pregnancy**

  No adequate and well-controlled studies of etravirine use in pregnant women have been conducted and very limited case report data are available on etravirine use in pregnancy. One small study described use of etravirine in combination with darunavir/ritonavir and other ARV drugs in four pregnant women; PK sampling was done to determine etravirine plasma concentration during the third trimester[1]. PK data from these women were similar to those in nonpregnant adults. Data on etravirine in postpartum cord blood and concurrent maternal plasma specimens were available for one patient with values of 112 ng/mL and 339 ng/mL (cord/maternal blood ratio 0.33). No maternal, fetal, or neonatal toxicity was reported; one infant was born with a small accessory auricle on the right ear with no other malformations; no birth defects were noted in the other children. Placental passage of etravirine was noted in another report of use of etravirine, darunavir/ritonavir, and enfuvirtide in a pregnant woman who gave birth to twins (cord blood levels 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2)[2]. In a separate report on two women receiving etravirine, darunavir/ritonavir, and raltegravir during pregnancy, no perinatal transmission of HIV or congenital abnormalities were observed.

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Nevirapine (Viramune, NVP) is classified as FDA 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 not known.

- **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 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, sufficient numbers of first-trimester exposures to nevirapine 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 nevirapine. Among cases of first-trimester nevirapine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (25 of 987 births, 95% CI, 1.6%–3.7 %) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance[1].

- **Placental and breast milk passage**

  Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90)[2]. Nevirapine is excreted into human breast milk; the median concentration in 4 breast milk samples obtained from 3 women during the first week after delivery was approximately 76% (range 54%–104%) of serum levels[2]. In 19 women receiving combination therapy with nevirapine, lamivudine, and zidovudine, breast milk nevirapine concentration was 6,795 ng/mL, which was 0.67 times that of maternal serum[3]. Median nevirapine breast milk concentration was 4,564 ng/mL in a Kenyan study of 67 HIV-infected nursing mothers receiving a combination of zidovudine, lamivudine, and nevirapine[3]. The median nevirapine concentration was 734 ng/mL in the infants, who received the drug only via breast milk.

- **Human studies in pregnancy**

  Short-Term Peripartum Prophylaxis:

  A Phase I study (PACTG 250) evaluated the safety and PKs of nevirapine administered to infected pregnant women as a single 200-mg dose at the onset of labor and as a single 2-mg/kg dose to infants 48–72 hours of age[2]. No adverse effects were seen in the women or the infants.

  The PK parameters of intrapartum nevirapine were similar in pregnant women and in nonpregnant adults, but variability was increased during pregnancy, possibly as a result of incomplete drug absorption associated with impaired gastrointestinal function during labor. Nevirapine elimination was

prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life.

The safety, toxicity, and PKs of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants[4]. Initial-dose PK profiles in pregnant women were similar to those seen in nonpregnant adults. Serum nevirapine concentrations fell below the 100 ng/mL target concentration by Day 7 of life in four of eight infants, suggesting that nevirapine elimination was accelerated in infants whose mother received chronic nevirapine administration compared with newborns whose mothers received only a single intrapartum dose.

The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) with zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of transmission of HIV by nearly 50% during the first 14–16 weeks of life compared with zidovudine[5]. However, the women in this African trial were not receiving any other ARV drugs.

In the United States, most infected women who know their HIV status during pregnancy receive combination ARV prophylaxis regimens, usually including zidovudine, as well as intravenous zidovudine during delivery, with 6 weeks of zidovudine given to their infants. A Phase III perinatal trial (PACTG 316) conducted in the United States, Europe, the Bahamas, and Brazil evaluated whether the HIVNET 012 single-dose nevirapine regimen in combination with standard combination prophylaxis regimens (at minimum the PACTG 076 zidovudine regimen; 77% of women in the trial received combination ARV regimens) would provide additional benefits in reducing transmission. Transmission was not significantly different between those who received single-dose nevirapine (1.4%) and those who did not (1.6%)[6].

