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

May 24, 2010

Revisions to the April 29, 2009 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

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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**).

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Perinatal HIV-1 Guidelines Panel Members

Revisions to the April 29, 2009, 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 May 24, 2010)

Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal HIV transmission have evolved considerably in the United States over the last 25 years, reflecting changes in the epidemic and the science of prevention *[1-2]*. Treatment of HIV disease in general and during pregnancy has progressed with an increasing proportion of women receiving combination antiretroviral therapy or triple antiretroviral drug prophylaxis throughout pregnancy. With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral prophylaxis, scheduled cesarean delivery, and avoidance of breastfeeding, the rate of perinatal HIV transmission has dramatically diminished to less than 2% in the United States and Europe *[3-4]*.

These guidelines update the April 29, 2009, 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 antiretroviral drugs during pregnancy and use of elective cesarean delivery to reduce perinatal HIV transmission. 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 antiretroviral agents for HIV-infected women during pregnancy must take into account two separate but related issues:

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

The benefits of antiretroviral therapy for a pregnant woman must be weighed against the risk 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 HIV transmission *[2, 5]*. After counseling and discussion, a pregnant woman's informed choice on whether to take antiretroviral drugs either for her treatment or for prevention of mother-to-child transmission or to follow other medical recommendations intended to reduce perinatal HIV transmission should be respected. Coercive and punitive policies are potentially counterproductive in that 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. Key issues and new information discussed in these guidelines include:

- **Rating Scheme for Guidelines (Table 2).** Recommendations are now rated based on strength of recommendation and quality of evidence.

- **Lessons Learned from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission and Table 3 (Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child HIV Transmission).** Update on recent international clinical trials, including trials of prevention of postnatal transmission and drug resistance in infants infected despite infant or maternal antiretroviral prophylaxis of postnatal infection. The Panel reaffirms that in the United States, where safe, affordable, and feasible alternatives are available and culturally acceptable, breastfeeding is not recommended for HIV-infected women (including those receiving combination antiretroviral therapy or triple antiretroviral drug prophylaxis).
- **Recommendations for Use of Antiretroviral Drugs during Pregnancy.** New discussion of the categories and the criteria used for recommendations about use of specific drugs or drug regimens in pregnancy.
- **Special Situations.** Additional discussion of options for antiretroviral prophylaxis when an HIV/hepatitis B virus (HBV) coinfected pregnant woman does not require antiretroviral therapy for her own health or treatment for hepatitis B disease.
- **Stopping Antiretroviral Therapy during Pregnancy.** Discussion of stopping non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and strategies to reduce the risk of resistance, including short-term continuation of a dual nucleoside reverse transcriptase inhibitor (NRTI) component or switching to a protease inhibitor (PI) prior to discontinuing therapy.
- **Special Considerations for the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants.** Updated information on combination antiretroviral drug use and pregnancy outcome and nevirapine hepatic toxicity in pregnancy.
- **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy.** New information regarding resistance following discontinuation of triple drug prophylaxis after delivery and new information from clinical trials on response to therapy following single-dose nevirapine exposure.
- **Intrapartum Antiretroviral Therapy/Prophylaxis.** New references on use of dual NRTI "tail" to reduce risk of nevirapine resistance.
- **Mode of Delivery.** Reorganization and update of section.
- **Neonatal Postnatal Care.**
  - **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis.** Caution on use of lopinavir-ritonavir (and other boosted PIs) in newborns, particularly preterm infants, due to reports of cardiac toxicity (heart block).
  - **Infant Feeding Practices and the Risk of HIV Transmission.** Discussion of new data on feeding infants premasticated food and risk of HIV transmission.
  - **The National Perinatal HIV Hotline.** Contact information for the National Perinatal HIV Hotline, a free consultation service for clinicians.

These recommendations have been developed for use in the United States. Although perinatal HIV transmission occurs worldwide, alternative strategies may be appropriate in other countries. Policies and practices in other countries regarding the use of antiretroviral drugs for reduction of perinatal HIV transmission may differ from the recommendations in these guidelines and will depend on local considerations, including availability and cost of antiretroviral drugs, access by pregnant women to 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

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Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents in pregnant women for treatment of HIV infection and for prevention of mother-to-child transmission (MTCT) 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 (e.g., training in either obstetrics/gynecology or women's health) and interventions to prevent MTCT (e.g., pediatric specialists in HIV infection), as well as community representatives with knowledge of HIV infection in pregnant women and interventions to prevent MTCT. The U.S. government representatives, appointed by their agency, include at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent the U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. A list of current Panel members can be found on **Page iv** of this document.
Financial disclosure	All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in the **Appendix** section of this document.
Users of the guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
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 a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.

Table 1. Outline of the Guidelines Development Process
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Topic	Comment
Other guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Separate guidelines outline the use of antiretroviral therapy in nonpregnant HIV-infected adults and adolescents, HIV-infected children, and those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). There is brief discussion of preconception management for nonpregnant women of reproductive age 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, dosing formulations, or frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDS*info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	After release of an update on the AIDS*Info* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether revisions are indicated. The public is also able to 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

References

1. Centers for Disease Control and Prevention (CDC). Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. *MMWR Morb Mortal Wkly Rep.* 2006;55(21):592-597.
2. Jamieson DJ, Clark J, Kourtis AP, et al. Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S26-32.
3. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
4. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981.
5. 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. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal Transmission of HIV (Updated May 24, 2010)

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]*. In PACTG 076, zidovudine was started orally at 14 to 34 weeks gestation, given intravenously to the mother during labor, and administered to the infant for 6 weeks.

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 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]*. However, although new perinatal HIV infections are becoming rare in resource-rich countries, infections continue to occur, and the 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 antiretroviral regimens; and lack of full implementation of routine, universal prenatal HIV counseling and testing *[10]*.

Within resource-limited settings, the complexity and cost of the three-part PACTG 076 regimen significantly limit its applicability and implementation. Thus, 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 antiretroviral 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 antiretroviral drugs in reducing perinatal transmission and in determining optimal regimens for use in the United States and other resource-rich countries, as discussed below.

MECHANISMS OF ACTION OF ANTIRETROVIRAL PROPHYLAXIS IN REDUCING PERINATAL TRANSMISSION OF HIV

Panel's Recommendation:

- ***Antiretroviral drugs reduce perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and pre- and post-exposure prophylaxis of the infant. Therefore, for prevention of perinatal transmission of HIV, combined antepartum, intrapartum, and infant antiretroviral prophylaxis is recommended (AI).***

There are a number of mechanisms through which zidovudine or other antiretroviral drugs can reduce perinatal transmission. One important mechanism is by decreasing maternal viral load in the blood and genital secretions via antenatal drug administration, particularly in women with high viral loads. However, antiretroviral drugs have been shown to reduce the risk of transmission even among women with HIV RNA levels <1,000 copies/mL *[11]*. Additionally, the level of HIV RNA at delivery and receipt of antenatal antiretroviral therapy are each independently associated with the risk of transmission, suggesting that antiretroviral prophylaxis does not work solely through reduction in viral load *[2, 12]*.

An additional mechanism of protection is pre-exposure infant prophylaxis provided by administration of antiretroviral drugs that cross the placenta from the mother to the infant, resulting in adequate systemic drug levels in the infant. This mechanism of protection is likely particularly important during the infant's passage through the birth canal, a time of intensive exposure to maternal genital tract virus. Post-exposure infant prophylaxis is provided through administration of drug to the infant after birth. This mechanism protects the infant from cell-free or cell-associated virus that might have obtained access to the fetal/infant systemic circulation through maternal-fetal transfusion during uterine contractions occurring in labor or through systemic dissemination of virus swallowed by the infant during passage through the birth canal.

It is likely that efficacy of antiretroviral drugs in reducing perinatal transmission is multi-factorial, and each of these mechanisms is contributory. The efficacy of antiretroviral regimens administered only during labor and/or to the newborn in reducing perinatal transmission, as discussed below, demonstrates the importance of the pre- and post-exposure components of prophylaxis in reducing perinatal transmission *[13-19]*.

LESSONS FROM INTERNATIONAL CLINICAL TRIALS OF SHORT-COURSE REGIMENS FOR PREVENTION OF PERINATAL TRANSMISSION OF HIV

Panel's Recommendations:

- ***Combination antepartum antiretroviral drug regimens are more effective than single-drug regimens in reducing perinatal transmission and should be used for maternal prophylaxis (AI).***
- ***Longer duration of antepartum antiretroviral prophylaxis (e.g., starting at 28 weeks gestation) is more effective than shorter duration (e.g., starting at 36 weeks gestation). Therefore, for women who do not require immediate initiation of therapy for their own health, prophylaxis should be started after the first trimester and no later than 28 weeks gestation (see Recommendations for Use of Antiretroviral Drugs during Pregnancy) (AI).***
- ***In the absence of antepartum antiretroviral therapy, intrapartum antiretroviral drugs should be administered in combination with infant antiretroviral prophylaxis to reduce the risk of perinatal transmission (see Intrapartum Care) (AI), although this combination is not as effective as antepartum/intrapartum/infant prophylaxis.***
- ***If women do not receive antepartum or intrapartum antiretroviral drugs, postnatal infant antiretroviral prophylaxis is recommended with 6 weeks of zidovudine (see Neonatal Postnatal Care) (AII).***
- ***In the United States, the addition of single-dose intrapartum/newborn nevirapine to the standard antepartum combination antiretroviral regimens used for prophylaxis or treatment in pregnant women is not recommended because it does not appear to provide additional efficacy in reducing transmission and may be associated with the development of nevirapine resistance (AI).***
- ***Breastfeeding is not recommended for HIV-infected women (including those receiving combination antiretroviral therapy) in the United States, where safe, affordable and feasible alternatives are available and culturally acceptable (AII).***

A number of simple regimens have been identified that are effective in reducing perinatal transmission in resource-limited countries (see **Table 3**). Because the studies involved different patient populations residing in different geographic locations, infected with different viral subtypes and having different infant feeding practices, direct comparison of results between trials is difficult. However, some general conclusions can be drawn from the study results that are relevant to understanding use of antiretroviral drugs in both resource-limited and -rich countries.

Short-term efficacy has been demonstrated for a number of short-course antiretroviral regimens, including those with zidovudine alone; zidovudine plus lamivudine; single-dose nevirapine; and, more recently, combining single-dose nevirapine with either short-course zidovudine or zidovudine/lamivudine *[13-14, 16-23]*. In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission. Additionally, when it is feasible and affordable, a longer three-part regimen given antenatally, intrapartum, and postpartum is superior in preventing perinatal transmission than a shorter two-part antepartum/intrapartum or intrapartum/postpartum regimen *[14, 24-25]*.

Almost all trials in resource-limited countries have included an oral intrapartum prophylaxis component, 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 *[20-22]*. However, longer duration of antenatal therapy (starting at 28 weeks gestation) is more effective than shorter duration (starting at 36 weeks gestation), suggesting that a significant proportion of *in utero* transmission occurs between 28 and 36 weeks gestation *[23]*. More prolonged post-exposure prophylaxis of the infant does not appear to substitute for longer duration of maternal therapy *[23]*.

Because some women may lack antenatal care and first present for care during labor (possibly the majority of pregnant women in some resource-limited settings), regimens that do not include maternal therapy during pregnancy have been evaluated. Regimens that include only intrapartum and postpartum drug administration have also been shown to be effective in reducing perinatal transmission *[13-14, 16]*. However, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor (NRTI) drugs (zidovudine/lamivudine), without continued post-exposure prophylaxis of the infant, is not effective in reducing transmission*[14]*. 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 *[16]*.

In some situations, maternal antepartum and intrapartum therapy may not be possible, and only infant prophylaxis can be provided. Based on epidemiologic data *[15]*, in resource-rich countries, the standard prophylaxis regimen in the absence of maternal therapy is 6 weeks of infant zidovudine. To define the optimal infant prophylaxis regimen in the absence of maternal therapy, an ongoing multi-national study in infants born to women who have not received antenatal therapy is comparing the standard 6-week infant zidovudine regimen to 6 weeks of zidovudine combined with either one or two additional drugs.

In resource-limited settings, administration of even 6 weeks of infant zidovudine may be difficult to achieve, and single-dose nevirapine is widely used. In a study in South Africa of infants born to mothers who did not receive antenatal or intrapartum therapy, administration of single-dose infant nevirapine given within 24 hours of delivery was compared to 6 weeks of infant zidovudine therapy; overall perinatal transmission rates were not significantly different *[19]*. A trial in Malawi compared single-dose infant nevirapine to a combination of single-dose nevirapine with a week of zidovudine therapy when no antenatal maternal therapy was received. The addition of 1 week of zidovudine therapy to infant single-dose nevirapine reduced the risk of transmission by 36% compared to infant single-dose nevirapine alone *[17]*. However, when maternal intrapartum nevirapine was received, thereby providing pre-exposure prophylaxis in addition to post-exposure prophylaxis, single-dose infant nevirapine alone was as effective as the combined nevirapine/zidovudine infant post-exposure prophylaxis regimen *[18]*. One problem with the use of single-dose infant nevirapine alone or in combination with a week of zidovudine to prevent transmission is the risk of nevirapine resistance emerging in infants who become infected despite receiving antiretroviral prophylaxis *[26]*. Thus, in the United States, the standard recommendation for infant prophylaxis in the absence of maternal antenatal and intrapartum therapy remains 6 weeks of infant zidovudine.

In an attempt to improve the efficacy of short-course regimens but retain a regimen cost-appropriate for resource-limited countries, more recently researchers have evaluated whether the addition of a potent intrapartum intervention—the single-dose nevirapine regimen—to short-course regimens might increase efficacy. In the setting of short-course antenatal zidovudine alone or zidovudine/lamivudine, the Perinatal HIV Prevention Trial (PHPT)-2 study in nonbreastfeeding women in Thailand, the DITRAME studies in a partially breastfeeding population in the Cote d'Ivoire, and the Mashi study in Botswana (in the formula-fed, but not the breastfed, strata) demonstrated that the addition of single-dose nevirapine did significantly increase efficacy *[24, 27-28]*. The relative importance of the maternal and infant components of single-dose nevirapine in the context of short-course zidovudine regimens remains unclear. The Thailand PHPT-2 study suggests that the infant nevirapine dose at 48–72 hours of life may not add significant efficacy to the maternal nevirapine dose alone; however, the Botswana Mashi study suggests that maternal nevirapine may not be necessary when infant single-dose nevirapine is provided at birth *[27-28]*.

Whether single-dose nevirapine provides any additional efficacy when combined with the standard recommended antiretroviral prophylaxis regimens used in the United States (e.g., combination antiretroviral drugs in women with HIV RNA >1,000 copies/mL) 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 antiretroviral therapy throughout pregnancy and very low viral load at the time of delivery *[7]*. Thus, the addition of single-dose intrapartum nevirapine is generally not recommended for women in the United States who are receiving the standard recommended antenatal antiretroviral prophylaxis regimens (see **Intrapartum Care** section).

In the United States and other parts of the world where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, breastfeeding by HIV-infected women (including those receiving antiretroviral drugs) is not recommended. A number of studies have evaluated the use of maternal or infant antiretroviral 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 may likewise decrease postnatal infection *[29-36]*. However, neither infant nor maternal postpartum antiretroviral prophylaxis completely eliminates the risk of HIV transmission through breast milk, and the combination of maternal and infant postpartum regimens has not been evaluated. Therefore, breastfeeding is not recommended for HIV-infected women in the United States (including those receiving combination antiretroviral drug regimens), where safe, affordable and feasible alternatives are available and culturally acceptable. Both infant nevirapine prophylaxis and maternal triple drug prophylaxis during breastfeeding may be associated with the development of antiretroviral drug resistance in infants who become infected despite prophylaxis *[37-40]*. Three studies have found multi-class drug resistance in breastfeeding infants who became infected despite maternal triple drug prophylaxis *[38-40]*.

PERINATAL TRANSMISSION OF HIV AND MATERNAL HIV RNA COPY NUMBER

Panel's Recommendation:

- ***Use of antiretroviral drugs during pregnancy for prevention of perinatal transmission should be discussed with and provided to all infected pregnant women regardless of HIV RNA level (AI).***

Initial data regarding the correlation of viral load with risk of perinatal transmission were conflicting. Some studies suggested an absolute correlation between HIV RNA copy number and risk of transmission *[41]*. However, although higher HIV RNA levels have been observed in women who transmitted HIV to their infants, overlap in HIV RNA copy number has been observed in both women who did and women who did not transmit the virus. Transmission has been observed across the entire range of HIV RNA levels (including in women with undetectable viral load), and the predictive value of HIV RNA copy number for transmission in an individual woman is modest *[42-44]*. In PACTG 076, antenatal maternal HIV RNA copy number was associated with HIV transmission in women receiving placebo. In women receiving zidovudine, the relationship was markedly attenuated and no longer statistically significant *[12]*. 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 *[12, 45]*.

More recent data from larger numbers of zidovudine-treated, HIV-infected pregnant women indicate that HIV RNA levels correlate with risk of transmission even in women treated with antiretroviral agents *[46-49]*. Although the risk of perinatal transmission in women with undetectable HIV RNA levels appears to be extremely low, transmission from mother to infant has been reported among women with all levels of maternal HIV RNA. Additionally, although HIV RNA may be an important risk factor for transmission, other factors also appear to play a role *[46, 49-50]*.