Nevirapine resistance can be induced by a single mutation. As a result of its long half-life, the drug can be detected in plasma up to 3 weeks after administration of a single intrapartum dose[7]. This period of persistent subtherapeutic drug levels exerts selective pressure that predisposes to the development of resistant strains of HIV[8]. Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of ARV-naive women in HIVNET 012 and 15% of a subset of women receiving additional ARV drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor[9-10]. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13–18 months postpartum[11]. Evaluation at later time points was not done in PACTG 316. Single-dose nevirapine appears to be as effective in preventing HIV transmission in subsequent pregnancies as when it is used for the first time[12-13]. Current data suggest that women starting NNRTI-based therapy within 12–24 months of single-dose nevirapine exposure have higher rates of viral failure than those without single-dose nevirapine exposure and that use of a protease inhibitor (PI)-based regimen (such as lopinavir/ritonavir) would be recommended in such situations[14-16]. Administration of postpartum ARVs to the mother can significantly reduce the frequency of detection of nevirapine-resistant strains[8, 17-22].

Longer Term Antenatal Combination Therapy:

The PKs of nevirapine have been evaluated in pregnant women receiving nevirapine as part of combination ART during pregnancy. A study that determined nevirapine PKs in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4–12 weeks after delivery found that pregnancy did not alter nevirapine PK parameters[23]. In contrast, nevirapine clear-

ance was 20% greater, AUC was 28% lower, and maximum plasma concentration (C_{max}) was 30% lower in 16 pregnant women compared with 13 nonpregnant women, based on nevirapine PK data from a therapeutic drug monitoring program that included 12-hour sampling[24].

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, have 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 a combination regimen for post-exposure prophylaxis of nosocomial or sexual exposure to HIV[25]. These toxicities have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. The greatest risk of severe rash or hepatic events occurs during the first 6–18 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 5.5–7.3 times more common in women than men and has been reported in pregnant women[26-28]. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men[29]. Several studies suggest that the degree of risk of hepatic toxicity varies with CD4 cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4 counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity[29]. Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash[27]. Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of nonpregnant women but not in association with CD4 cell counts >250 cells/mm^3 [30]. In general, in controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5%–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%–0.40%[29, 31]. Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine[31].

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination ARV regimen, it is uncertain if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other ARV drugs[32]. In an analysis of 2 multicenter prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 95% CI: 3.4–6.5), although nevirapine use was not, regardless of pregnancy status[33]. Additional data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination ART versus non-nevirapine-based combination ART[34]. In a cohort of 612 pregnant and nonpregnant women starting nevirapine-based therapy, CD4 cell count at initiation of therapy but not liver enzyme elevation was a predictor of rash; pregnancy was not an independent risk factor for the development of toxicity[35]. These data suggest that nevirapine is no more toxic in pregnant women than in nonpregnant women.

Women initiating nevirapine with CD4 cell counts >250 cells/mm^3, including pregnant women receiving ARV drugs solely for prevention of transmission, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening and, in some cases fatal[36]. Therefore, nevirapine should be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Women with CD4 cell counts < 250/mm^3 can receive nevirapine-based regimens, and women who become pregnant while taking nevirapine and who are tolerating their regimens well can continue therapy, regardless

of CD4 cell count. Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV.

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, monthly through 4 months, and every 1–3 months thereafter (Adult Antiretroviral Guidelines); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter[37]. 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) is classified as FDA 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[1].

- **Reproduction/fertility**

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

- **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 (Updated September 14, 2011)

Glossary of Terms for Supplement
Clastogenic = causing disruption of or breakages in chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Genotoxic = damaging to genetic material such as DNA and chromosomes
Carcinogenic = producing or tending to produce cancer
Notes:
• 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.

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, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir. Data in pregnancy are limited for darunavir, fosamprenavir, and indinavir. No 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 Protease Inhibitor Therapy and Hyperglycemia and Combination Antiretroviral Therapy and Pregnancy Outcome in the perinatal guidelines.

Amprenavir (Agenerase, APV) is no longer available in the United States.

Atazanavir (Reyataz, ATV) 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 2.8–2.9-fold higher than those in humans at the recommended therapeutic dose (300 mg/day atazanavir boosted with 100 mg/kg/day ritonavir). 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.

- **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.

- **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/day atazanavir boosted with 100 mg/day ritonavir). 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.

  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 2 miscarriages at 12 and 16 weeks, 26 infants born, and 5 women still pregnant[1]. No infant required phototherapy and no birth defects were seen; none of the infants was 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 2.4% (12 of 502 births, 95% confidence interval [CI], 1.2%–4.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance[2].

  Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir. Studies have demonstrated that infants born to mothers who received atazanavir during pregnancy do not have pathologic or dangerous bilirubin elevations in the neonatal period[1, 3-7].

- **Placental and breast milk passage**

  In studies of women receiving atazanavir/ritonavir-based combination therapy during pregnancy, the median cord blood atazanavir concentration was 13%–21% of maternal serum levels at delivery[3, 5-6]. 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%[8].

- **Human studies in pregnancy**

  Several studies have investigated the pharmacokinetics (PKs) of atazanavir with ritonavir in pregnancy. In some of these studies, virological results were also analyzed. Overall, most pregnant patients were able to achieve HIV RNA less than 50 copies/mL at time of delivery[9]. In some studies, almost all pregnant patients achieved HIV RNA <50 copies/mL at time of delivery[4, 6-7]. 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[1]. Three studies have evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy. In all of these studies, atazanavir AUC was lower during pregnancy than in historic data from HIV-infected nonpregnant patients[3, 5, 10]. In 1 of the 3 studies, there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than in nonpregnant HIV-infected historic controls[3]. In the other 2 studies, atazanavir AUC was 25% lower during pregnancy than in the same patients postpartum[5, 10]. However, in both these studies (BMS AI424182 and IMPAACT P1026 atazanavir cohort), the postpartum AUC was elevated compared with nonpregnant HIV-infected historic control patients. For example, in study AI424182, 34

women were treated with 300 mg atazanavir plus 100 mg ritonavir at 4–12 weeks postpartum and were observed to have a 34% increase in geometric AUC compared with the historic control of HIV-infected, nonpregnant patients (62 µg*hr/mL vs. 46.1 µg*hr/mL respectively)[6]. Because of the postpartum elevation in AUC in this study, the atazanavir drug label recommends that postpartum patients should be closely monitored for adverse events during the first 2 months after delivery.

Although use of atazanavir with ritonavir combined with tenofovir and emtricitabine as a complete once-a-day dosing combination ARV regimen is becoming increasingly common in pregnancy, tenofovir reduces atazanavir exposure by 25% in nonpregnant adults[11]. This drug-drug interaction also is present during pregnancy, with a 25% reduction in atazanavir AUC in pregnant women also receiving tenofovir compared with the same women postpartum and a 50% reduction compared with postpartum levels in women who did not receive tenofovir[5].

Use of an increased dose of atazanavir of 400 mg with 100 mg ritonavir during pregnancy has been investigated in two studies[10 5]. In both studies pregnant women receiving the increased dose without tenofovir had an atazanavir AUC equivalent to that seen in historic nonpregnant 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 nonpregnant HIV-infected patients receiving standard-dose atazanavir and tenofovir[9].

In the prescribing information for atazanavir[6], the dose recommended for most pregnant women is 300 mg with 100 mg of ritonavir. For additional details about dosing with interacting concomitant medications, please see Table 5 (Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy).

Neonatal elevations in bilirubin have been reported in some—but not all—studies of infants born to mothers receiving atazanavir during pregnancy[3, 5, 10]. Phototherapy was needed to control hyperbilirubinemia in 5 of 29 infants in 1 study[7]. In study AI424182, 6 of 39 infants received phototherapy[12]. Decisions to use phototherapy to treat infants with hyperbilirubinemia frequently are subjective and guidelines for phototherapy of infants vary between countries, making it difficult, therefore, to compare the severity of hyperbilirubinemia between patients within a study and in different studies. Elevated neonatal bilirubin is more likely in infants with uridine diphosphate glucuronosyltransferase 1 (UGT1A1) genotypes associated with decreased UGT function[10].

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis has been reported in 3 of 38 atazanavir-exposed infants with glucose samples collected in the first day of life. All 3 hypoglycemic infants' glucose samples were adequately collected and processed in a timely fashion[13]. This finding of infant hypoglycemia is similar to a prior report in which 2 (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life[14].

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Darunavir (Prezista, DRV) is classified as FDA 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 AUC) were between 0.4- and 0.7-fold (mice) and 0.7-and 1-fold (rats) of those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

- **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 pre- 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–1,000 mg/kg at age 12 days) caused mortality. The deaths were associated with convulsions in some of the animals. Within this age range, exposures in plasma, liver, and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the cytochrome P450 (CYP450) liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, and mating performance of offspring were not affected by maternal treatment. No data are available in humans.