Although there is a general correlation between viral load in plasma and in the genital tract, discordance has also been reported, particularly between HIV proviral load in blood and genital secretions, especially in the presence of other genital tract infections *[51-54]*. If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV RNA levels might not always be an accurate indicator of risk. Long-term changes in one body compartment (such as can occur with antiretroviral treatment) may or may not be associated with comparable changes in other compartments. Further studies are needed to determine the effect of antiretroviral drugs on genital tract viral load and the association of such effects on the risk of perinatal HIV transmission. In the short-course zidovudine trial in Thailand, plasma and cervicovaginal HIV RNA levels were reduced by zidovudine treatment, and each independently correlated with perinatal transmission *[55]*. Use of antiretroviral drugs during pregnancy for prevention of perinatal transmission should be discussed with and offered to all infected pregnant women regardless of their HIV RNA level.

Results of epidemiologic and clinical trials suggest that women receiving potent combinations of antiretroviral drugs that effectively reduce HIV RNA to <1,000 copies/mL or undetectable levels have very low rates of perinatal transmission *[2, 6-7, 56]*. However, because transmission can occur even at low or undetectable HIV RNA copy numbers, HIV RNA levels should not be a determining factor when deciding whether to use antiretroviral drugs for prevention of perinatal transmission. Additionally, the efficacy of antiretroviral drugs is not solely related to lowering viral load *[2, 11-12, 57]*. Therefore, antiretroviral prophylaxis should be given even to women who have a very low or undetectable viral load on no therapy.

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

Study Location(s) Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission Rate and Efficacy
PACTG 076 United States, France *[1]* Formula feeding	ZDV vs placebo	Long (from 14 weeks) Intravenous 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 *[22]* 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 Côte d'Ivoire, Burkina Faso *[21, 58]* 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 Côte d'Ivoire *[20-21]* 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 *[14]* 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 to 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 to placebo: 34%, 18%, and 0%, respectively).
HIVNET 012 trial Uganda *[13]* 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 to 8 weeks (42% efficacy); 15.7% in NVP arm vs 25.8% in ZDV arm at 18 months (41% efficacy).
SAINT trial South Africa *[16]* 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 *[23]* 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 *[7]* 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 + intravenous 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 *[27]* 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 Abidjan, Côte d'Ivoire *[24]* 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 Abidjan, Côte d'Ivoire *[24]* 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%.
NVAZ trial Malawi *[17]* 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 to 8 weeks. MTCT rate at 6 to 8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP + ZDV trial Malawi *[18]* 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 to 8 weeks (difference not statistically significant). MTCT rate at 6 to 8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.
Post-exposure Infant Prophylaxis South Africa *[19]* 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 vs14.1% 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 *[28, 59]* 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 <200 receive combination therapy	1st randomization ZDV from 34 weeks Oral IP: ZDV + either sdNVP vs placebo	2nd randomization Breastfeeding + ZDV (infant) 6 months + sd NVP, 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.
SWEN Uganda, Ethiopia, India *[30]* 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

PEPI-Malawi Trial Malawi *[29]* 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 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 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 *[36]* 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 6 months was 4.9% (postnatal MTCT between 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study (KiBS) Kenya *[31]* Breastfeeding	Maternal triple drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 >250) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 >250) for 6 months; infant sdNVP	• MTCT at 6 months was 5.0% (postnatal MTCT between 7 days and 6 months was 2.6%).
MITRA-PLUS Tanzania *[33]* Breastfeeding	Maternal triple drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 >200) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 >200) for 6 months; infant ZDV/3TC for 1 week	• MTCT at 6 months was 5.0% (postnatal MTCT between 6 weeks and 6 months was 0.9%), not significantly different from 6 months infant prophylaxis in MITRA.

Kesho Bora Multi-African *[35]* Breastfeeding primarily	Antepartum ZDV/ sdNVP with no postnatal prophylaxis vs maternal triple drug prophylaxis in women with CD4 between 200 and 500	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 2.2% with ZDV/sdNVP Arm 2, not significantly different. • MTCT at 12 months was 5.5% with maternal triple drug prophylaxis Arm 1 and 9.5% with ZDV/sdNVP (with no further postnatal prophylaxis after 1 week) Arm 2 (p=0.04).
Mma Bana Botswana *[34]* Breastfeeding	Maternal triple drug prophylaxis (compares 2 regimens) in women with CD4 >200	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 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 *[32]* Breastfeeding	Postpartum maternal triple drug prophylaxis vs infant NVP in women with CD4 ≥250	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 2 weeks: - MTCT at 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 (<0.001 vs control). • No significant difference between maternal triple drug prophylaxis Arm 2 and infant NVP Arm 3 (p=0.12).

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

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med.* 1994;331(18):1173-1180.
2. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
3. Wortley PM, Lindegren ML, Fleming PL. Successful implementation of perinatal HIV prevention guidelines. A multistate surveillance evaluation. *MMWR Recomm Rep.* 2001;50(RR-6):17-28.
4. Centers for Disease Control and Prevention (CDC), Mofenson LM, Taylor AW, et al. Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. *MMWR Morb Mortal Wkly Rep.* 2006;55(21):592-597.
5. European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. European collaborative study. *AIDS.* 2001;15(6):761-770.
6. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
7. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV-1 transmission: a randomized trial. *JAMA.* 2002;288(2):189-198.
8. McKenna MT, Hu X. Recent trends in the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection in the United States. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S10-16.
9. Peters V, Liu KL, Dominguez K, et al. Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, pediatric spectrum of HIV disease cohort. *Pediatrics.* 2003;111(5 Part 2):1186-1191.
10. Mofenson LM. Successes and challenges in the perinatal HIV-1 epidemic in the United States as illustrated by the HIV-1 Serosurvey of childbearing women. *Arch Pediatr Adolesc Med.* 2004;158(5):422-425.
11. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. *J Infect Dis.* 2001;183(4):539-545.
12. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1996;335(22):1621-1629.
13. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868.
14. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
15. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
16. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* 2003;187(5):725-735.
17. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet.* 2003;362(9391):1171-1177.
18. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA.* 2004;292(2):202-209.
19. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS.* 2005;19(12):1289-1297.
20. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet.* 1999;353(9155):781-785.
21. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS.* 2002;16(4):631-641.
22. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet.* 1999;353(9155):773-780.

23. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med.* 2000;343(14):982-991.
24. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS.* 2005;19(3):309-318.
25. Leroy V, Sakarovitch C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS.* 2005;19(16):1865-1875.
26. Eshleman SH, Hoover DR, Chen S, et al. Resistance after single-dose nevirapine prophylaxis emerges in a high proportion of Malawian newborns. *AIDS.* 2005;19(18):2167-2169.
27. Lallemant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med.* 2004;351(3):217-228.
28. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS.* 2006;20(9):1281-1288.
29. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med.* 2008;359(2):119-129.
30. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet.* 2008;372(9635):300-313.
31. Thomas T, Masaba R, Ndivo R, et al. PMTCT of HIV-1 among mothers using HAART: the Kisumu Breastfeeding Study, Kisumu, Kenya 2003-2007. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 45aLB, page 87.
32. Chasela C, Hudgens M, Jaimeson D, et al. Maternal antiretrovirals or infant nevirapine to reduce HIV-1 transmission. *N Eng J Med.* 2010 (in press).
33. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus study. *J Acquir Immune Defic Syndr.* 2009;52(3):406-416.
34. Shapiro R, Hughes M, Ogwu A, et al. A randomized comparison of antiretroviral regimens used to prevent mother-to-child HIV transmission among breastfeeding women in Botswana. *N Engl J Med.* 2010 (in press).
35. de Vincenzi I, Kesho Bora Study Group. Triple-antiretroviral prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1: the Kesho Bora randomized controlled clinical trial in five sites in Burkina Faso, Kenya and South Africa. Paper presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 19-22, 2009; Capetown, South Africa. Abstract LBPE C01.
36. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr.* 2008;48(3):315-323.
37. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. *PLoS One.* 2009;4(1):e4096.
38. Zeh C, Weidle P, Nafisa L, et al. Emergence of HIV-1 Drug Resistance among Breastfeeding Infants Born to HIV-infected Mothers Taking Antiretrovirals for Prevention of Mother-to-Child Transmission of HIV: The Kisumu Breastfeeding Study, Kenya. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 84LB.
39. Lidstrom J, Guay L, Musoke P, et al. Multi-class drug resistance arises frequently in HIV-infected breastfeeding infants whose mothers initiate HAART postpartum. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 920.
40. Lidstrom J, Kumwenda N, Kafulafula G, et al. Antiretroviral treatment of HIV-infected women can induce multi-class drug resistance in their breastfeeding infants. *Antiviral Ther.* 2009;14 Suppl 1:A158.
41. Dickover RE, Garratty EM, Herman SA, et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. *JAMA.* 1996;275(8):599-605.
42. Cao Y, Krogstad P, Korber BT, et al. Maternal HIV-1 viral load and vertical transmission of infection: The Ariel Project for the prevention of HIV transmission from mother to infant. *Nat Med.* 1997;3(5):549-552.

43. Mayaux MJ, Dussaix E, Isopet J, et al. Maternal virus load during pregnancy and the mother-to-child transmission of human immunodeficiency virus type 1: the French Perinatal Cohort Studies. *J Infect Dis.* 1997;175(1):172-175.
44. Thea DM, Steketee RW, Pliner V, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. *AIDS.* 1997;11(4):437-444.
45. Shapiro DE, Sperling RS, Coombs RW. Effect of zidovudine on perinatal HIV-1 transmission and maternal viral load. *Lancet.* 1999;354(9173):156; author reply 157-158.
46. Shaffer N, Roongpisuthipong A, Siriwasin W, et al. Maternal virus load and perinatal human immunodeficiency virus subtype E transmission, Thailand. *J Infect Dis.* 1999;179(3):590-599.
47. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
48. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med.* 1999;341(6):394-402.
49. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. The European Collaborative Study. *AIDS.* 1999;13(11):1377-1385.
50. Mock PA, Shaffer N, Bhadrakom C, et al. Maternal viral load and timing of mother-to-child HIV transmission, Bangkok, Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. *AIDS.* 1999;13(3):407-414.
51. Hart CE, Lennox JL, Pratt-Palmore M, et al. Correlation of human immunodeficiency virus type 1 RNA levels in blood and the female genital tract. *J Infect Dis.* 1999;179(4):871-882.
52. Iversen AK, Larsen AR, Jensen T, et al. Distinct determinants of human immunodeficiency virus type 1 RNA and DNA loads in vaginal and cervical secretions. *J Infect Dis.* 1998;177(5):1214-1220.
53. Shaheen F, Sison AV, McIntosh L, et al. Analysis of HIV-1 in cervicovaginal secretions and blood of pregnant and non-pregnant women. *J Hum Virol.* 1999;2(3):154-166.
54. Rasheed S, Li Z, Xu D, et al. Presence of cell-free human immunodeficiency virus in cervicovaginal secretions is independent of viral load in the blood of human immunodeficiency virus-infected women. *Am J Obstet Gynecol.* 1996;175(1):122-129.
55. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. *J Infect Dis.* 2000;181(1):99-106.
56. McGowan JP, Crane M, Wiznia AA, et al. Combination antiretroviral therapy in human immunodeficiency virus-infected pregnant women. *Obstet Gynecol.* 1999;94(5 Pt 1):641-646.
57. Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14(3):232-236.
58. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la Transmission Mère-Enfant. *Lancet.* 1999;353(9155):786-792.
59. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA.* 2006;296(7):794-805.

Preconceptional Counseling and Care for HIV-Infected Women of Childbearing Age

(Updated May 24, 2010)

Panel's Recommendations:

- ***Contraceptive counseling is an essential component of care for HIV-infected women of reproductive age and should include counseling on effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy (AI).***
- ***Preconception counseling should include counseling on safe sexual practices and eliminating alcohol, illicit drug use, and smoking, which are important for the health of the woman as well as for fetal/infant health should pregnancy occur (AII).***
- ***Evaluation of the HIV-infected woman should include assessment of her HIV disease status and need for antiretroviral therapy for her own health (AII).***
- ***If already on therapy, her regimen should be reviewed in terms of potential pregnancy (e.g., teratogenic potential of the drugs in the regimen) (AII).***
- ***Choice of an antiretroviral treatment regimen for HIV-infected women of childbearing potential needs to include 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).***
- ***HIV-infected women who are on therapy and wish to become pregnant should attain a stable maximally suppressed viral load prior to conception (AIII).***

The Centers for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG), and other national organizations recommend offering all women of childbearing age 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 prior to 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 *[2-3]* it is important that preconception care be integrated into routine health visits. Therefore, HIV care providers who routinely care for women of reproductive age play an important role in promoting preconception health.

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 *[4]*. Because many women infected with HIV are aware of their HIV status prior to pregnancy, issues that impact pregnancy may be addressed prior to conception during their routine medical care for HIV disease. In addition to those outlined by the CDC Preconception Care Work Group *[5]*, the following components of preconception counseling and care are specifically recommended for HIV-infected women. Health care providers should:

a. Offer all women effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Providers should be aware of potential interactions of antiretroviral drugs with hormonal contraceptives that could lower contraceptive efficacy (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***, Tables 13, 14a, 14b) *[6]*.

b. 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 HIV strains.

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

d. 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 that breastfeeding by HIV-infected women is not recommended in the United States due to risk of HIV transmission and the availability of safe and sustainable infant feeding alternatives.

e. When prescribing antiretroviral treatment to women of childbearing potential, consider the regimen's effectiveness for treatment of HIV, hepatitis B disease status, the drugs' potential for teratogenicity should pregnancy occur, and possible adverse outcomes for mother and fetus *[7-8]*.

f. For women who are contemplating pregnancy, strongly consider the use of antiretroviral regimens that do not contain efavirenz or other drugs with teratogenic potential.

g. For women who are on antiretroviral therapy and want to get pregnant, set attaining a stable, maximally suppressed maternal viral load prior to conception as a primary treatment goal to decrease the risk of mother-to-child transmission of HIV.

h. Evaluate and appropriately manage therapy-associated side effects that may adversely impact maternal-fetal health outcomes (e.g., hyperglycemia, anemia, hepatic toxicity).

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

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

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

l. Counsel regarding available reproductive options, such as intrauterine or intravaginal insemination, that prevent HIV exposure to an uninfected partner. Expert consultation is recommended *[9]*.

m. Counsel regarding available reproductive options to reduce risk of transmission to an uninfected female partner with an HIV-infected male partner; expert consultation is recommended *[10]*.

MONITORING OF PREGNANT WOMEN WITH A PARTNER KNOWN TO BE HIV INFECTED

Increasingly clinicians 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 third-trimester testing and result, then 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 can be used in conjunction with an HIV antibody test, and HIV testing may be repeated in 4–6 weeks. 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 antiretroviral prophylaxis and consideration of elective cesarean delivery according to

established guidelines (see **Transmission and Mode of Delivery**). In cases where confirmatory testing results are not readily available (e.g., rapid testing during labor), it is appropriate to initiate interventions to reduce perinatal transmission even in the absence of confirmatory results (see **Infant Antiretroviral Prophylaxis**). If HIV testing results are negative, then pregnant women with HIV-infected partners should be regularly counseled regarding the ongoing risk of HIV transmission. If the partner's HIV status is at all uncertain, he should be encouraged to seek testing and appropriate care. All women and their partners should be counseled about the importance of correct and consistent condom use.

References

1. American College of Obstetricians and Gynecologists. ACOG Committee Opinion number 313, September 2005. The importance of preconception care in the continuum of women's health care. *Obstet Gynecol.* 2005;106(3):665-666.
2. Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect.* 1998;30(1):24-29, 46.
3. Johnson K, Posner SF, Biermann J, et al. Recommendations to improve preconception health and health care--United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep.* 2006;55(RR-6):1-23.
4. Lampe MA. Human immunodeficiency virus-1 and preconception care. *Matern Child Health J.* 2006;10(5 Suppl):S193-195.
5. Centers for Disease Control and Prevention (CDC). Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2003;52(RR-12):1-24.
6. 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. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
7. Cotter AM, Garcia AG, Duthely ML, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis.* 2006;193(9):1195-1201.
8. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med.* 2002;346(24):1863-1870.
9. Daar ES, Daar JF. Human immunodeficiency virus and fertility care: embarking on a path of knowledge and access. *Fertil Steril.* 2006;85(2):298-300; discussion 301.
10. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(5):651-681.

Antepartum Care (Updated May 24, 2010)

GENERAL PRINCIPLES REGARDING USE OF ANTIRETROVIRAL DRUGS DURING PREGNANCY

Panel's Recommendations:

- ***Initial evaluation of an infected pregnant woman should include an assessment of HIV disease status and recommendations regarding initiating antiretroviral therapy or altering her current antiretroviral regimen (AIII). The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.***
- ***Antiretroviral prophylaxis for prevention of perinatal transmission of HIV during the antepartum period should be recommended to all pregnant, HIV-infected women regardless of plasma HIV RNA copy number or CD4 cell count (AI).***
- ***The known benefits and potential risks of antiretroviral use during pregnancy should be discussed with all women (AIII).***
- ***Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity or documented resistance or the woman is already on a fully suppressive regimen (AIII).***
- ***If HIV RNA is detectable (e.g., >500–1,000 copies/mL), antiretroviral drug resistance studies should be performed before starting or modifying therapy (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) (AI).***
- ***The importance of adherence to the antiretroviral treatment or prophylaxis regimen should be emphasized (AII).***
- ***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, if necessary, should be assured as part of recommending antiretroviral drugs during pregnancy (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, past CD4+ cell counts, and past 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 such as *Pneumocystis jirovecii* pneumonia (PCP) or *Mycobacterium avium* complex (MAC) *[1];*

e. baseline complete blood cell count and renal and liver function testing;

f. history of prior and current antiretroviral therapy;

g. history of prior antiretroviral drug use for prevention of perinatal HIV transmission;

h. results of prior and current HIV antiretroviral drug resistance studies; and

i. assessment of supportive care needs.