- **Placental and breast milk passage**

  No animal studies of placental passage of darunavir have been reported. As noted above, passage of darunavir into breast milk has been noted in rats. It is unknown if placental or breast milk passage of darunavir occurs in humans.

- **Human studies in pregnancy**

  Currently, very limited data exist about darunavir in pregnancy[1-7]. Reports conflict about whether darunavir has low or moderate placental transfer[6-7]. Generally, PIs have a low degree of placental transfer. Darunavir is not recommended for children younger than 3 years of age. Darunavir is one of the study drugs in the ongoing International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1026: "Pharmacokinetic Study of Anti-HIV Drugs During Pregnancy." Few pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.

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Fosamprenavir (Lexiva, FPV) is classified as FDA 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 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 1,400 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 1,400 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 3–4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. At those doses, no affect was seen on the development or maturation of sperm in rats.

- **Teratogenicity/developmental toxicity**

  Fosamprenavir was studied in rabbits at 0.8 and in rats at twice the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination) the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at twice human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared with controls.

- **Placental and breast milk passage**

  It is unknown whether fosamprenavir crosses the placenta. Amprenavir is excreted in the milk of lac-

tating rats; it is not known if it is excreted in human milk.

- **Human studies in pregnancy**

  Very limited data exist on fosamprenavir in pregnant women. Fosamprenavir PKs have been reported in 15 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700 mg and ritonavir 100 mg, amprenavir AUC and 12-hour trough concentrations were somewhat lower during pregnancy and higher postpartum compared with historical data. Amprenavir exposure during pregnancy appeared to be adequate for patients without PI resistance mutations[1].

A pediatric liquid formulation of fosamprenavir has been approved for children older than 2 years of age, but there is no dosing information for neonates.

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Indinavir (Crixivan, IDV) is classified as FDA 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 pregnant 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 exacerbated 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%–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, sufficient numbers of first-trimester exposure 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 Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.1% (6 of 285 births, 95% CI, 0.8%–4.5%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance[1].

- **Placental and breast milk passage**

  Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In a Phase I study in pregnant women and their infants (PACTG 358, see below), transplacental passage of indinavir was minimal[2]. In addition, in a study of cord blood samples from 21 women treated with indinavir during pregnancy, the cord blood concentration of indinavir was less than the assay limit of detection in samples from all women[3]. 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); it is not known if indinavir is excreted in human milk.

- **Human studies in pregnancy**

  The optimal dosing regimen for use of indinavir in pregnant patients has not been established. A Phase I/II safety and PK study (PACTG 358) was conducted of indinavir (800 mg three times a day) in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants[2]. The mean indinavir plasma AUC0-8hr at 30–32 weeks' gestation (n =11) was 74% (95% CI, 50%–86%) lower than that observed 6 weeks postpartum. The PKs of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in nonpregnant patients in another study. In another study, two pregnant HIV-infected women receiving combination therapy including indinavir (800 mg three times a day) had significantly reduced AUC indinavir exposures in the third trimester compared with postpartum evaluations (52% and 86%, respectively)[4]. Therefore, given the substantially lower antepartum exposures observed in these studies and the generally limited data in this patient population, use of indinavir as a sole PI is not recommended in HIV-infected pregnant patients.

  Two studies have evaluated twice-daily dosing with indinavir combined with low-dose ritonavir. The first evaluated 2 women whose regimen included indinavir 800 mg and ritonavir 200 mg, both twice daily. Both patients achieved third-trimester AUC indinavir levels greater than those for historical nonpregnant controls[4]. A more recent study evaluated use of twice-daily combination therapy including indinavir (400 mg) and ritonavir (100 mg). Data are available for 28 women, 23 (82%) of whom had Ctrough values greater than the targeted cutoff of 120 ng/mL. Of the 5 women with low Ctrough values, 3 had undetectable HIV RNA viral loads at delivery[5]. Based on these data, indinavir may be used in pregnancy with ritonavir boosting. Given the limited data on appropriate dosing, HIV RNA levels and, potentially, trough drug levels should be monitored during indinavir use in pregnancy.