In general, guidelines for the use of antiretroviral drug treatment for the benefit of maternal health during pregnancy are the same as guidelines for women who are not pregnant. Antiretroviral prophylaxis is recommended for all pregnant women with HIV infection, regardless of viral load (see **HIV-Infected Pregnant Women Not on Antiretroviral Therapy Who Require Antiretroviral Prophylaxis Solely to Prevent Perinatal HIV Transmission**).

Decisions regarding initiating or altering antiretroviral drug regimens during pregnancy include considerations regarding the benefits and risks of antiretroviral drug use that are common to all HIV-infected adults in addition to considerations unique to pregnancy. Maternal toxicities and risks of therapy must be considered, along with the additional considerations of the potential impact of such therapy on the outcome of pregnancy and on the fetus and infant. These decisions are further complicated because there are only limited data on the long-term maternal consequences of antiretroviral drug use during pregnancy solely for prophylaxis of transmission. Similarly, there are only limited data on the long-term consequences of *in utero* antiretroviral exposure for the infant. The potential for drug-associated teratogenicity, toxicity, or the lack of data on specific drugs in pregnancy are important considerations in terms of drug regimen choice in a pregnant woman (**Table 3**).

Discussion of antiretroviral use with a pregnant woman should be noncoercive, and the final decision regarding use of antiretroviral drugs is the responsibility of the woman. The known benefits and known and unknown risks of antiretroviral drug use during pregnancy should be considered and discussed (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 should be discussed with the woman (**Table 4** and **Table 5**). Potential risks of these drugs should be placed into perspective by also discussing substantial benefits of antiretroviral drugs for the health of the infected woman and for reducing the risk of HIV transmission to her infant.

Discussion with the woman about initiation of antiretroviral therapy should include the following:

a. maternal risk of disease progression and the benefits and risks of initiation of therapy for her own health;

b. benefit of combination antiretroviral regimens for preventing perinatal HIV transmission *[2]*;

c. Potential adverse effects of antiretroviral drugs for mother, fetus, and infant;

d. the limited long-term outcome data for both infants with *in utero* antiretroviral exposure and for women who temporarily use antiretroviral drugs during pregnancy for prophylaxis of transmission; and

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

Although zidovudine should be a component of the antenatal antiretroviral regimen, there may be circumstances, such as the occurrence of severe zidovudine-related toxicity (e.g., severe anemia) or documented zidovudine resistance, when this is not possible. Additionally, women receiving an antiretroviral regimen that does not contain zidovudine but who have HIV RNA levels that are undetectable have a very low risk of perinatal transmission *[3]*, and there may be concerns that substitution of zidovudine for another component of the regimen or the addition of zidovudine to the current regimen could compromise adherence to treatment. In such cases, continuing a non-zidovudine-containing regimen that is fully suppressive is reasonable.

If plasma HIV RNA is detectable (greater than 500 to 1,000 copies/mL), antiretroviral drug resistance studies should be performed before starting antiretroviral therapy for maternal health or prophylaxis. However, if HIV is diagnosed late in pregnancy, therapy or prophylaxis should be initiated while

awaiting results of resistance testing (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**).

The importance of adherence to the antiretroviral treatment or prophylaxis regimen should be emphasized. Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment may be required. 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 adherence of the infected woman to the antiretroviral treatment regimen. Long-range plans should be developed with the woman regarding continuity of medical care and decisions about antiretroviral therapy for her own health after the birth of her infant.

Medical care of the HIV-infected pregnant woman requires coordination and communication between HIV specialists and obstetrical providers. General counseling should include current knowledge regarding risk factors for perinatal transmission. Potentially modifiable factors including cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk of perinatal HIV transmission *[4-8]*. In addition to 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 CDC recommends that HIV-infected women in the United States (including those receiving antiretroviral therapy) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk *[9]*.

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 antiretroviral drug regimens for HIV-infected pregnant women be based on the same principles used to choose regimens for non-pregnant individuals, unless there are compelling pregnancy-specific maternal or fetal safety issues regarding specific drug choices. The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review related to treatment of HIV-infected adult women, both pregnant and nonpregnant. The durability, tolerability, and simplicity of the medication regimen is of particular importance in order to preserve options in the future for those women who will be stopping medications following delivery and for those women who meet standard criteria for initiation of antiretroviral therapy per adult guidelines and will continue the regimen after pregnancy. Regimen selection should be individualized and should consider a number of factors including:

- comorbidities,
- patient adherence potential,
- convenience,
- potential adverse drug effects on the mother,
- potential drug interactions with other medications,
- results of genotypic resistance testing,
- pharmacokinetic (PK) changes in pregnancy, and
- potential teratogenic effects on the fetus and other adverse effects on the fetus or newborn.

Criteria 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 antiretroviral regimens with special attention to maternal toxicity and safety and teratogenic effects on the fetus;
- Specific knowledge about drug tolerability and simplified dosing regimens;
- Drug regimens that are known to be effective in reducing transmission to the fetus;
- Pharmacokinetic data during the prenatal period: The physiologic changes of pregnancy have the potential to alter the pharmacokinetics of drugs. Antiretroviral dosing during pregnancy should be based on pharmacokinetic 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.

Categories of antiretroviral 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 pharmacokinetic data are available to guide dosing; and no evidence of teratogenic effects on the fetus or established association with teratogenic or clinically significant adverse outcomes for the mother, fetus, 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: there is limited experience in pregnancy; there is lack of data on teratogenic effects on the fetus; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.

- ***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 the woman has comorbidities or requires concomitant medications that may limit drug choice (e.g., chronic hepatitis B infection, 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, potential serious safety concerns for the mother or fetus, or pharmacologic antagonism.

- ***Insufficient Data to Recommend:*** Although approved for use in adults, the drugs and drug combinations in this category do not have pregnancy-specific pharmacokinetic or safety data available or such data are too limited to make a recommendation for use for pregnancy.

All women who receive antiretroviral drugs during pregnancy either for treatment or prophylaxis should receive combination regimens containing at least three agents. A combination regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (with or without low-dose ritonavir) should be used. The preferred NRTI regimen in pregnancy, 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 use in pregnancy, is zidovudine/lamivudine. Alternate regimens may be used for women who have intolerance of zidovudine because of toxicity such as severe anemia or with known resistance to zidovudine. Tenofovir, a preferred NRTI in nonpregnant women, should be used only in special circumstances (such as intolerance or resistance to zidovudine or chronic hepatitis B infection) because of concerns regarding the potential for fetal toxicity. Animal studies 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. The combination of stavudine/didanosine should not be used in pregnant women because of fatal cases of lactic acidosis and hepatic failure reported in pregnant women who received this combination throughout pregnancy.

In addition to the two NRTIs, either an NNRTI or a PI should be included in antiretroviral regimens prescribed for maternal health. Efavirenz, the preferred NNRTI for nonpregnant adults, is not recommended for use in the first trimester of pregnancy because of animal data showing risk of anencephaly, micro-ophthalmia, and facial clefts as well as concerning case reports of several neural tube defects and a single case of anophthalmia with severe facial cleft in humans. Use of efavirenz after the first trimester of pregnancy may be considered if alternate agents are not tolerated. Nevirapine may be used in women with CD4+ lymphocyte counts less than 250 cells/mm^3 or continued for women already receiving a nevirapine-based regimen. Nevirapine should generally not be initiated for treatment-naïve women with CD4+ cell counts greater than 250 cells/mm^3 because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity. Etravirine has insufficient safety or pharmacokinetic data in pregnancy to recommend its use. Lopinavir/ritonavir is the preferred protease inhibitor regimen for pregnant women because of efficacy studies in adults and experience with use in pregnancy (see **Table 5** for dosing considerations). Alternative protease inhibitors include ritonavir-boosted atazanavir, saquinavir, or indinavir, although experience with these regimens in pregnancy is more limited and the latter two may be less well tolerated. Data on use in pregnancy for darunavir, fosamprenavir, and tipranavir are too limited to recommend routine use in pregnancy, although they may be considered if other agents are not tolerated.

Safety and pharmacokinetics 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 for women who have failed therapy with several other classes of antiretroviral drugs could be considered in consultation with HIV and obstetric specialists.

In addition, recommendations for the use of antiretroviral drugs for prophylaxis to prevent perinatal HIV transmission in women for whom therapy would not otherwise be indicated include the agents/combinations discussed above and some that are not considered preferred regimens in nonpregnant adults, such as triple NRTI regimens with abacavir and the use of nelfinavir with two NRTIs. These options are discussed in more detail below.

Although data are insufficient to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation, information to date does not support major teratogenic effects of the majority of antiretroviral drugs. (For further data, see **www.APRegistry.com**.) However, certain drugs are of more concern than others (**Table 4** and see **Teratogenicity** and **Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**). For example, efavirenz should be avoided during the first trimester of pregnancy.

Recommendations for antiretroviral therapy during pregnancy must be individualized according to the specific antiretroviral history of the HIV-infected pregnant woman. Some women may be receiving antiretroviral therapy for their own health at the time they become pregnant and present for obstetrical care on such therapy. Other HIV-infected women may not be receiving antiretroviral therapy at the time they present for obstetrical care. Some of these women have never received antiretroviral drugs before, while other women may have previously received antiretroviral drugs, either for treatment that was stopped or for prophylaxis to prevent perinatal HIV transmission in prior pregnancies. Considerations for initiating therapy will differ for such women according to whether antiretroviral drugs are currently indicated for maternal health or solely for fetal protection. The antiretroviral recommendations below are divided into sections according to antiretroviral treatment status at the time the woman presents for care and whether there are maternal indications for therapy.

Table 5 provides recommendations about the use of specific antiretroviral drugs in pregnancy as well as data on pharmacokinetics and toxicity in pregnancy. **Table 6** provides a summary of management recommendations for the mother and infant in a variety of clinical scenarios.

HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment

Panel's Recommendations:

- ***Pregnant women receiving and tolerating an antiretroviral treatment 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 of pregnancy (AIII).***
- ***HIV antiretroviral drug resistance testing is recommended if the pregnant woman has detectable viremia (e.g., >500–1,000 copies/mL) on therapy (see Failure of Viral Suppression) (AI).***
- ***Pregnant women receiving nevirapine-containing regimens who are virologically suppressed and tolerating the regimen should continue the regimen, regardless of CD4 count (AIII).***

In general, women who have been receiving antiretroviral treatment for their HIV infection 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 HIV transmission. Therefore, when pregnancy is identified after the first trimester in HIV-infected women receiving antiretroviral therapy at the time of conception, therapy should always be continued.

HIV-infected women receiving antiretroviral treatment who present for care during the first trimester of pregnancy should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be recommended. However, the use of efavirenz should be avoided during the first trimester of pregnancy. If a woman is receiving efavirenz and her pregnancy is recognized during the first trimester, an alternative antiretroviral 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 not fully suppressed. Results of this testing can be used to select a regimen that may have greater chance to suppress viral loads to undetectable. 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 ≥1,000 copies/mL; other assays can be performed with lower viral loads.

Pregnant women who are receiving nevirapine-containing regimens with viral suppression and are tolerating the regimen well should continue therapy, regardless of CD4 count. Although hepatic toxicity is a concern in women who have a CD4 count >250 cells/mm^3 when they first start a nevirapine-containing regimen, an increased risk of hepatic toxicity has not been seen in women who are receiving nevirapine-based therapy and have immune reconstitution with therapy.

HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naïve)

Panel's Recommendations:

- ***HIV-infected pregnant women who meet standard criteria for initiation of antiretroviral therapy per adult antiretroviral treatment guidelines should receive standard potent combination antiretroviral therapy as recommended for nonpregnant adults, taking into account what is known about the use of specific drugs in pregnancy and 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 of pregnancy (AII). (Note that the use of efavirenz should be avoided during the first trimester.)***
- ***HIV-infected pregnant women who do not require treatment for their own health should also receive three-drug combination antiretroviral regimens for prophylaxis of perinatal transmission (AII). The use of zidovudine alone as prophylaxis is controversial but may be considered for those women initiating prophylaxis with plasma HIV RNA levels <1,000 copies/mL on no therapy (CII).***
  - ***For women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, delaying initiation of prophylaxis until after the first trimester of pregnancy can be considered (BIII).***
- ***Zidovudine should be used as a component of the antiretroviral regimen when feasible (AIII).***
- ***HIV antiretroviral drug resistance testing should be performed prior to initiating antiretroviral prophylaxis or therapy (AI)*.***
- ***Nevirapine may be used as a component of initial therapy for pregnant women with CD4 cell counts <250 cells/mm^3. However, due to an increased risk of hepatic toxicity, nevirapine should only be used as a component of antiretroviral therapy in pregnant women with CD4 cell counts >250 cells/mm^3 if the benefit clearly outweighs the risk (AII).***

**Dependent on the resistance assay being used; some assays require HIV RNA levels of ≥1,000 copies/mL for performance of the resistance assay, while other assays can be used with lower levels of viral replication.*

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 *[10]*.

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 antiretroviral therapy as per adult antiretroviral guidelines should receive potent combination antiretroviral therapy, generally consisting of NRTIs plus an NNRTI or PIs, with continuation of therapy postpartum. 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, because the potential benefit of treatment for the mother outweighs potential fetal risks. The regimen should generally be chosen from those recommended for nonpregnant adults (e.g., a preferred or alternative regimen), taking into account what is known about use of the drugs during pregnancy and risk of teratogenicity (see **Table 5** and **Teratogenicity**) *[10]*.

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 *[11-12]*. Therefore, nevirapine should only be used as a component of a combination regimen when antiretroviral therapy is being initiated in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk. If nevirapine is used, frequent and careful monitoring of

transaminase levels, particularly during the first 18 weeks of treatment, is required (see **Nevirapine and Hepatic/Rash Toxicity**). Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis.

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

HIV-infected pregnant women should be counseled regarding the benefits of antiretroviral drugs for prevention of perinatal transmission even when initiation of antiretroviral therapy for maternal health is not recommended or is considered optional on the basis of current guidelines for treatment of nonpregnant persons *[10]*. Although such women are at low risk of clinical disease progression if antiretroviral treatment is delayed, use of an antiretroviral regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal HIV transmission and lessens the need for consideration of elective cesarean delivery as an intervention to reduce transmission risk.

Because the fetus is most susceptible to the potential teratogenic effects of drugs during the first 10 weeks of gestation and the risks of antiretroviral therapy during that period are not fully known, women in the first trimester of pregnancy who do not require immediate initiation of therapy for their own health may consider delaying initiation until after 10 to 12 weeks gestation. This decision should be carefully considered by the health care provider and the woman; a discussion should include an assessment of the woman's health status, the benefits and risks to her of delaying initiation of therapy for several weeks, and the fact that most perinatal HIV transmission likely occurs late in pregnancy or during delivery.

Antiretroviral 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 (e.g., <1,000 copies/mL), there is no threshold below which lack of transmission can be assured *[2, 13-14]*. The mechanism by which antiretroviral 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, antiretroviral prophylaxis is effective even in women with low viral load *[15-19]*. Additional mechanisms of protection include pre-exposure prophylaxis of the infant, provided by passage of the antiretroviral drug across the placenta so that inhibitory levels of drug are present in the fetus particularly during the birth process, and post-exposure prophylaxis through continued administration to the infant. Although placental passage of zidovudine is excellent, that of many other antiretroviral drugs may be variable (**Table 4**). Therefore, when combination antiretroviral therapy is initiated during pregnancy, zidovudine should be included as a component of antenatal therapy whenever possible. If antenatal zidovudine use is not possible, at least one agent with known transplacental passage should be part of the antiretroviral regimen (see **Table 4**).

Combination antiretroviral regimens containing at least three drugs for prevention of perinatal HIV transmission should be discussed and offered to all pregnant women with HIV infection. A number of studies suggest that antenatal use of combination antiretroviral regimens further reduces transmission compared to use of zidovudine alone. In a longitudinal epidemiologic study conducted in the United States since 1990, transmission was observed in 20% of women with HIV infection who received no antiretroviral treatment during pregnancy, 10.4% who received zidovudine alone, 3.8% who received combination therapy without protease inhibitors (primarily dual NRTIs), and 1.2% who received combination therapy with protease inhibitors *[2]*. However, in these older studies, zidovudine alone was often used in women with higher viral load and lower CD4, in whom treatment would now be recommended. In more recent data from the United Kingdom and Ireland, perinatal transmission occurred among 9.1% of women who received no antiretroviral drugs, 0.5% of women who received single drug prophylaxis (primarily zidovudine, as recommended by U.K. guidelines for women with HIV RNA levels less than 10,000 copies/mL), 0.8% of women who received dual drug prophylaxis,

and 1.0% of women who received triple drug regimens for treatment or prophylaxis. There were no significant differences in transmission rate between the drug regimen groups; the majority of women in all groups were delivered by scheduled cesarean delivery. Among 2,117 infants born to women on triple drug combination antiretroviral therapy or prophylaxis with HIV RNA less than 50 copies/mL at delivery, only 0.1% were infected *[20]*.