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Lopinavir + Ritonavir (Kaletra, 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 lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male rats at doses that produced approximately 1.6–2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on AUC0–24hr measurement). Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

- **Reproduction/fertility**

  Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

- **Teratogenicity/developmental toxicity**

  No evidence exists of teratogenicity with administration of lopinavir/ritonavir 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 (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 peri- and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred with exposure to 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lopinavir/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 lopinavir/ritonavir. Among cases of first-trimester lopinavir/ritonavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (16 of 738 births, 95% CI, 1.2%–3.5%) compared with a total prevalence of 2.7% in the U.S. population, based on CDC surveillance[1].

- **Placental and breast milk passage**

  Lopinavir crosses the human placenta; in the P1026s PK study, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20 ± 0.13. For ritonavir, data in humans

indicate only minimal transplacental passage (see ritonavir). Lopinavir and ritonavir are secreted in the breast milk of lactating rats; it is not known if either drug is excreted in human milk.

- **Human studies in pregnancy**

  The capsule formulation of lopinavir/ritonavir is no longer available; it has been replaced by a new tablet formulation of lopinavir 200 mg/ritonavir 50 mg that is heat stable and does not have a food requirement.

  In nonpregnant adults, plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg lopinavir/ritonavir tablets are similar to those achieved with three 133/33 mg lopinavir/ritonavir capsules given with food, although with less PK variability. In a study of 51 pregnant women, plasma trough lopinavir levels during the third trimester were compared among 28 women receiving the capsule and 23 women receiving the tablet formulations at standard dosing. No statistical difference was found between the groups, with a mean lopinavir trough level of 4.86 mg/L (capsule) and 4.57 mg/L (tablets)[2]. However, the inter-individual variability was lower with the tablets than with the capsules. Five of 28 women (17.8%) in the capsule group and 4 of 23 women (17.4%) in the tablet group had trough levels less than the target (3 mg/L); 7 of the 9 women had HIV RNA levels less than detection at the time of their sampling, and 2 with subtherapuetic levels (0.7 and 2.44 mg/L) had plasma RNA of 83 and 56 copies/mL, respectively, at the time of their sampling.

  P1026s evaluated lopinavir PKs following standard dosing with the new lopinavir/ritonavir tablet formulation (2 tablets twice daily) until 30 weeks' gestation, followed by an increase to 3 tablets twice daily and return to standard dosing at postpartum hospital discharge. Median AUC was 72 µg*h/mL in 7 women receiving standard dosing during the second trimester, 97 µg*h/mL in 25 women receiving the increased dose during the third trimester, and 129 µg*h/mL in 19 women receiving standard dosing at 2 weeks postpartum. These data suggest that the higher lopinavir/ritonavir dose should be used in the third trimester; that it should be considered in the second trimester, particularly in women who are PI experienced; and that lopinavir/ritonavir can be reduced to standard dosing shortly after delivery[3]. An alternative strategy for increasing lopinavir/ritonavir exposure during pregnancy is to add a pediatric lopinavir/ritonavir tablet (100/25 mg) to the standard dose of 2 adult tablets (200/50 mg)[4].

  Once-daily dosing of lopinavir/ritonavir capsules or tablets is not recommended in pregnancy because no data exist to address whether drug levels are adequate with such administration.

  Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Reduced metabolism by the liver and reduced kidney function in newborns can lead to an accumulation of lopinavir (the active ingredient) as well as alcohol and propylene glycol. Preterm babies may be at increased risk of health problems because they cannot metabolize propylene glycol; this could lead to accumulation and adverse events such as serious heart, kidney, or breathing problems. Postmarketing surveillance has identified 10 neonates (babies <4 weeks of age), 9 of whom were born prematurely, who received lopinavir/ritonavir and experienced life-threatening events[5]. Lopinavir/ritonavir 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) is classified as FDA pregnancy category B.

- **Animal carcinogenicity studies**

  Nelfinvair 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 1,000 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 midpregnancy 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, sufficient numbers of first-trimester exposures to nelfinavir 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 nelfinavir. Among cases of first-trimester nelfinavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.9% (46 of 1,193 births, 95% CI, 2.8%–5.1%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance[1].