A three-drug combination antiretroviral regimen not regarded as one of the standard first-line regimens recommended for adults who require therapy may be considered for the pregnant woman if the regimen is given solely to reduce perinatal transmission, is only needed because the woman is pregnant, and will be discontinued postpartum. The triple NRTI combination zidovudine/lamivudine/abacavir regimen may be considered because of known pharmacokinetic profiles and published data suggesting acceptable toxicities during pregnancy. Testing for HLA-B*5701 identifies patients at risk of hypersensitivity reactions *[21-22]* and should be done and documented as negative before starting abacavir. Triple drug regimens containing the PI nelfinavir, which is not part of standard first-line therapy, may also be considered because there is a large experience with its safe use during pregnancy. However, these regimens have inferior long-term virologic efficacy, and for women with high CD4 counts but high viral load (i.e., CD4 count >350/mm^3 and HIV RNA >100,000 copies/mL), the use of first-line, more potent regimens should be considered. Dual NRTI therapy without the addition of a third drug (i.e., a PI, NNRTI, or a third NRTI) is not recommended because of the potential for inadequate viral suppression and rapid development of resistance *[10, 23]*.

The time-limited use of zidovudine alone during pregnancy for chemoprophylaxis against perinatal transmission is controversial. However, some women who may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of transmitting HIV to their infants may opt for use of zidovudine alone. Additionally, for women with low viral load, time-limited use of zidovudine during the second and third trimesters of pregnancy is less likely to induce the development of resistance than in women with higher viral loads because of the low level of viral replication in the virologically suppressed women and the short duration of exposure to the antiretroviral drug *[24-25]*. For example, the development of zidovudine resistance was unusual among the healthy population of women who participated in PACTG 076 *[26]*. Thus, although controversial, the use of zidovudine chemoprophylaxis alone during pregnancy might be an appropriate option for this subset of women (i.e., women with HIV RNA levels <1,000 on no treatment).

In general, if antiretroviral drugs are given solely for prevention of perinatal HIV transmission, the antiretroviral drugs are discontinued postnatally, with the option to reinitiate standard potent treatment regimens in the future according to the usual criteria for nonpregnant individuals. Discussion regarding the decision to continue or stop antiretrovirals postpartum should occur before beginning antiretrovirals during pregnancy. Generally, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, as discussed later (see **Stopping Antiretroviral Therapy during Pregnancy**), in women receiving NNRTI-based regimens, continuing the dual NRTI backbone for a period of time after stopping the NNRTI should be considered to reduce the development of NNRTI resistance. An alternative strategy is to replace the NNRTI with a PI drug while continuing the NRTIs, then to discontinue all the drugs at the same time *[27]*. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. In patients receiving an efavirenz-based NNRTI regimen after the first trimester, detectable drug concentrations may be observed for more than 3 weeks after stopping efavirenz. Therefore, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days in such patients.

HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications

Panel's Recommendations:

- ***Obtain an accurate history of all prior antiretroviral regimens used for treatment of HIV disease or prevention of transmission and results of prior resistance testing (AIII).***
- ***Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy (AI).***
- ***Initiate a combination antiretroviral drug regimen, with regimen chosen based on resistance testing and prior antiretroviral therapy history, and avoid drugs with teratogenic potential (efavirenz in the first trimester of pregnancy) or with known adverse potential for the pregnant mother (e.g., combination stavudine/didanosine) (AII).***
- ***Women who do not show an appropriate virologic response to their antiretroviral regimens (see Monitoring of the Woman and Fetus During Pregnancy) require repeat antiretroviral drug resistance testing (AI), as well as consultation with a clinician experienced in HIV treatment, to guide changes in antiretroviral therapy.***

There are no data to guide the choice of antiretroviral regimens to be used in a subsequent pregnancy for women who previously received antiretroviral prophylaxis for prevention of perinatal HIV transmission. Although there is concern that time-limited use of antiretroviral drugs during pregnancy may lead to genotypic resistance, reduced efficacy of standard regimens, particularly those containing the dual NRTI backbone of zidovudine and lamivudine, in successive pregnancies has not been demonstrated. Given the lack of substantive data, it is reasonable to make preliminary decisions about antiretroviral regimens based on results of initial resistance testing. However, interpretation of resistance testing following discontinuation of antiretroviral drugs can be complex because the assay may not detect low-level drug-resistant viral variants. Thus, careful monitoring of virologic response to the chosen antiretroviral regimen is important. Decisions to alter therapy based on lack of virologic response should be guided by repeat resistance testing.

Some women may have received antiretroviral treatment for their own health in the past, having discontinued the drugs for a variety of reasons and for variable lengths of time prior to pregnancy. Appropriate choice of antiretroviral drugs will vary according to the history of antiretroviral use, the indication for stopping therapy, and the results of past and current resistance testing. For example, women with a history of prior antiretroviral therapy 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 may be able to restart the same regimen. Alternatively, selection of an appropriate antiretroviral regimen for women with advanced HIV disease, a history of extensive prior antiretroviral therapy, or history of significant toxicity to antiretroviral drugs in the past may be challenging even for health care providers experienced in HIV care. In addition to obtaining genotypic resistance testing as described above, it is recommended that specialists in the treatment of HIV infection be consulted about the choice of antiretroviral therapy in such cases.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.
2. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.

3. Shapiro D, Tuomala R, Pollack H, et al. Mother-to child HIV transmission risk according to antiretroviral therapy, mode of delivery, and viral load in 2895 U.S. women (PACTG 367). 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 99.
4. Burns DN, Landesman S, Muenz LR, et al. Cigarette smoking, premature rupture of membranes and vertical transmission of HIV-1 among women with low $CD4^+$ levels. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1994;7(7):718-726.
5. Turner BJ, Hauck WW, Fanning R, Markson LE. Cigarette smoking and maternal-child HIV transmission. *J Acquir Immune Defic Syndr Human Retrovirol.* 1997;14(4):327-337.
6. Rodriguez EM, Mofenson LM, Chang BH, et al. Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. *AIDS.* 1996;10(3):273-282.
7. Bulterys M, Landesman S, Burns DN, et al. Sexual behavior and injection drug use during pregnancy and vertical transmission of HIV-1. *J Acquir Immune Defic Syndr Human Retrovirol.* 1997;15(1):76-82.
8. Matheson PB, Thomas PA, Abrams EJ, et al. Heterosexual behavior during pregnancy and perinatal transmission of HIV-1. *AIDS.* 1996;10(11):1249-1256.
9. CDC. Revised recommendations for HIV testing of adults, adolescents and pregnant women in health care settings. *MMWR.* 2006;55(RR-14):1-17.
10. 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. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
11. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S21-33.
12. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. Revised June 24, 2008.
13. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
14. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med.* 1999;341(6):394-402.
15. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. *J Infect Dis.* 2001;183(4):539-545.
16. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
17. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868.
18. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
19. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* 2003;187(5):725-735.
20. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981.
21. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
22. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.
23. Clarke JR, Braganza R, Mirza A, et al. Rapid development of genotypic resistance to lamivudine when combined with zidovudine in pregnancy. *J Med Virol.* 1999;59(3):364-368.
24. Read P, Costelloe S, Mullen J, et al. New mutations associated with resistance not detected following zidovudine monotherapy in pregnancy when used in accordance with British HIV Association guidelines. *HIV Med.* 2008;9(7):448-451.
25. Larbalestier N, Mullen J, O'Shea S, et al. Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS.* 2003;17(18):2665-2667.

26. Eastman PS, Shapiro DE, Coombs RW, et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in Pediatric AIDS Clinical Trial Group Protocol 076. *J Infect Dis.* 1998;177(3):557-564.
27. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.

Table 4. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy (See *Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy* for more detail on drugs.)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental Passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (ABC)/ Ziagen	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver and thyroid in female rats and preputial and clitoral glands in mice and rats at 6–32x human exposure)	Positive (rodent anasarca and skeletal malformations at 1,000 mg/kg [35x human exposure] during organogenesis; not seen at 8.5x human exposure in rabbits)
Didanosine (ddI)/ Videx	B	Yes (humans) 0.5	Negative (no tumors in lifetime rodent study at 0.7–3x maximum human exposure)	Negative (at 12x and 14.2x human exposure in rabbits and rats, respectively)
Emtricitabine (FTC)/ Emtriva	B	Yes (mice and rabbits) 0.4–0.5	Negative (no tumors in lifetime rodent study at 26–31x human exposure)	Negative (at 60x, 60x, and 120x human exposure in rats, mice, and rabbits, respectively)
Lamivudine (3TC)/ Epivir	C	Yes (humans) ~1.0	Negative (no tumors in lifetime rodent study at 10–58x human exposure)	Negative (at 35x human exposure in rats and rabbits; however, embryolethality seen in rabbits at 1x human exposure)
Stavudine (d4T)/ Zerit	C	Yes (rhesus monkeys) 0.76	Positive (in mice and rats at very high dose exposure; liver and bladder tumors [rats only] at 250x and 732x human exposure in mice and rats, respectively)	Negative (at 399x [rats] and 183x [rabbits] human exposure, although sternal bone ossification decreased and rat neonatal mortality increased at 399x human exposure in rats)
Tenofovir DF (TDF)/ Viread	B	Yes (humans) 0.95–0.99	Positive (hepatic adenomas in female mice only at 16x human exposure)	Negative (at 14x and 19x human exposure in rats and rabbits, respectively)
Zidovudine (AZT, ZDV)/ Retrovir	C	Yes (humans) 0.85	Positive (nonmetastasizing vaginal epithelial tumors at 3x and 24x human exposure in mice and rats, respectively)	Positive (increased fetal malformations associated with maternal toxicity at 300x human exposure in rats. Increased fetal resorptions at 66–226x and 12–87x human exposure in rats and rabbits, respectively, with no developmental abnormalities)
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz (EFV)/ Sustiva	D	Yes (cynomolgus monkeys, rats, rabbits) ~1.0	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female mice at 1.7x human exposure; no increases in tumors in rats at 0.2x human exposure)	Positive (anencephaly, anophthalmia, microophthalmia, and cleft palate in cynomolgus monkey at exposures comparable to human exposure; no reproductive toxicities in pregnant rabbits at 0.5–1x human exposure)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental Passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Non-nucleoside reverse transcriptase inhibitors (cont)				
Etravirine (ETR)/ Intelence	B	Unknown	Positive (hepatocellular adenomas and carcinomas in female mice at 0.6x human exposure; no findings in rats at 0.2–0.7x human exposure)	Negative (in rats and rabbits at exposures comparable to human exposures)
Nevirapine (NVP)/ Viramune	B	Yes (humans) ~1.0	Positive (hepatocellular adenomas and carcinomas in mice and rats at less than human exposure)	Negative (in rats and rabbits at 1–1.5x human exposure; however, decreased fetal body weight in rats at 1.5x human exposure)
Protease inhibitors				
Atazanavir (ATV)/ Reyataz	B	Minimal/variable (humans)	Positive (benign hepatocellular adenomas in female mice at 7.2x human exposure)	Negative (at 2x and 1x human exposure in rats and rabbits, respectively)
Darunavir (DRV)/ Prezista	C	Unknown	Positive (hepatic adenomas, carcinomas [male mice], thyroid neoplasms [rats only] at 0.1–0.3x and 0.7–1x human exposure in mice and rats, respectively)	Negative (at 0.5x and 0.05x human exposure in rats/mice and rabbits, respectively)
Fosamprenavir (f-APV)/ Lexiva)	C	Unknown	Positive (hepatic adenomas and carcinomas [mice and rats]; thyroid adenomas, interstitial cell hyperplasia, and uterine endometrial adenocarcinoma [rats only] at 0.1–0.7x and 0.3–1.4x human exposure in mice and rats, respectively	Negative (at 0.8x and 2x human exposure in rabbits and rats respectively; increased incidence of abortions in rabbits at 0.8x human exposure)
Indinavir (IDV)/ Crixivan	C	Minimal (humans)	Positive (thyroid adenomas in male rats at 1.3x human exposure)	Negative (however supernumerary ribs in rats at exposures less than or slightly greater than human exposure)
Lopinavir + Ritonavir (LPV/r)/ Kaletra)	C	Yes (humans) 0.20±0.13	Positive (hepatic adenomas and carcinomas at 1.6–2.2x and 0.5x human exposure in mice and rats, respectively)	Positive (no effects in rabbits and dogs at ~1x human exposure; decreased fetal viability and body weight, delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses [at 0.7x and 1.8x human exposure for lopinavir and ritonavir, respectively])
Nelfinavir (NFV)/ Viracept	B	Minimal/variable (humans)	Positive (thyroid follicular adenomas and carcinomas at 1–3x human exposure in rats)	Negative (in rats at human exposure and in rabbits at significantly lower than human exposure)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Protease inhibitors (cont)				
Ritonavir (RTV)/ Norvir	B	Minimal (humans)	Positive (hepatic adenomas and carcinomas in male mice at 0.3x human exposure)	Positive (early resorptions, decreased fetal body weight, ossification delays, and developmental variations in rats at maternally toxic dose [~0.3x human exposure]; cryptorchidism in rats at 0.22x human exposure)
Saquinavir (SQV) Invirase	B	Minimal (humans)	Negative (at 0.29x and 0.65x human exposure [coadministration with ritonavir] in rats and mice, respectively)	Negative (at 0.29x and 0.21x human exposure [coadministration with ritonavir] in rats and rabbits, respectively)
Tipranavir (TPV)/ Aptivus	C	Unknown	Positive (hepatic adenomas and carcinomas in mice at less than human exposure; thyroid follicular cell adenoma in female rats at exposures comparable to human exposure)	Negative (decreased ossification and pup weights in rats at 0.8x human exposure)
Entry inhibitors				
Enfuvirtide (T-20)/ Fuzeon	B	None (based on very limited human data)	Not conducted	Negative
Maraviroc (MVC)/ Selzentry	B	Unknown	Negative (in transgenic mice and rats at 11x human exposure)	Negative (at 20x and 5x human exposure in rats and rabbits, respectively)
Integrase inhibitors				
Raltegravir (RAL)/ Isentress	C	Yes (rats, rabbits) † Rats: 1.5–2.5 Rabbits: 0.02	In progress	Negative (however, supernumerary ribs in rats at 3x human exposure)

* Food and Drug Administration Pregnancy Categories:
A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

† Values obtained from fetal (not newborn) blood samples. See text under "Placental and breast milk passage" in section on Raltegravir (Isentress) in ***Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy***.

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

(See also "Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy" 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.)