- **Placental and breast milk transfer**

  In a Phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal[2]. In addition, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 µg/mL) in the remaining 14 women[3]. Nelfinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- **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[2]. In the first nine 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 nonpregnant adults with both twice- and three-times-daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1,250 mg twice daily), which resulted in adequate levels of the drug in pregnancy. However, in another study of women given 1,250 mg nelfinavir twice daily in the second and third trimesters, drug concentrations in the third trimester were lower than in the second trimester or in nonpregnant women[4].

  In a PK study of combination therapy including the new nelfinavir 625-mg tablet formulation (given as 1,250 mg twice daily) in 25 women at 30–36 weeks' gestation (and 12 at 6–12 weeks postpartum), peak levels and AUC were lower in the third trimester than postpartum[5]. Only 16% (4 of 25) of women during the third trimester and 8% (1 of 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 Antiretroviral Pregnancy Registry. 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) is classified as FDA 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 AUC, 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, 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 Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.4% (33 of 1,401 births; 95% CI, 1.6%–3.3%) compared with a total prevalence of 2.7% in the U.S. population, based on CDC surveillance[1].

- **Placental and breast milk transfer**

  Transplacental passage of ritonavir has been observed in rats with fetal tissue to maternal serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses. In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue[2]. In a Phase I study in pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal[3]. Additionally, in a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 83% and was only 0.38 µg/mL in the remaining woman[4]. Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk.

- **Human studies in pregnancy**

  A Phase I/II safety and PK 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[3]. 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 PIs[5-6].

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Saquinavir (Invirase [Hard-Gel Capsule], SQV) is classified as FDA 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 (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.

- **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[1]. 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[2]. Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- **Human studies in pregnancy**

  Three studies have evaluated the PKs of saquinavir-hard gel capsules combined with low-dose ritonavir (saquinavir-hard gel capsules 1,000 mg/ritonavir 100 mg given twice daily) in a total of 19 pregnant women; trough levels were greater than the target in all but 1 woman[3-4]. In a small study of 2 women who received saquinavir-hard gel capsules 1,200 mg/ritonavir 100 mg given once daily, trough levels were 285 and 684 ng/mL and the AUC0–24 were 28,010 and 16,790 ng hour/mL, greater than the target AUC of 10,000 ng hour/mL[5]. Thus, the limited available data suggest that saquinavir-hard gel capsules 1,000 mg/ritonavir 100 mg given twice daily should achieve adequate trough levels in HIV-infected pregnant women. Data are too limited to recommend once-daily dosing at present. However, a recent analysis of saquinavir-hard gel capsules administered once daily at 1,200 mg/100 mg ritonavir combined with various NRTIs during 46 pregnancies demonstrated saquinavir levels greater than the target minimum plasma concentration (C_{min}) in 46 (93.4%) of pregnancy episodes and undetectable viral load at delivery in 88% of episodes[6]. Target levels were achieved in the other 3 women with a dose of 1,600 mg/100 mg. The drug was well tolerated.

  The PKs of the new 500-mg tablet formulation of saquinavir boosted with ritonavir in a dose of saquinavir 1,000 mg/ritonavir 100 mg given twice daily were studied in 14 HIV-infected pregnant women at 33 weeks gestation and parameters were comparable to those observed in nonpregnant individuals; none of the women had a subtherapeutic trough level[7].

  One study of a saquinavir/ritonavir-based combination ARV drug regimen in 42 women during pregnancy reported abnormal transaminase levels in 13 women (31%) within 2–4 weeks of treatment initiation, although the abnormalities were mild (toxicity Grade 1–2 in most, Grade 3 in 1 woman)[8].

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Tipranavir (Aptivus, TPV) is classified as FDA 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 tipranavir/ritonavir 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 tipranavir/ritonavir combination group. Incidence of hepatocellular carcinoma was increased in female mice given the high dose of tipranavir and in both sexes receiving tipranavir/ritonavir. 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 AUC or maximum plasma concentration [C_{max}]) 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 tipranavir/ritonavir 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 per day of tipranavir/ritonavir).

- **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 developments 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.

- **Placental and breast milk transfer**

  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. Tipranavir is one of the study drugs in the ongoing IMPAACT P1026: "Pharmacokinetic Study of Anti-HIV Drugs During Pregnancy".

Entry Inhibitors (Updated September 14, 2011)

Glossary of Terms for Supplement
Clastogenic = causing disruption of or breakages in chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Genotoxic = damaging to genetic material such as DNA and chromosomes
Carcinogenic = producing or tending to produce cancer
Notes:
• 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.