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
NRTIs/ NtRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	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. (Zidovudine alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL.)
Recommended Agents			
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[1]*.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum (see **Special Considerations: Hepatitis B Virus Coinfection**).	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[3]*.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience. Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity, stavudine use, documented resistance, or the woman is already on a fully suppressive regimen.
Alternate Agents			
Abacavir*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; fatal reactions occur in a much smaller percentage of persons and are usually associated with rechallenge. Rate of hypersensitivity reactions in pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions *[4-5]* and should be done and documented as negative before starting abacavir. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen. #
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[6]*.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[7-8]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents (continued)			
Emtricitabine†	Pharmacokinetic study shows slightly lower levels in third trimester compared to postpartum *[9]*. No clear need to increase dose.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[10]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[7-8]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Use in Special Circumstances			
Tenofovir†	Limited studies in human pregnancy; data indicate AUC lower in third trimester than postpartum but trough levels similar.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Studies in monkeys at doses approximately 2-fold higher than dosage for human therapeutic use show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy *[11]*. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown *[12-13]*. 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)**.	Because of limited data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of other alternatives. Because of potential for renal toxicity, renal function should be monitored.
NNRTIs		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear if increased in pregnancy.	NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended Agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[14-15]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250/mm^3 when first initiating therapy *[16-17]*; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4 counts >250 cells/mm^3 only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 count.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Use in Special Circumstances			
Efavirenz†	Small study in 13 breastfeeding women in Rwanda of 600 mg once daily; postpartum peak levels during lactation were 61% higher than previously reported in HIV-infected nonpregnant individuals at that dose *[18]*.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving 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 *[2, 19-20]*; relative risk unclear.	Use of efavirenz 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 efavirenz is to be continued postpartum, adequate contraception must be assured. Women of childbearing potential must be counseled regarding the teratogenic potential of efavirenz and avoidance of pregnancy while on the drug. Because of the known failure rates even with contraception, alternate antiretroviral regimens should be strongly considered in women of childbearing potential.
Insufficient Data to Recommend Use			
Etravirine	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Protease Inhibitors (PIs)		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 text).	PIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended Agents			
Lopinavir/ ritonavir	Pharmacokinetic studies of the new lopinavir/ ritonavir tablet formulation are under way, but data are not yet available.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated in Phase I/II studies.	Pharmacokinetic studies of the new tablet formulation are under way but are not yet conclusive as to the optimal dose in pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation pharmacokinetic data, would increase the dose of the tablet formulation during the third trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. Once-daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents			
Atazanavir (recommended to be combined with low-dose ritonavir boosting)	Two of three intensive pharmacokinetic studies of atazanavir with ritonavir boosting during pregnancy suggest that standard dosing results in decreased plasma concentrations compared to nonpregnant adults *[21-23]*. Atazanavir concentrations further reduced ~25% with concomitant tenofovir use *[23]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Transplacental passage is low, with cord blood concentration averaging 10%–16% of the maternal delivery atazanavir concentration *[21, 23]*. Theoretical concern re: increased indirect bilirubin levels exacerbating physiologic hyperbilirubinemia in the neonate not observed in clinical trials to date *[21-24]*.	Alternative PI for use in combination regimens in pregnancy. Should give as low-dose ritonavir-boosted regimen, may use once-daily dosing. In treatment-naïve patients unable to tolerate ritonavir, 400 mg once-daily dosing without ritonavir boosting may be considered, although there are no data describing atazanavir concentrations or efficacy under these circumstances. If coadministered with tenofovir, atazanavir must be given with low-dose ritonavir boosting.
Indinavir (combined with low-dose ritonavir boosting)	Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen *[25-26]*. In a study of ritonavir-boosted indinavir (400 mg indinavir/100 mg ritonavir twice daily), 82% of women met the target trough level *[27]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI for use in combination regimens in pregnancy. Must give as low-dose ritonavir-boosted regimen.
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250 mg given twice daily, although levels are variable in late pregnancy *[28-30]*. 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 nelfinavir than women in the second trimester *[30]*. 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 *[31]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Given pharmacokinetic data and extensive experience with use in pregnancy, nelfinavir is an alternative PI for combination regimens in pregnant women receiving combination antiretroviral drugs only for perinatal prophylaxis. In clinical trials of initial therapy in nonpregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir-ritonavir or efavirenz-based regimens but similar viral response to atazanavir- or nevirapine-based regimens.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents (continued)			
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum *[2, 32]*.	Limited experience at full dose in human pregnancy; has been used as low-dose ritonavir boosting with other PIs.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir "boost" to increase levels of second PI.
Saquinavir HGC (combined with low-dose ritonavir boosting)	Limited pharmacokinetic data on saquinavir HGC and the new 500-mg tablet formulation suggest that 1,000 mg saquinavir HGC/100 mg ritonavir given twice daily achieves adequate saquinavir drug levels in pregnant women *[33]*.	Well-tolerated, short-term safety demonstrated for mother and infant for saquinavir in combination with low-dose ritonavir.	There are only limited pharmacokinetic data on saquinavir HGC and the new tablet formulation in pregnancy. Ritonavir-boosted saquinavir HGC or saquinavir tablets are alternative PIs for combination regimens in pregnancy and are alternative initial antiretroviral recommendations for nonpregnant adults. Must give as low-dose ritonavir-boosted regimen.
Insufficient Data to Recommend Use			
Darunavir (combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Must give as low-dose ritonavir-boosted regimen.
Fosamprenavir (recommended to be combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	Limited experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Recommended to be given as low-dose ritonavir-boosted regimen.
Tipranavir (combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Must give as low-dose ritonavir-boosted regimen.
Entry Inhibitors			
Insufficient Data to Recommend Use			
Enfuvirtide	No pharmacokinetic studies in human pregnancy.	Minimal data in human pregnancy *[34]*.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Maraviroc	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Integrase Inhibitors			
Insufficient Data to Recommend Use			
Raltegravir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Abbreviations: AUC: area under the curve; HGC: hard gel capsule; NRTI: nucleoside reverse transcriptase inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir; lamivudine and abacavir are included as a fixed-dose combination in Epzicom.

† Emtricitabine and tenofovir are included as a fixed-dose combination in Truvada; emtricitabine, tenofovir, and efavirenz are included as a fixed-dose combination in Atripla.

\# Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based combination antiretroviral drug regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based combination regimen cannot be used (e.g., due to significant drug interactions).

References

1. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis.* 1998;178(5):1327-1333.
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol.* 1993;168(5):1510-1516.
4. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
5. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.
6. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus--infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis.* 1999;180(5):1536-1541.
7. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
8. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-59.
9. Best B, Stek A, Hu C, et al. for the PACTG/IMPAACT P1026S team. High-dose lopinavir and standard-dose emtricitabine pharmacokinetics during pregnancy and postpartum. 15th Conference on Retroviruses and Opportunistic Infections, February 3-8, 2008; Boston, MA. Abstract 629.
10. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis.* 2004;190(12):2167-2174.
11. Tarantal AF, Castillo A, Ekert JE, et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). *J Acquir Immune Defic Syndr.* 2002;29(3):207-220.
12. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718.

13. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS.* 2002;16(9):1257-1263.
14. Aweeka F, Lizak P, Frenkel L, et al. Steady state nevirapine pharmacokinetics during 2nd and 3rd trimester pregnancy and postpartum: PACTG 1022. 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 932.
15. Mirochnick M, Siminski S, Fenton T, et al. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis J.* 2001;20(8):803-805.
16. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
17. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis.* 2004;38 Suppl 2:S80-89.
18. Schneider S, Peltier A, Gras A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr.* 2008;48(4):450-454.
19. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med.* 2002;162(3):355.
20. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS.* 2002;16(2):299-300.
21. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS.* 2007;21(18):2409-2415.
22. Eley T, Vandeloise E, Child M, et al. Steady State Pharmacokinetics and Safety of Atazanavir after Treatment with ATV 300 mg Once Daily/Ritonavir 100 mg Once Daily + ZDV/3TC during the Third Trimester in HIV+ Women. 15th Conference on Retoviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 624.
23. Mirochnick M, Kafulafula G, Kreitchmann R, et al. The pharmacokinetics (PK) of tenofovir disoproxil fumarate (TDF) after administration to HIV-1 infected pregnant women and their newborns. 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada Abstract 939.
24. Natha, M. Hay, P. Taylor, G. et al. . Atazanavir use in pregnancy: a report of 33 cases. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 750.
25. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother.* 2007;51(2):783-786.
26. Hayashi S, Beckerman K, Homma M, et al. Pharmacokinetics of indinavir in HIV-positive pregnant women. *AIDS.* 2000;14(8):1061-1062.
27. Ghosn J, De Montgolfier I, Cornélie C, et al. Antiretroviral therapy with a twice-daily regimen containing 400 milligrams of indinavir and 100 milligrams of ritonavir in human immunodeficiency virus type 1-infected women during pregnancy. *Antimicrob Agents Chemother.* 2008;52(4):1542-1544.
28. Bryson Y, Stek A, Mirochnick M, et al. for the PACTG 353 Team. Pharmacokinetics, antiviral activity and safety of nelfinavir (NFV) in combination with ZDV/3TC in pregnant HIV-infected women and their infants: PACTG 353 Cohort 2. 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 795-W.
29. Aweeka F, Tierney C, Stek A, et al. ACTG 5153s: pharmacokinetic exposure and virological response in HIV-1-infected pregnant women treated with PI. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 739.
30. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and nonpregnant women. *Br J Clin Pharmacol.* 2006;62(3):309-315.
31. Read, J. Best, B. Stek, A. et al. . Nelfinavir pharamacokinetics (625 mg tablets) during the third trimester of pregnancy and postpartum. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 740.
32. Scott GB, Rodman JH, Scott WA, et al. for the PACTG 354 Protocol Team. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (XDV) and lamivudine (3TC) in HIV-1 infected pregnant women and their infants. 9th conference on Retroviruses and opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 794-W.
33. Burger DM, Eggink A, van der Ende ME, et al. The pharmacokinetics of saquinavir new tablet formulation + ritonavir (1000/100 mg BID) in HIV-1-infected pregnant women. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 741.
34. Meyohas MC, Lacombe K, Carbonne B, et al. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS.* 2004;18(14):1966-1968.

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

Clinical Scenario	Recommendations
Nonpregnant HIV-infected woman of childbearing potential who has indications for initiating antiretroviral therapy	• Initiate combination antiretroviral drug therapy as per adult treatment guidelines. • Avoid drugs with teratogenic potential (e.g., efavirenz) if the woman is trying to conceive or is not using adequate contraception. Exclude pregnancy before starting treatment with efavirenz.
HIV-infected woman on combination antiretroviral drug therapy who becomes pregnant	**Woman:** • In general, if woman requires treatment, antiretroviral drugs should not be stopped during the first trimester or during pregnancy. • Continue current combination antiretroviral therapy regimen 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 antiretroviral drug resistance testing if the woman has detectable viremia on therapy. • Continue combination antiretroviral therapy regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected pregnant woman who is antiretroviral naïve and has indications for antiretroviral therapy	**Woman:** • Perform HIV antiretroviral drug resistance testing prior to initiating combination antiretroviral drug therapy and repeat after initiating therapy if viral suppression is suboptimal. • Initiate combination antiretroviral 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). - Use zidovudine as a component of the antiretroviral regimen when feasible. - Use nevirapine as a component of the antiretroviral regimen only if the woman has CD4 count ≤250 cells/mm^3. If the woman has CD4 count >250 cells/mm^3, use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • If woman requires immediate initiation of therapy for her own health, initiate treatment as soon as possible, including in the first trimester. • Continue combination antiretroviral therapy regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]

Clinical Scenario	Recommendations
HIV-infected pregnant woman who is antiretroviral naïve and does not require treatment for her own health	**Woman:** • Perform HIV antiretroviral drug resistance testing prior to initiating combination antiretroviral drug therapy and repeat after initiation of therapy if viral suppression is suboptimal. • Prescribe a combination antiretroviral drug prophylaxis regimen (i.e., at least 3 drugs) for prophylaxis of perinatal transmission. - Consider delaying initiation of antiretroviral prophylaxis until after first trimester is completed. - 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). - Use zidovudine as a component of the antiretroviral regimen when feasible. - If the woman has CD4 count >250 cells/mm^3 use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Although use of zidovudine prophylaxis alone is controversial, consider if woman has plasma HIV RNA level <1,000 copies/mL on no therapy. • Continue antiretroviral prophylaxis regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continuing the combination regimen postpartum; discontinue the combination regimen unless the woman has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs at least 7 days after stopping NNRTI. (Only limited data exist on this; see **Stopping Antiretroviral Therapy** and **Prevention of Antiretroviral Drug Resistance**.) • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant**: • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected pregnant woman who is antiretroviral experienced but not currently receiving antiretroviral drugs	**Woman:** • Obtain full antiretroviral treatment history, including prior resistance testing, and evaluate need for antiretroviral treatment for maternal health. • Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy and repeat after initiating combination antiretroviral regimen if suboptimal viral suppression. • Initiate a combination antiretroviral regimen (e.g., at least 3 drugs), with regimen chosen based on resistance testing and prior therapy history. - 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). - Use zidovudine as a component of the antiretroviral regimen when feasible. - If woman has CD4 count >250 cells/mm^3, use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Continue the combination regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continuing the combination regimen postpartum; discontinue the combination regimen unless the woman has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs at least 7 days after stopping NNRTI. (Limited data exist on this; see **Stopping Antiretroviral Therapy** and **Prevention of Antiretroviral Drug Resistance**.)

Clinical Scenario	Recommendations
	• Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant**: • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected woman who has received no antiretroviral therapy prior to labor	Zidovudine **Woman:** Give zidovudine as continuous infusion[1] during labor. **Infant:** Start zidovudine as soon as possible after birth and administer for 6 weeks.[2] ***OR*** Combination Zidovudine + Single-dose Nevirapine **Woman:** Give zidovudine as continuous infusion[1] during labor, plus single-dose nevirapine [3] at onset of labor. Consider adding lamivudine during labor and maternal zidovudine/lamivudine for at least 7 days postpartum, which may reduce development of nevirapine resistance. **Infant:** Give single-dose nevirapine[3] plus zidovudine for 6 weeks. ***OR*** **Woman:** Give zidovudine as continuous infusion[1] during labor. **Infant:** Although some clinicians may choose to use zidovudine in combination with additional drugs in the infant, appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consider consultation with a pediatric HIV specialist. • Evaluate need for initiation of maternal therapy postpartum.
Infant born to HIV-infected woman who has received no antiretroviral therapy prior to or during labor	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[2] ***OR*** • Although some clinicians may choose to use zidovudine in combination with additional drugs, appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consider consultation with a pediatric HIV specialist. • Evaluate need for initiation of maternal therapy postpartum.

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

[2] Zidovudine dosing for infants <35 weeks 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 gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.

[3] Single-dose nevirapine: Mother: 200 mg given once orally at onset of labor; Infant: 2 mg/kg body weight given once orally at 2–3 days of age if mother received intrapartum single-dose nevirapine or given at birth if mother did not receive intrapartum single-dose nevirapine.

Hepatitis B Virus Coinfection

Panel's Recommendations:

- ***Screening for hepatitis B virus (HBV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy (AII).***
- ***Pregnant women who screen negative for hepatitis B should receive the HBV vaccine series (AII).***
- ***Pregnant women with HBV infection should be screened for hepatitis A virus (HAV) and those who screen negative should receive the HAV vaccine series (AII).***
- ***Interferon-alpha and pegylated interferon-alpha are not recommended during pregnancy (AIII).***
- ***Because the optimal management for pregnant and postpartum women with HIV/HBV coinfection is not well defined, consultation with an expert in HIV and HBV is strongly recommended (AIII).***
- ***Decisions about the choice of antiretroviral regimen during pregnancy for HIV/HBV-coinfected women should take into account indications for HIV therapy as determined by maternal CD4 cell count and HIV disease status, HBV levels and indications for HBV therapy, gestational age when starting the antiretroviral regimen, and patient preference (AIII).***
- ***The determination of optimal antepartum antiretroviral regimen for an HIV/HBV-coinfected woman depends on whether she requires anti-HIV treatment for her own health, anti-HBV treatment, both, or neither.***
    - ***For coinfected women with indications for antiretroviral therapy for their own health and who are expected to continue drugs postpartum and/or who require treatment for HBV infection:***
        - ***A three-drug combination antepartum antiretroviral regimen including two agents with anti-HBV activity (e.g., tenofovir plus either lamivudine or emtricitabine) should be used and continued postpartum (BII).***
    - ***For coinfected women who receive antiretroviral drugs during pregnancy solely as prophylaxis for prevention of mother-to-child transmission of HIV, who are expected to discontinue antiretroviral prophylaxis after delivery, and who do not require treatment for HBV infection, the choice is more complex and can include:***
        - ***A three-drug combination antepartum antiretroviral regimen including two NRTI agents with anti-HBV activity (e.g., tenofovir plus either lamivudine or emtricitabine) and stopping prophylaxis after delivery (with monitoring for HBV flare) (BIII); or***
        - ***A three-drug combination antepartum antiretroviral regimen that includes only NRTI agents without anti-HBV activity (e.g., abacavir, didanosine, stavudine, or zidovudine) and stopping prophylaxis after delivery (BIII); or***
        - ***A three-drug combination antepartum antiretroviral regimen including lamivudine as the sole anti-HBV agent could be considered for women presenting late in pregnancy (e.g., after 28 weeks gestation) and stopping prophylaxis after delivery (with monitoring for HBV flare) (CIII).***
- ***Pregnant women with HBV/HIV coinfection receiving antiretroviral drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis and then at least monthly (BIII).***
- ***Infants born to women with hepatitis B infection should receive hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccine series within 12 hours of birth; the second and third doses of vaccine should be administered at 1 and 6 months of age, respectively (AI).***

For additional information on hepatitis B and HIV, see *Hepatitis B Virus Infection* (pages 75–84) in the "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Recommendations from CDC, NIH, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)" at **http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf** *[1]*.

All HIV-infected pregnant women should be screened for hepatitis A, B, and C. The management of HBV/HIV coinfection 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 hepatitis B on the basis of hepatitis B surface antigen for at least 6 months and who are hepatitis A IgG negative should receive the hepatitis A virus (HAV) vaccine series because of the added risk of acute hepatitis A in persons with chronic viral hepatitis.

HIV-infected women who are found to be hepatitis B surface antibody and hepatitis B surface antigen negative should receive the HBV vaccine series. Some patients test positive for anti-HBc alone, which might signify a false-positive result; exposure in the past with subsequent loss of anti-HBs; or "occult" HBV infection, which can be confirmed by detection of HBV DNA *[2-3]*. The clinical significance of isolated anti-HBc is unknown *[4-5]*. Some specialists recommend that HIV-infected persons with anti-HBc alone should be tested for HBV DNA before vaccination for HBV or before initiating antiretroviral drug treatment or prophylaxis because of the risk of reactivation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS) *[1]*. There are limited data regarding the optimal treatment of HIV-infected pregnant women with chronic HBV coinfection (i.e., hepatitis B surface antigen positive for >6 months). There are no definitive studies on the safety of antiviral therapy for hepatitis B infection during pregnancy and breastfeeding; interferon and peg-interferon are not recommended during pregnancy.

Current treatment guidelines for HBV/HIV-coinfected nonpregnant adults who require treatment of their HIV infection recommend the NRTI combination of tenofovir plus emtricitabine or tenofovir plus lamivudine as the dual NRTI backbone of an antiretroviral regimen, regardless of the need for concomitant HBV treatment *[6]*.Tenofovir, lamivudine, and emtricitabine all show activity against HBV. Because of the risk of development of HBV-resistant mutants, use of two agents active against HBV (tenofovir plus lamivudine or emtricitabine) is recommended as the dual NRTI backbone when antiretroviral treatment is required.