Two drugs have been approved in this new class of antiretrovirals (ARVs) 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 coreceptor 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 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 6 years of age or older. Maraviroc interferes with viral entry at the chemokine coreceptor level; it is a CCR5 coreceptor antagonist approved for combination therapy for HIV infection in adults infected with CCR5-tropic virus.

Enfuvirtide (Fuzeon, T-20) is classified as FDA pregnancy category B.

- **Animal carcinogenicity studies**

  Enfuvirtide was neither mutagenic or 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 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on an m^2 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^2 body surface area basis.

- **Placental and breast milk passage**

  Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or metabolites (e.g., amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide crosses the human placenta or is excreted in human milk. A published case report of two peripartum pregnant patients and their neonates and data from an ex vivo human placental cotyledon perfusion model suggest that enfuvirtide does not cross the placenta[1-2].

- **Human studies in pregnancy**

  Very limited data exist on the use of enfuvirtide in pregnant women[1, 3-4]; no data exist in neonates.

References

1. Brennan-Benson P, Pakianathan M, Rice P, et al. Enfurvitide prevents vertical transmission of multidrug-resistant HIV-1 in pregnancy but does not cross the placenta. *AIDS*. 2006 Jan 9;20(2):297-299.

2. Ceccaldi PF, Ferreira C, Gavard L, Gil S, Peytavin G, Mandelbrot L. Placental transfer of enfuvirtide in the ex vivo human placenta perfusion model. *Am J Obstet Gynecol*. 2008 Apr;198(4):433 e431-432.

3. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS*. 2005 Jun 10;19(9):989-990.

4. Meyohas MC, Lacombe K, Carbonne B, Morand-Joubert L, Girard PM. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS*. 2004 Sep 24;18(14):1966-1968.

Maraviroc (Selzentry, MVC) is classified as 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 found no increase in tumor incidence in mice (transgenic rasH2 mice) and rats at exposures up to 11-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).

- **Reproduction/fertility animal studies**

  Reproductive toxicity has been evaluated in rats. Maraviroc produced no adverse effects on fertility of male or female rats or sperm of male rats at exposures up to 20-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).

- **Teratogenicity/developmental toxicity animal studies**

  Studies in rats and rabbits revealed no evidence of harm to the fetus from maraviroc administered in doses up to 20-fold higher in rats and 5-fold higher in rabbits than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).

- **Placental and breast milk passage**

  It is unknown if maraviroc crosses the placenta in humans. In a study of four macaques, a single oral dose of either 60 mg/kg or 100 mg/kg was given 2 hours before cesarean delivery. Median maternal concentration at delivery was 974 ng/mL (range 86–2,830 ng/mL) and median infant concentration

was 22 ng/mL (range 4–99 ng/mL) for a cord/maternal ratio of .023[1]. Maternal levels were detectable for 48 hours after a single dose, whereas infant levels were detectable for only 3.5 hours after birth. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.

- **Human studies in pregnancy**

  No studies of maraviroc have been conducted in pregnant women or neonates.

- **Additional concerns**

  Although no increase in cancer has been observed with maraviroc, the drug has the potential to increase risk because of its mechanism of action and possible effects on immune surveillance.

Reference

1. Winters MA, Van Rompay KK, Kashuba AD, Shulman NS, Holodniy M. Maternal-fetal pharmacokinetics and dynamics of a single intrapartum dose of maraviroc in rhesus macaques. *Antimicrob Agents Chemother.* 2010 Oct;54(10):4059-4063.

Integrase Inhibitors (Updated September 14, 2011)

Glossary of Terms for Supplement
Clastogenic = causing disruption of or breakages in chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Genotoxic = damaging to genetic material such as DNA and chromosomes
Carcinogenic = producing or tending to produce cancer
Notes:
• 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.

One drug has been approved in this new class of antiretrovirals (ARVs) aimed at inhibiting integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the host 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. This second step in the integration process is targeted by the integrase inhibitor drug class. 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.

Raltegravir (Isentress) is classified as FDA 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 animal carcinogenicity studies of raltegravir are ongoing.