Lamivudine is a recommended NRTI and emtricitabine is an alternative NRTI for use in pregnancy. There are only limited data on the use of tenofovir during pregnancy. Tenofovir is not teratogenic in animals but reversible bone changes at high doses were seen in multiple animal species. Although tenofovir is not generally recommended in pregnancy as a first-line agent for antiretroviral regimens being used solely for prophylaxis of mother-to-child transmission of HIV, HBV/HIV coinfection in pregnancy may be a special circumstance where tenofovir may be more strongly considered (see **Table 5**). For pregnant women with HBV/HIV coinfection who require treatment of HIV disease for their own health or who require treatment of chronic HBV disease, the benefit of tenofovir outweighs potential risks, and tenofovir plus lamivudine or emtricitabine is recommended as the dual NRTI backbone of a three-drug therapeutic regimen. Although zidovudine should generally be a component of antiretroviral regimens in pregnancy, in HBV/HIV-coinfected women this may not be feasible.

A three-drug regimen including tenofovir plus lamivudine or emtricitabine is also recommended for HBV/HIV-coinfected pregnant women who do not require treatment of HIV but who do require treatment of their HBV disease. In nonpregnant coinfected patients who require treatment of HBV disease but not of HIV, pegylated interferon-alpha treatment is recommended. However, this drug is not recommended in pregnancy. Additionally, the use of tenofovir plus lamivudine or emtricitabine without a third antiretroviral drug should be avoided because of the rapid development of drug-resistant HIV mutations. Entecavir should not be used for treatment of HBV infection without concomitant combination treatment for HIV infection because recent data suggest that the M184V resistance mutation may emerge in HIV-infected patients receiving entecavir alone *[7]*. Entecavir is associated with skeletal anomalies in rats and rabbits but only at high, maternally toxic doses. Data on use of entecavir in human pregnancy are not available. Postpartum, the patient could stop the antiretroviral regimen and initiate HBV-specific therapy (e.g., pegylated interferon-alpha) to continue HBV treatment or continue the three-drug antiretroviral regimen.

There is controversy regarding the appropriate approach to therapy for pregnant women with HBV/HIV coinfection who do not require treatment of HIV or HBV disease, and therefore are receiving antiretroviral drugs solely for prevention of perinatal transmission of HIV and will discontinue therapy postpartum. Although there are only limited data about the safety of tenofovir in pregnancy, some experts recommend use of a three-drug regimen that includes the anti-HBV drug tenofovir plus lamivudine or emtricitabine as the dual NRTI backbone due to concern about HBV immune reconstitution inflammatory syndrome (IRIS) with initiation of therapy. Although concern about antiretroviral treatment-induced HBV IRIS should be less in this group of pregnant women because they do not require therapy for their own health and therefore do not have severe immunodeficiency (the greatest risk factor for development of IRIS following initiation of antiretroviral therapy), treating a potential HBV flare in the postpartum period after discontinuing HBV-active therapy may be associated with less risk than treating an immune-mediated flare during pregnancy. In addition, using drugs with anti-HBV activity during pregnancy will lower HBV levels and potentially decrease the risk of failure of hepatitis B immune globulin (HBIG) and hepatitis B vaccine to prevent perinatal transmission of HBV, which is increased among women with very high HBV DNA levels. If such an approach is followed, liver function should be carefully monitored postpartum following discontinuation of drugs; if severe flare-up of HBV disease occurs postpartum, initiation of anti-HBV-specific therapy such as pegylated interferon-alpha can be considered.

Alternatively, for women who require prophylaxis of perinatal HIV infection but do not require treatment for HBV infection, some experts choose to use an antiretroviral regimen without anti-HBV activity (e.g., use of a dual NRTI backbone that contains drugs other than tenofovir, lamivudine, or emtricitabine, such as zidovudine and didanosine, could be considered) to avoid the possibility of an HBV flare when treatment is discontinued postpartum. Another alternative used by some specialists for women who require prophylaxis of perinatal HIV infection but do not require treatment of HBV infection is a highly active antiretroviral regimen that includes lamivudine as the only antiretroviral agent with activity against HBV, especially if the regimen is started later in pregnancy because of late care or delayed HIV diagnosis. This option avoids the use of tenofovir during pregnancy because there are only limited data on safety, while still treating HBV; the risk of HBV development of resistance to lamivudine with short-term temporary exposure of less than 6 months is extremely low *[8]*.

An elevation in hepatic enzymes following initiation of antiretroviral therapy may occur in HBV/HIV-coinfected women due to an immune-mediated flare in HBV disease secondary to immune reconstitution with therapy, particularly in women with low CD4+ cell count at the time of initiation of therapy. HBV infection may also increase hepatotoxic risk of certain antiretroviral agents, specifically protease inhibitors and nevirapine. Pregnant women with HBV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly. If hepatic toxicity occurs, substitution of a less hepatotoxic drug regimen may need to be considered or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. It can be difficult to differentiate a flare in HBV disease due to immune reconstitution from drug toxicity, and consultation with an expert in HIV infection is recommended.

All infants born to HBV surface antigen positive mothers should receive hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccination series within 12 hours of birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207; quiz CE201-204.

2. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. *J Med Virol.* 2000;62(4):450-455.
3. Hofer M, Joller-Jemelka HI, Grob PJ, et al. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis.* 1998;17(1):6-13.
4. Silva AE, McMahon BJ, Parkinson AJ, et al. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. *Clin Infect Dis.* 1998;26(4):895-897.
5. Lok AS, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. *Hepatology.* 1988;8(4):766-770.
6. 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. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
7. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med.* 2007;356(25):2614-2621.
8. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology.* 1999;30(5):1302-1306.

Hepatitis C Virus Coinfection

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).***
- ***Pegylated interferon-alpha is not recommended and ribavirin is contraindicated during pregnancy (AII).***
- ***Recommendations for antiretroviral drug use during pregnancy are the same for women who are coinfected with HCV as for those without HCV coinfection (BIII).***
- ***Pregnant women with HCV/HIV coinfection receiving antiretroviral drugs should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly (BIII).***
- ***Decisions concerning mode of delivery in HCV/HIV-coinfected pregnant women should be based on considerations related to HIV infection alone (see Intrapartum Care) (BIII).***
- ***Infants born to women with HCV/HIV coinfection should be evaluated for HCV infection (AIII) by HCV RNA testing between 2 and 6 months of age and/or HCV antibody testing after 15 months of age (CIII).***
- ***Because of the added risk of acute hepatitis A and B in persons with chronic viral hepatitis C, women who are found to have chronic HCV infection should be screened for hepatitis A and hepatitis B infections. If women with chronic hepatitis C are hepatitis A IgG negative, they should receive the hepatitis A virus (HAV) vaccine series, and if they are hepatitis B uninfected (e.g., hepatitis B surface Ag 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* (pages 84–91) of the "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents, Recommendations from CDC, NIH, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)" at **http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf** *[1]*.

HCV/HIV coinfection is not uncommon in HIV-infected women, particularly among women infected via parenteral drug use; among HIV-infected pregnant women, the HCV seroprevalence rate ranges from 17%–54% *[2]*. Screening for 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 may occur among HIV-infected persons, particularly those with very low CD4 counts, but this is uncommon with the most sensitive immunoassays. If serologic test results are indeterminate or HCV infection is suspected due to elevated aminotransaminases or risk factors such as a history of intravenous drug use, testing for HCV RNA should be performed.

There are few data on the optimal management of HIV-infected pregnant women with HCV coinfection. There are no definitive studies on the safety of HCV antiviral therapy during pregnancy. Interferon and peg-interferon are not recommended for use in pregnancy, and ribavirin is contraindicated in pregnancy. 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 *[3]*. Ribavirin is labeled as FDA pregnancy category X because of its teratogenicity at low doses in multiple animal species; defects noted in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Pregnancy does not appear to influence the course of HCV infection and women with chronic viral hepatitis generally do quite well during pregnancy, providing that they have not progressed to decompensated cirrhosis *[4]*.

Because of the added risk of acute hepatitis A and B in persons with chronic viral hepatitis C, women who are found to have chronic HCV infection should be screened for hepatitis A and hepatitis B infections. If women with chronic HCV infection are hepatitis A IgG negative, they should receive the HAV vaccine series, and if they are hepatitis B uninfected (e.g., hepatitis B surface Ag negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series.

Coinfection with HIV has been shown to increase significantly the risk of perinatal transmission of HCV, likely related to increase in HCV viremia and/or other HIV-related impact on HCV disease activity *[5]*. A European study of perinatal transmission of HCV found that use of effective combination antiretroviral therapy was associated with a strong trend for reduction in HCV transmission (OR 0.26, 95% CI, 0.07–1.01) *[6]*. However, although the median HCV viral load was lower among women treated with combination antiretroviral regimens compared to women on a single drug or receiving no treatment (656,101 copies/mL vs. 850,000 copies/mL, respectively), this difference was neither statistically nor clinically significant. Maternal HCV/HIV coinfection may also increase the risk of perinatal transmission of HIV *[7]*. Therefore, potent combination antiretroviral therapy with three drugs should be considered for all HCV/HIV-coinfected pregnant women, regardless of CD4 count or HIV viral load, with discontinuation of therapy postpartum in women who do not require therapy for their own health.

Similar to HBV infection, an elevation in hepatic enzymes following initiation of antiretroviral therapy may occur in HCV/HIV-coinfected women. This elevation in hepatic enzymes may be due to an immune-mediated flare in HCV disease secondary to immune reconstitution with therapy, particularly in women with low CD4 cell count at the time of initiation of therapy. Like HBV, HCV infection may increase hepatotoxic risk of certain antiretroviral agents, specifically protease inhibitors and nevirapine. Pregnant women with HCV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly. If hepatic toxicity occurs, substitution of a less hepatotoxic drug regimen may need to be considered or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. It can be difficult to differentiate a flare in HCV disease due to immune reconstitution from drug toxicity, and consultation with an expert in HIV infection is recommended.

Similar to HIV transmission, internal fetal monitoring and duration of membrane rupture greater than 6 hours may increase risk of HCV transmission; general recommendations for intrapartum management are unchanged from those for women with HIV infection alone (see **Intrapartum Care**). Data are inconclusive regarding the role of scheduled cesarean delivery in reducing the risk of HCV transmission in the setting of HIV infection. Currently, there is no evidence from randomized controlled trials upon which to base any practice recommendations regarding scheduled cesarean delivery versus vaginal delivery for preventing mother-to-infant transmission of HCV *[8]*. In two observational studies from the European Hepatitis C Virus Network, the first study reported that scheduled cesarean delivery was protective against HCV transmission in HIV-coinfected women, but the second study found no benefit to scheduled cesarean delivery, possibly related to the increased use of combination antiretroviral drug regimens in the second report *[9]*. At the current time, decisions concerning mode of delivery in HCV/HIV-coinfected pregnant women should be based on HIV considerations alone (see **Intrapartum Care**).

Infants born to women with HCV/HIV coinfection should be assessed for HCV infection by HCV RNA virologic testing between 2 and 6 months of age (at least two negative tests are needed to exclude HCV infection because HCV viremia can be intermittent) and/or testing for anti-HCV antibody after age 15 months *[10]*.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.
2. Thomas SL, Newell ML, Peckham CS, et al. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. *Int J Epidemiol.* 1998;27(1):108-117.
3. Boskovic R, Wide R, Wolpin J, et al. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.
4. Sookoian S. Effect of pregnancy on pre-existing liver disease: chronic viral hepatitis. *Ann Hepatol.* 2006;5(3):190-197.
5. Polis CB, Shah SN, Johnson KE, et al. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. *Clin Infect Dis.* 2007;44(8):1123-1131.
6. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis.* 2005;192(11):1872-1879.
7. Hershow RC, Riester KA, Lew J, et al. Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfected mothers. Women and Infants Transmission Study. *J Infect Dis.* 1997;176(2):414-420.
8. McIntyre PG, Tosh K, McGuire W. Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. *Cochrane Database Syst Rev.* 2006(4):CD005546.
9. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. *BJOG.* 2001;108(4):371-377.
10. National Institutes of Health Consensus Development Conference statement Management of Hepatitis C: 2002 June 10-12, 2002. *HIV Clin Trials.* 2003;4(1):55-75.

Stopping Antiretroviral Therapy during Pregnancy

Panel's Recommendations:

- ***If an antiretroviral drug regimen is stopped acutely for severe or life-threatening toxicity or severe pregnancy-induced hyperemesis unresponsive to anti-emetics, all drugs should be stopped at the same time and reinitiated at the same time (AIII).***
- ***If an antiretroviral drug regimen is stopped electively and the patient is receiving an NNRTI drug, consideration should be given to either (1) stopping the NNRTI first and continuing the other antiretroviral drugs for a period of time or (2) switching from an NNRTI to a PI prior to interruption and continuing the PI with the other antiretroviral drugs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. Given the potential for prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral 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 prior to restarting therapy, nevirapine should be restarted with the 2-week dose escalation period (AII).***

Discontinuation of antiretroviral drug regimens during pregnancy may be indicated in some situations including serious drug-related toxicity, pregnancy-induced hyperemesis, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient request.

Continuation of all drugs during the intrapartum period is generally recommended. Women who are having an elective cesarean section can take oral medications prior to the scheduled surgery and restart drugs following

surgery. Given that most drugs are given once or twice daily, the woman would either not miss any doses or at most receive the postpartum dose a few hours late.

When short-term drug interruption is indicated, in most cases, all antiretroviral drugs should be stopped and reintroduced at the same time. This can be problematic with drugs that have a long half-life. However, in conditions such as severe or life-threatening toxicity or severe pregnancy-induced hyperemesis unresponsive to anti-emetics, the clinician has no choice but to stop all therapy at the same time.

NNRTI drugs like 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 *[1-5]*. As the other drugs with shorter half-lives are cleared, only the NNRTI drug may persist, resulting in persistent subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in slower rate of clearance. These polymorphisms may be more common among some ethnic groups, such as in African Americans and in Hispanics *[3, 5]*. To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other antiretroviral drugs for a period of time *[2]*. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; detectable levels of NNRTIs may be present from less than 1 week to greater than 3 weeks after discontinuation (the longer duration is primarily observed with efavirenz) *[5]*. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual 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 prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV-RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual-NRTIs *[6]*. The optimal duration needed to continue either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is not known; at least 7 days is recommended based on studies to reduce resistance following single-dose nevirapine *[7]*. With efavirenz use, there is the potential of prolonged detectable NNRTI concentrations for more than 3 weeks; therefore some suggest if stopping efavirenz-based therapy, the dual nucleosides 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.

An additional consideration is reintroduction of nevirapine if it is temporarily stopped for some reason and subsequently restarted. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing 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, it is recommended that another 2-week dose escalation be used when it is reintroduced.

Failure of Viral Suppression

Panel's Recommendations:

- ***If there is failure of viral suppression after an adequate period of treatment:***
  - ***Assess resistance and adherence (AII).***
  - ***Consult an expert in the care of HIV-infected adults (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).***

The management of women on chronic antiretroviral therapy who have suboptimal suppression of HIV RNA (i.e., detectable virus at any time during pregnancy) should include evaluation for resistant virus, assessment of adherence, incorrect dosing or potential problems with absorption (e.g., with nausea/vomiting or lack of attention to food requirements), and consideration of modification of antiretroviral therapy. Experts in the care

of antiretroviral-experienced adults should be consulted, in particular when a change in drug regimen is necessary.

HIV RNA levels should be assessed 2 to 6 weeks following initiation or change of antiretroviral drug regimen to provide an initial assessment of efficacy *[8]*. Baseline HIV RNA levels have been shown to affect the time course of response in pregnant as well as nonpregnant individuals *[9]*. Most patients with an adequate viral response at 24 weeks have had at least a 1 $\log_{10}$ copies/mL HIV RNA decrease by 1 to 4 weeks after starting therapy *[8]*. Treatment-naïve 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 HIV transmission, 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**).

References

1. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
2. Mackie NE, Fidler S, Tamm N, et al. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med.* 2004;5(3):180-184.
3. Nolan M, Fowler MG, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. *J Acquir Immune Defic Syndr.* 2002;30(2):216-229.
4. Sadiq ST, Fredericks S, Khoo SH, et al. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS.* 2005;19(15):1716-1717.
5. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis.* 2006;42(3):401-407.
6. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.
7. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
8. 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. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
9. European Collaborative Study, Patel D, Cortina-Borja M, et al. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis.* 2007;44(12):1647-1656.