- **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 1,000 mg/kg/day. In a case report of use in late pregnancy, the raltegravir cord blood-to-maternal blood ratio at delivery was 1.06[1]. Raltegravir is secreted in the milk of lactating rats, with mean drug concentrations in milk about 3-fold higher than in maternal plasma at a maternal dose of 600 mg/kg/day. No effects in rat offspring were attributable to raltegravir exposure through breast milk.

- **Human studies in pregnancy**

Only limited data exist on the use of raltegravir in pregnancy. Raltegravir pharmacokinetics (PKs) 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 nonpregnant individuals; thus the standard dose appears appropriate in pregnancy[2]. Raltegravir readily crossed the placenta; in 6 deliveries with evaluation, the ratio of cord blood to maternal plasma was 0.98 (95% confidence interval [CI], 0.09–2.26). In a separate report, 3 pregnant women with multiresistant HIV-1 were given raltegravir in late pregnancy to rapidly reduce maternal viral load[3]. Raltegravir concentrations within 3 hours of delivery in the neonates of 2 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. However, no adverse reactions were observed in mothers or infants. Whether raltegravir is secreted in human milk is unknown.

References

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2. Best BM, Capparelli EV, Stek A, et al. Raltegravir pharmacokinetics during pregnancy. Paper presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); Sep. 12-15, 2010; Boston, MA.

3. McKeown DA, Rosenvinge M, Donaghy S, et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. *AIDS*. 2010 Sep 24;24(15):2416-2418.

Antiretroviral Pregnancy Registry (Updated September 14, 2011)

The Antiretroviral Pregnancy Registry is an epidemiologic project to collect observational, nonexperimental data on 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 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 Antiretroviral Pregnancy Registry. 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 B: Acronyms

3TC	lamivudine
ABC	abacavir
ALT	alanine aminotransferase
AOR	adjusted odds ratio
AP	antepartum
APV	amprenavir
ART	antiretroviral therapy/treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AUC	area under the curve
BID	twice daily
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CVS	chorionic villus sampling
CYP	cytochrome P
CYP3A4	cytochrome P450 3A4
d4T	stavudine
ddC	zalcitibine
ddI	didanosine

DLV	delavirdine
DMPA	depot medroxyprogesterone acetate
DRV	darunavir
DRV/r	darunavir/ritonavir
DSMB	Data and Safety Monitoring Board
EFV	efavirenz
EKG	electrocardiogram
EMS	ethyl methane sulfonate
ETR	etravirine
FDA	Food and Drug Administration
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitibine
HAV	hepatitis A virus
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HCV	hepatitis C virus
HELLP	hemolysis, elevated liver enzymes, and low platelets (syndrome)
HHS	Department of Health and Human Services
HRSA	Health Resources and Services Administration
HSV	herpes simplex virus
IC50	50% inhibitory concentration
IDV	indinavir
IgG	immunoglobulin G
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IP	intrapartum
IQR	interquartile range

IRIS	immune reconstitution inflammatory syndrome
IUD	intrauterine device
LPV/r	lopinavir/ritonavir
MAC	*Mycobacterium avium* complex
MIRIAD	Mother-Infant Rapid Intervention at Delivery (study)
mtDNA	mitochondrial DNA
MVC	maraviroc
NAAT	nucleic acid amplification testing
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OARAC	Office of AIDS Research Advisory Council
OC	oral contraceptive
OCTANE	Optimal Combination Therapy After Nevirapine Exposure (study)
OI	opportunistic infection
OR	odds ratio
PBMC	peripheral blood mononuclear cell
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PHACS	Pediatric HIV/AIDS Cohort Study
PI	protease inhibitor
PK	pharmacokinetic
po	orally

PP	postpartum
PPI	proton pump inhibitor
RAL	raltegravir
RDS	respiratory distress syndrome
RPV	rilpivirine
RR	relative risk
RTV	ritonavir
sd	single-dose
SQV	saquinavir
SQV/r	saquinavir/ritonavir
STI	sexually transmitted infection
SWEN	Six Week Extended-Dose Nevirapine (study)
T-20	enfuvirtide
TAM	thymidine-associated mutation
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TID	three times daily
TMP-SMX	trimethoprim-sulfamethoxazole
TPV	tipranavir
TPV/r	tipranavir/ritonavir
UGT	uridine diphosphate glucuronosyltransferase
WHO	World Health Organization
WITS	Women and Infants Transmission Study
ZDV	zidovudine