MONITORING OF THE WOMAN AND FETUS DURING PREGNANCY

Panel's Recommendations:

- ***CD4 cell count should be monitored at the initial antenatal visit (AI) and at least every 3 months during pregnancy (BIII).***
- ***Plasma HIV RNA levels should be monitored at the initial visit (AI); 2 to 4 weeks after initiating (or changing) antiretroviral therapy (BI); monthly until RNA levels are undetectable (BII); and then at least every 3 months during pregnancy (BIII). HIV RNA levels should also be assessed at approximately 34 to 36 weeks gestation to inform decisions on mode of delivery (see Transmission and Mode of Delivery) (AIII).***
- ***Antiretroviral drug resistance testing should be performed in all pregnant women prior to initiating antiretroviral treatment or prophylaxis, in pregnant women who have suboptimal viral suppression after initiation of antiretroviral drugs (failure to achieve a 1 log_{10} copies/mL drop in HIV RNA at 30 days or lack of progressive decline to undetectable HIV RNA levels by 16 to 24 weeks of therapy), and in pregnant women who have persistently detectable plasma HIV RNA levels after treatment previously suppressed the virus to lower than the assay level of detection (AII).***
- ***Monitoring for complications of antiretroviral drugs during pregnancy should be based on what is known about side effects of the drugs the woman is receiving (AIII).***
- ***First-trimester ultrasound is recommended for confirmation of gestational age and potential timing for scheduled cesarean delivery, if needed (see Transmission and Mode of Delivery) (AII).***
- ***Given the limited data on the effect of combination therapy on the fetus, most experts would recommend second-trimester ultrasound to assess fetal anatomy for women who have received combination antiretroviral therapy (particularly if the regimen included efavirenz) during the first trimester (BIII).***
- ***Among women on combination antiretroviral drug 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 combination antiretroviral drug therapy or prophylaxis and ideally when HIV RNA levels are undetectable (BIII).***

CD4 cell count should be monitored in HIV-infected pregnant women at the initial visit and at least every 3 months during pregnancy, similar to recommendations in nonpregnant adults. Viral load should be monitored in HIV-infected pregnant women at the initial visit, 2 to 4 weeks after initiating or changing antiretroviral therapy, monthly until undetectable, and then at least every 3 months. If there is concern regarding adherence, more frequent monitoring is recommended because of the potential increased risk of perinatal HIV infection if there is 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 perinatal transmission risk. Therefore, there is a need to identify pregnant women whose decline in viral load is slower than expected. Adult antiretroviral guidelines note that patients should have a decrease in plasma HIV RNA level by at least one log_{10} copies/mL by 1 month after initiation of potent therapy (Adult guidelines). Generally, most treatment-adherent individuals not harboring resistance mutations to the drugs they are receiving achieve viral suppression in 16 to 24 weeks, although rarely it may take longer for some patients. Viral load should also be assessed at approximately 34 to 36 weeks gestation to inform decisions on mode of delivery (see **Transmission and Mode of Delivery**).

Due to physiologic changes such as hemodilution during pregnancy, CD4 percentage may be more stable than absolute CD4 count during pregnancy *[1-2]*. However, because parameters for initiating therapy are based primarily on absolute CD4 count, most clinicians still rely on CD4 count to evaluate immune status during pregnancy.

Antiretroviral drug resistance testing should be performed in pregnant women prior to initiating antiretroviral treatment or prophylaxis and in those women who have suboptimal viral suppression after initiation of antiretroviral drugs or who have persistently detectable plasma HIV RNA levels after treatment previously suppressed the virus to lower than the assay level of detection (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**). Drug resistance testing in the setting of viral failure should be performed while the patient is receiving antiretroviral drugs or immediately (i.e., up to 4 weeks) after discontinuing therapy.

Monitoring for potential complications of antiretroviral drugs during pregnancy should be based on what is known about the side 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 antiretroviral drugs. Hepatic dysfunction has been observed in pregnant women on protease inhibitors, and hepatic steatosis and lactic acidosis in pregnancy has been related to NRTI use. Women, particularly those with CD4 counts >250 cells/mm^3, have an increased risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity within the first 18 weeks after initiation of therapy. Pregnant women initiating therapy with nevirapine should have more frequent and careful monitoring of transaminase levels (see **Nevirapine and Hepatic/Rash Toxicity**).

First-trimester ultrasound is recommended for confirmation of gestational age and, if needed, to guide potential timing of scheduled cesarean delivery because scheduled cesarean deliveries for prevention of perinatal HIV transmission should be performed at 38 weeks gestation (see **Transmission and Mode of Delivery**). Research studies show that first-trimester ultrasound, which is currently recommended by the American Congress of Obstetricians and Gynecologists is the most accurate procedure for dating of pregnancy *[3-4]*. If the patient is not seen until later in gestation, then second-trimester ultrasound can be used for both anatomy scanning and determining gestational age.

Because less is known about the effect of combination antiretroviral therapy 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 antiretroviral therapy 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 if the woman was 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 and any maternal comorbidities.

In the pre-HAART era, invasive procedures such as amniocentesis and chorionic villus sampling were associated with a two- to four-fold increased risk of vertical transmission of HIV *[5-7]*. Data from the HAART era are still limited but do not suggest an increased risk of transmission for women receiving combination antiretroviral drug regimens before amniocentesis or other invasive diagnostic procedure. In an evaluation of transmission rates over time among women with or without amniocentesis, the transmission rate among women undergoing the procedure from 1984 to 1996 (pre-HAART) was 3 (30%) of 10 compared to 40 (16.2%) of 247 among women without amniocentesis (NS) *[8]*. No transmissions were noted among 18 women undergoing amniocentesis between 1997 and 2000 and receiving antiretroviral drug regimens *[8]*. In a multi-center study from Italy including deliveries between 1997 and 2003, 2 (3.3%) of 60 infants were HIV infected after early invasive diagnostic procedures (chorionic villus sampling, amniocentesis, or cordocentesis) during pregnancy compared to 1.7% of 712 infants born to women without invasive procedures (p = 0.30) *[9]*. No transmissions occurred among 45 women on combination antiretroviral drug regimens during the

procedure. One mother of an infected infant had not been diagnosed as HIV infected at the time of amniocentesis so was not receiving antiretroviral 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 the 6 and 9 liveborns after amniocentesis among HIV-infected pregnant women on combination antiretroviral drug regimens *[10-11]*. In the largest series to date, no transmissions were seen among 81 women receiving combination antiretroviral drug regimens at the time of amniocentesis *[12]*. Thus among 159 cases reported to date of amniocentesis or other invasive diagnostic procedures among women on combination antiretroviral 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 serum marker screening, should be counseled about the potential risk of HIV transmission along with other risks of the procedure and allowed to make an informed decision about testing. Some experts consider chorionic villus sampling and cordocentesis too risky to offer to HIV-infected women and recommend limiting procedures to amniocentesis *[10]*. Women should be on a combination antiretroviral drug regimen (e.g., at least 3 drugs), ideally with an undetectable HIV RNA level, before any procedure. Any procedure should be done under continuous ultrasound guidance, and the placenta should not be traversed during amniocentesis.

References

1. Miotti PG, Liomba G, Dallabetta GA, et al. T lymphocyte subsets during and after pregnancy: analysis in human immunodeficiency virus type 1-infected and -uninfected Malawian mothers. *J Infect Dis.* 1992;165(6):1116-1119.
2. Tuomala RE, Kalish LA, Zorilla C, et al. Changes in total, CD4+, and CD8+ lymphocytes during pregnancy and 1 year postpartum in human immunodeficiency virus-infected women. The Women and Infants Transmission Study. *Obstet Gynecol.* 1997;89(6):967-974.
3. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 58. Ultrasonography in pregnancy. *Obstet Gynecol.* 2004;104(6):1449-1458.
4. Bennett KA, Crane JM, O'Shea P, et al. First trimester ultrasound screening is effective in reducing postterm labor induction rates: a randomized controlled trial. *Am J Obstet Gynecol.* 2004;190(4):1077-1081.
5. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol.* 1996;175(3 Pt 1):661-667.
6. Shapiro DE, Sperling RS, Mandelbrot L, et al. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol.* 1999;94(6):897-908.
7. Tess BH, Rodrigues LC, Newell ML, et al. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *AIDS.* 1998;12(5):513-520.
8. Maiques V, Garcia-Tejedor A, Perales A, et al. HIV detection in amniotic fluid samples. Amniocentesis can be performed in HIV pregnant women? *Eur J Obstet Gynecol Reprod Biol.* 2003;108(2):137-141.
9. Somigliana E, Bucceri AM, Tibaldi C, et al. Early invasive diagnostic techniques in pregnant women who are infected with the HIV: a multicenter case series. *Am J Obstet Gynecol.* 2005;193(2):437-442.
10. Coll O, Suy A, Hernandez S, et al. Prenatal diagnosis in human immunodeficiency virus-infected women: a new screening program for chromosomal anomalies. *Am J Obstet Gynecol.* 2006;194(1):192-198.
11. Ekoukou D, Khuong-Josses MA, Ghibaudo N, et al. Amniocentesis in pregnant HIV-infected patients. Absence of mother-to-child viral transmission in a series of selected patients. *Eur J Obstet Gynecol Reprod Biol.* 2008;140(2):212-217.
12. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol.* 2009;200(2):160 e161-169.

SPECIAL CONSIDERATIONS REGARDING THE USE OF ANTIRETROVIRAL DRUGS BY HIV-INFECTED PREGNANT WOMEN AND THEIR INFANTS

Panel's Recommendations:

- ***All cases of antiretroviral drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com) (AIII).***
- ***Some protease inhibitors (e.g., lopinavir/ritonavir) may require altered dosing during pregnancy (see Table 5) (AIII).***
- ***Efavirenz is an FDA Pregnancy Category D drug because of animal data showing an increased risk of central nervous system (CNS) defects and a small number of concerning case reports in humans. Efavirenz should not be used in the first trimester of pregnancy and women on efavirenz should be counseled to avoid pregnancy (AIII).***
- ***Although currently published data are conflicting, clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving protease inhibitor-based combination antiretroviral therapy or prophylaxis; however, given the clear benefits of such therapy for both the woman's health and the prevention of mother-to-child transmission, protease inhibitors should not be withheld for fear of altering pregnancy outcome (AIII).***
- ***Women with CD4 counts >250 cells/mm^3 initiating nevirapine-containing regimens have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity that can be severe, life-threatening, and in some cases fatal. Pregnancy does not seem to modify this risk. Therefore, nevirapine should only be used in this setting if the benefits clearly outweigh the risks (AII). However, nevirapine-related toxicity has not been observed with use of single-dose nevirapine for prevention of mother-to-child transmission of HIV.***
- ***HIV-infected women receiving antiretroviral therapy during pregnancy should receive glucose screening with a standard, 1-hour, 50-gram glucose loading test at 24 to 28 weeks gestation (AIII). Some experts would perform earlier glucose screening in women with ongoing chronic protease inhibitor-based therapy initiated prior to pregnancy, similar to recommendations for women with high-risk factors for glucose intolerance (BIII).***

Recommendations regarding the choice of antiretroviral drugs for treatment of 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 antiretroviral drugs that may be magnified in the pregnant woman;

c. the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, including the potential for preterm birth, teratogenicity, mutagenicity, or carcinogenicity, which may not be known for certain antiretroviral drugs; and

d. the pharmacokinetics and toxicity of transplacentally transferred drugs.

Treatment recommendations for pregnant women infected with HIV have been based on the concept that therapies 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 benefit to the woman *[1]*. Pregnancy should not preclude the use of optimal therapeutic regimens. The decision to use any antiretroviral 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 antiretroviral drugs in pregnant women are more limited than in nonpregnant individuals, there are sufficient data on some of the available antiretroviral drugs to be able to provide recommendations related to drug choice. **Table 5** provides information on pharmacokinetics in pregnancy and pregnancy-related concerns for each of the available antiretroviral drugs; drugs are classified for use in pregnancy as recommended, alternative, insufficient information, or not recommended. 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.

Pharmacokinetic Changes

Physiologic changes that occur during pregnancy may 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 *[2-3]*. During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in 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 in the pregnant woman.

Currently available data on the pharmacokinetics of antiretrovirals in pregnancy are summarized in **Table 5**. In general, the pharmacokinetics of NRTI and NNRTI drugs are similar in pregnant and nonpregnant women, although protease inhibitor (e.g., lopinavir/ritonavir) pharmacokinetics are more variable, particularly in later pregnancy.

Teratogenicity

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 the 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 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 *[4]*. Limited data exist regarding placental passage, long-term animal carcinogenicity, and animal teratogenicity for the FDA-approved antiretroviral drugs (**Table 4**).

Human data on teratogenicity of FDA-approved antiretrovirals are summarized in **Table 5**. Concerns have been raised about the risk of several of the antiretroviral agents. In cynomolgus monkeys treated with efavirenz from gestational days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human therapeutic exposure, significant malformations were observed in 3 of 20 infant monkeys *[5]*. 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 July 2009, birth defects were observed in 14 (2.8%) of 501 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 *[6]*. 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 *[6]*. In addition, there have been 5 retrospectively detected cases of central nervous system defects, including myelomeningocele, in infants born to mothers receiving efavirenz during the first trimester *[5]*.

Although a causal relationship of these events to the use of efavirenz has not been established, 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 antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception. Use after the first trimester can be considered if, after consideration of other alternatives, this is the best choice for an individual woman. If efavirenz is to be continued postpartum, adequate contraception must be assured (**Table 5**).

Zalcitabine has been associated with an increased risk of hydrocephalus at very high doses in rodents and delavirdine has been associated with an increased risk of ventricular septal defects in rodents. Neither drug is currently available for use in the United States.

Tenofovir has not demonstrated teratogenicity in rodents or monkeys. At 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 756 women with first-trimester tenofovir exposure, similar to that in the general population *[6]*. However, because of the limited data on use in human pregnancy and concern regarding potential fetal bone effects and potential nephrotoxicity, tenofovir should be used as a component of maternal combination regimen only after careful consideration of alternatives (**Table 5**).

Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 4.6% (17/370), compared to a rate of 1.9% (5/257) among those with exposures later in pregnancy *[6]*. 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 to the frequency of birth defects observed in the general population and with the use of other antiretroviral 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.

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

Health care providers who are treating HIV-infected pregnant women and their newborns are strongly advised to report instances of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. This registry is an epidemiologic project to collect observational, nonexperimental data regarding antiretroviral 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.

Combination Antiretroviral Therapy and Pregnancy Outcome

Early data were conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes, in particular preterm delivery. The European Collaborative Study and the Swiss Mother + Child HIV Cohort Study investigated the effects of combination antiretroviral therapy in a population of 3,920 mother-child pairs. Adjusting for CD4 count and intravenous drug use, they found a roughly 2-fold increased odds of preterm delivery for infants exposed to combination therapy with or without protease inhibitors, compared to no treatment; women receiving combination therapy that had been initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester *[7]*. However, protease inhibitor-based combination therapy was 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 protease inhibitors more often, but their advanced HIV infection may have actually caused the preterm births). Exposure to NRTI single-drug prophylaxis (primarily zidovudine) was not associated with prematurity. An updated report from the European Collaborative Study including 2,279 mother-child pairs found, in an adjusted analysis, a 1.9-fold increased risk of delivery at less than 37 weeks with combination antiretroviral therapy started during pregnancy and 2.1-fold for combination antiretroviral therapy started prepregnancy compared to mono- or dual-NRTI prophylaxis *[8]*. In this report, 767 women received combination antiretroviral therapy during pregnancy, although the proportion receiving protease inhibitors was not specified. The risk of delivery before 34 weeks of gestation was increased by 2.5-fold for those starting combination antiretroviral therapy during pregnancy and 4.4-fold for those entering pregnancy on combination antiretroviral therapy.

In contrast, in an analysis of 7 prospective clinical studies that included 2,123 HIV-infected pregnant women who delivered infants during 1990–1998 and had received antenatal antiretroviral therapy and 1,143 women who did not receive antenatal antiretroviral therapy, the use of multiple antiretroviral drugs compared to no treatment or treatment with 1 drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth *[9]*. Nor were any significant associations between use of antiretrovirals by class or by category, including combination antiretroviral therapy, and adverse pregnancy outcome found in an analysis from the Women and Infants Transmission Study, including 2,543 HIV-infected women (some of whom were included in the previous meta-analysis) *[10]*.

More recent data have continued to be conflicting as to whether preterm delivery is increased with combination antiretroviral therapy. A prospective cohort study including 681 women from Brazil, Argentina, Mexico, and the Bahamas did not find significant associations between use of combination antiretroviral therapy and preterm birth or low birth weight *[11]*. 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

protease inhibitor-containing combination antiretroviral therapy compared to other combination therapy, after adjustment for possible confounding variables *[12]*. However, women receiving protease inhibitor-containing combination antiretroviral therapy uniformly were women with advanced disease or those who had failed other combination therapy. The risk of low birth weight and stillbirth were not increased in any therapy groups. A recent meta-analysis of 14 European and American clinical studies found no increase in risk of preterm birth with either antiretroviral therapy compared to no therapy, or combination antiretroviral therapy regimens including protease inhibitors compared to no therapy *[13]*. A slightly increased risk of preterm birth in women who received protease inhibitor combination therapy compared to combination regimens without protease inhibitors was found (OR 1.35; 95% CI, 1.08–1.70).

Other studies have detected small but significant increases (OR of 1.2–1.5 in the largest studies) in preterm birth with protease inhibitor or non-protease inhibitor-based combination antiretroviral therapy as well *[14-17]*. Another variable that may confound these observational studies is the increased rate of preterm birth if combination antiretroviral therapy is begun before conception compared to later during pregnancy, which itself may again reflect confounding by severity or indication *[18]*. When data from the IMPAACT P1025 observational cohort were examined by multivariable analysis to correct for HIV disease stage, protease inhibitor-based combination antiretroviral therapy was no more likely than non-protease inhibitor-based combination antiretroviral therapy to be associated with spontaneous preterm birth (OR 1.22; 95% CI, 0.70–2.12) *[19]*. Clinicians should be aware of a possible increased risk of preterm birth with combination antiretroviral therapy use, but 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 therapy for their HIV infection should continue their provider-recommended regimens. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

Nevirapine and Hepatic/Rash Toxicity

Increases in hepatic transaminase levels (ALT and 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 *[20]*. The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women *[21-22]*. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than men *[23-24]*. The degree of risk of hepatic toxicity also appears to vary with CD4 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, rash-associated, nevirapine-related hepatotoxicity *[23]*; a single-center study also found higher CD4 counts to be associated with increased risk of severe nevirapine-associated skin rash *[21]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 0%–11.0%) of patients who received nevirapine; severe or life-threatening rash occurred in approximately 2% of patients receiving nevirapine *[25]*.

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared to other antiretroviral drugs *[26-27]*. Recent data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy *[28]*. In an analysis of two multi-center prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 5% CI; 3.4–6.5), but nevirapine use was not, regardless of pregnancy status *[28]*. Further data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination antiretroviral therapy versus non-nevirapine-based combination antiretroviral therapy *[29]*. 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 therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through month 4, and every 1 to 3 months thereafter (see the *Hepatotoxicity* section of Table 12 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 therapy and then monthly *[20]*. 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., >5 times the upper limit of normal) should stop nevirapine and not receive nevirapine therapy in the future.

Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV *[30]*. Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well may continue therapy, regardless of CD4 count.

NRTI Drugs and Mitochondrial Toxicity

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 depletion and dysfunction *[31]*. 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 *[32]*. In a recent study, didanosine and didanosine-containing regimens were associated with the greatest degree of mitochondrial suppression *[33]*. 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 *[31]*. 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 *[34-35]*. These syndromes have similarities to rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: acute fatty liver and the syndrome of hemolysis, elevated liver enzymes, and low platelets (the 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 *[36-39]* and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity. HELLP may also occur postpartum among women with severe pre-eclampsia *[40]*. In addition to low platelets and elevated liver enzymes, other laboratory findings reported among HIV-infected pregnant women on antiretroviral therapy include mitochondrial placental depletion but without evidence of ultrastructual damage to placental cells. The clinical significance of reduced mitochondrial DNA in placentas exposed to antiretroviral drugs remains unknown *[41]*.

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 long periods (>6 months). In a report from the FDA Spontaneous Adverse Event Program, typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness *[42]*. Metabolic acidosis with elevated serum lactate and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight.

The incidence of this syndrome may be increasing, possibly as a result of increased use of combination NRTI therapy or increased recognition of the syndrome.

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 *[43]*. 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 therapy during pregnancy included stavudine and didanosine in combination with other antiretroviral agents (either a protease inhibitor or nevirapine) *[44-45]*. All women were receiving treatment with 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 in pregnant women receiving combination stavudine-didanosine also have been reported *[46]*.

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 antiretroviral combination during pregnancy. The combination stavudine-didanosine is also 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 antiretroviral drugs during pregnancy identified 8 infants with *in utero* or neonatal exposure to either zidovudine/lamivudine (4 infants) or zidovudine alone (4 infants) who developed indications of mitochondrial dysfunction after the first few months of life *[47]*. 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 *[48]*. All children had perinatal antiretroviral exposure; risk was higher among infants exposed to combination antiretroviral drugs (primarily zidovudine/lamivudine) than to zidovudine alone. The children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or episode 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* NRTI exposure *[49-50]*. 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 (0.30.5%) *[51]*.

Clinical studies in the United States and Europe generally have not duplicated the French reports *[52-58]*. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring

among children born to HIV-infected women and followed during 1986–1999 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 >16,000 uninfected children born to HIV-infected women with and without antiretroviral drug exposure *[53]*. However, most of the infants with antiretroviral exposure 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 antiretroviral exposure *[55]*. No association of clinical manifestations suggestive of mitochondrial abnormalities was found with perinatal antiretroviral exposure. Of the 4 children with seizures in this cohort, none had perinatal antiretroviral exposure. 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 *[57]*. Definitive diagnosis was not available because none of the children had biopsies for mitochondrial function. Three of the 20 children had no exposure to antiretroviral drugs. In the 17 remaining children, although overall exposure to NRTI drugs was not associated with symptoms, there was an association of symptoms with first exposure to zidovudine/lamivudine limited to the third trimester.

Laboratory abnormalities without clinical symptoms have been reported among infants with perinatal antiretroviral exposure compared to unexposed infants in a number of studies, most of which are limited by small numbers of subjects. In 1 study, mitochondrial DNA quantity was lower in cord and peripheral blood white cells at age 1 and 2 years among 20 infants born to HIV-infected women compared to 30 infants born to uninfected women and was lowest among 10 HIV-exposed infants with zidovudine exposure compared to 10 without zidovudine exposure *[59]*. 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 *[60]*. Similar morphologic changes and mitochondrial DNA 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 antiretroviral-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 mitochondrial DNA levels were higher and blood mitochondrial RNA levels were lower in the HIV- and antiretroviral-exposed infants compared to infants without HIV and antiretroviral exposure *[61]*. In another study, transient hyperlactatemia during the first few weeks of life was reported among 17 HIV-exposed infants with perinatal antiretroviral exposure; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up *[62]*. Similarly, the French Perinatal cohort study has reported asymptomatic hyperlactatemia in one-third of zidovudine-exposed newborns, which resolved following perinatal drug exposure *[51]*. Clinically asymptomatic hematologic findings have been reported by several investigators among uninfected infants with *in utero* exposure to antiretroviral therapy in the United States and Europe *[63-65]*, and infants with triple combination antiretroviral therapy exposure were found to be at increased risk of lowered hemoglobin compared to those with perinatal exposure to zidovudine or zidovudine/lamivudine *[66]*. The clinical significance of these 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 antiretroviral therapy.

Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure, 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 compared to the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more *[55, 67-68]*. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings. These results emphasize the importance of the

existing HHS recommendation for long-term follow-up for any child with *in utero* exposure to antiretroviral drugs.

Protease Inhibitor Therapy and Hyperglycemia

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with receipt of protease inhibitor antiretroviral drugs by HIV-infected patients *[69-72]*. In addition, pregnancy is itself a risk factor for hyperglycemia. However, the majority of data to date have not shown an increased risk of glucose intolerance with protease inhibitor therapy during pregnancy. One small retrospective study that included 41 women receiving protease inhibitor-based combination antiretroviral therapy found an increased risk of glucose intolerance, but not gestational diabetes, among women on combination antiretroviral therapy compared to zidovudine alone *[73]*, while two other retrospective studies did not find an increased risk of glucose intolerance with protease inhibitors *[74-75]*. Secondary analyses of two large cohorts did not find an association with type of antiretroviral therapy and gestational diabetes, except for an association of protease inhibitor initiation before pregnancy or during the first trimester and gestational diabetes in the PACTG 316 cohort *[10, 76]*. 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 protease inhibitor-containing and non-protease inhibitor-containing regimens *[77]*. The rate of impaired glucose tolerance was high (38%) in both groups, likely related to high body mass index and race/ethnicity among trial subjects.

HIV-infected women receiving antiretroviral therapy during pregnancy should receive standard glucose screening with a standard, 1-hour, 50-gram glucose loading test at 24 to 28 weeks of gestation. Some experts would perform earlier glucose screening in women with ongoing protease inhibitor-based therapy initiated prior to 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.

References

1. Minkoff H, Augenbraun M. Antiretroviral therapy for pregnant women. *Am J Obstet Gynecol.* 1997;176(2):478-489.
2. Mirochnick M, Capparelli E. Pharmacokinetics of antiretrovirals in pregnant women. *Clin Pharmacokinet.* 2004;43(15):1071-1087.
3. Roustit M, Jlaiel M, Leclercq P, et al. Pharmacokinetics and therapeutic drug monitoring of antiretrovirals in pregnant women. *Br J Clin Pharmacol.* 2008;66(2):179-195.
4. Mills JL. Protecting the embryo from X-rated drugs. *N Engl J Med.* 1995;333(2):124-125.
5. Bristol-Myers Squibb. Sustiva drug label, 9/23/2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020972s033,021360s021lbl.pdf.
6. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
7. European Collaborative Study, Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS.* 2000;14(18):2913-2920.
8. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS.* 2004;18(17):2337-2339.
9. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med.* 2002;346(24):1863-1870.
10. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr.* 2005;38(4):449-473.
11. Szyld EG, Warley EM, Freimanis L, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. *AIDS.* 2006;20(18):2345-2353.

12. Cotter AM, Garcia AG, Duthely ML, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis.* 2006;193(9):1195-1201.
13. Kourtis AP, Schmid CH, Jamieson DJ, et al. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS.* 2007;21(5):607-615.
14. Townsend CL, Cortina-Borja M, Peckham CS, et al. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS.* 2007;21(8):1019-1026.
15. Schulte J, Dominguez K, Sukalac T, et al. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989-2004. *Pediatrics.* 2007;119(4):e900-906.
16. Ravizza M, Martinelli P, Bucceri A, et al. Treatment with protease inhibitors and coinfection with hepatitis C virus are independent predictors of preterm delivery in HIV-infected pregnant women. *J Infect Dis.* 2007;195(6):913-914; author reply 916-917.
17. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. *HIV Med.* 2008;9(1):6-13.
18. Machado ES, Hofer CB, Costa TT, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. *Sex Transm Infect.* 2009;85(2):82-87.
19. Patel K, Shapiro DE, Brogly SB, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis.* 2010;201(7):1035-1044.
20. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003;23(2):173-182.
21. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* 2001;32(1):124-129.
22. Mazhude C, Jones S, Murad S, et al. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS.* 2002;16(11):1566-1568.
23. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
24. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S21-33.
25. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. Revised June 24, 2008.
26. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med.* 2006;7(4):255-260.
27. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr.* 2004;36(3):772-776.
28. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS.* 2009;23(18):2425-2430.
29. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS.* 2010;24(1):109-114.
30. McKoy JM, Bennett CL, Scheetz MH, et al. Hepatotoxicity associated with long- versus short-course HIV-prophylactic nevirapine use: a systematic review and meta-analysis from the Research on Adverse Drug events And Reports (RADAR) project. *Drug Saf.* 2009;32(2):147-158.
31. Brinkman K, Ter Hofstede HJM, Burger DM, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS.* 1998;12(14):1735-1744.
32. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother.* 2002;46(3):716-723.
33. Saitoh A, Haas RH, Naviaux RK, et al. Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells. *Antimicrob Agents Chemother.* 2008;52(8):2825-2830.
34. Currier JS. Sex differences in antiretroviral therapy toxicity: lactic acidosis, stavudine, and women. *Clin Infect Dis.* 2007;45(2):261-262.
35. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis.* 2007;45(2):254-260.
36. Ibdah JA, Bennett MJ, Rinaldo P, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med.* 1999;340(22):1723-1731.

37. Strauss AW, Bennett MJ, Rinaldo P, et al. Inherited long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and a fetal-maternal interaction cause maternal liver disease and other pregnancy complications. *Semin Perinatol.* 1999;23(2):100-112.
38. Sims HF, Brackett JC, Powell CK, et al. The molecular basis of pediatric long-chain 3-hydroxyacyl Co-A dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. *Proc Natl Acad Sci USA.* 1995;92(3):841-845.
39. Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab.* 2000;71(1-2):182-189.
40. Gasem T, Al Jama FE, Burshaid S, et al. Maternal and fetal outcome of pregnancy complicated by HELLP syndrome. *J Matern Fetal Neonatal Med.* 2009;22(12):1140-1143.
41. Gingelmaier A, Grubert TA, Kost BP, et al. Mitochondrial toxicity in HIV type-1-exposed pregnancies in the era of highly active antiretroviral therapy. *Antivir Ther.* 2009;14(3):331-338.
42. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis.* 2004;38(8):e79-80.
43. Luzzati, R. Del Bravo, P. Di Perri, G. Luzzani, A. Concia, E. Riboflavine and severe lactic acidosis. *Lancet.* 1999;353(9156):901-902.
44. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
45. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-59.
46. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS.* 2003;17(2):272-273.
47. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354(9184):1084-1089.
48. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS.* 2003;17(12):1769-1785.
49. Landreau-Mascaro A, Barret B, Mayaux MJ, et al. Risk of early febrile seizure with perinatal exposure to nucleoside analogues. *Lancet.* 2002;359(9306):583-584.
50. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS.* 2003;17(14):2053-2061.
51. Benhammou V, Tardieu M, Warszawski J, et al. Clinical mitochondrial dysfunction in uninfected children born to HIV-infected mothers following perinatal exposure to nucleoside analogues. *Environ Mol Mutagen.* 2007;48(3-4):173-178.
52. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trials Group 076 Study. *AIDS.* 1998;12(14):1805-1813.
53. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. *J Acquir Immune Defic Syndr.* 2000;25(3):261-268.
54. Lipshultz SE, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. *N Engl J Med.* 2000;343(11):759-766.
55. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;32(4):380-387.
56. Alimenti A, Forbes JC, Oberlander TF, et al. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. *Pediatrics.* 2006;118(4):e1139-1145.
57. Brogly SB, Ylitalo N, Mofenson LM, et al. In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. *AIDS.* 2007;21(8):929-938.
58. Hankin C, Lyall H, Peckham C, et al. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. *AIDS.* 2007;21(7):867-869.
59. Poirier MC, Divi RL, Al-Harthi L, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr.* 2003;33(2):175-183.
60. Divi RL, Leonard SL, Kuo MM, et al. Transplacentally exposed human and monkey newborn infants show similar evidence of nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity. *Environ Mol Mutagen.* 2007;48(3-4):201-209.
61. Cote HC, Raboud J, Bitnun A, et al. Perinatal exposure to antiretroviral therapy is associated with increased blood mitochondrial DNA levels and decreased mitochondrial gene expression in infants. *J Infect Dis.* 2008;198(6):851-859.

62. Giaquinto C, De Romeo A, Giacomet V, et al. Lactic acid levels in children perinatally treated with antiretroviral agents to prevent HIV transmission. *AIDS.* 2001;15(8):1074-1075.
63. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis.* 2006;194(8):1089-1097.
64. European Collaborative Study. Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-1-infected mothers. *AIDS.* 2004;18(15):2009-2017.
65. Bunders M, Thorne C, Newell ML, et al. Maternal and infant factors and lymphocyte, CD4 and CD8 cell counts in uninfected children of HIV-1-infected mothers. *AIDS.* 2005;19(10):1071-1079.
66. Feiterna-Sperling C, Weizsaecker K, Buhrer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr.* 2007;45(1):43-51.
67. Morris AA, Carr A. HIV nucleoside analogues: new adverse effects on mitochondria? *Lancet.* 1999;354(9184):1046-1047.
68. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
69. Food and Drug Administration. FDA Public Health Advisory: reports of diabetes and hyperglycemia in patients receiving protease inhibitors for treatment of human immunodeficiency virus (HIV). Food and Drug Administration, Public Health Service, Department of Health and Human Services. Rockville, MD: June 11, 1997.
70. Visnegarwala F, Krause KL, Musher DM. Severe diabetes associated with protease inhibitor therapy. *Ann Intern Med.* 1997;127(10):947.
71. Eastone JA, Decker CF. New-onset diabetes mellitus associated with use of protease inhibitor [letter]. *Ann Intern Med.* 1997;127(10):948.
72. Dube MP, Sattler FR. Metabolic complications of antiretroviral therapies. *AIDS Clin Care.* 1998;10(6):41-44.
73. Chmait R, Franklin P, Spector SA, et al. Protease inhibitors and decreased birth weight in HIV-infected pregnant women with impaired glucose tolerance. *J Perinatol.* 2002;22(5):370-373.
74. Dinsmoor MJ, Forrest ST. Lack of an effect of protease inhibitor use on glucose tolerance during pregnancy. *Infect Dis Obstet Gynecol.* 2002;10(4):187-191.
75. Tang JH, Sheffield JS, Grimes J, et al. Effect of protease inhibitor therapy on glucose intolerance in pregnancy. *Obstet Gynecol.* 2006;107(5):1115-1119.
76. Watts DH, Balasubramanian R, Maupin RT, Jr., et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *Am J Obstet Gynecol.* 2004;190(2):506-516.
77. Hitti J, Andersen J, McComsey G, et al. Protease inhibitor-based antiretroviral therapy and glucose tolerance in pregnancy: AIDS Clinical Trials Group A5084. *Am J Obstet Gynecol.* 2007;196(4):331.e331-337.

ANTIRETROVIRAL DRUG RESISTANCE AND RESISTANCE TESTING IN PREGNANCY

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

Panel's Recommendations:

- ***HIV drug resistance testing is recommended for:***
  - ***All pregnant women not currently receiving antiretroviral drugs, before starting treatment or prophylaxis (AIII).***
  - ***All pregnant women receiving antenatal antiretroviral therapy who have persistently detectable HIV RNA levels (AI) or who have suboptimal viral suppression after initiation of antiretroviral therapy (AII).***
- ***For optimal prevention of perinatal transmission, empiric initiation of antiretroviral therapy before results of resistance testing are available may be warranted, with adjustment as needed after the test results are available (BIII).***

Resistance testing is recommended for all antiretroviral-naïve pregnant women 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 be done at a preconception visit to allow receipt of results and selection of an antiretroviral drug regimen to be used during pregnancy or started before pregnancy if maternal therapy is indicated. There is accumulating evidence that:

- transmitted resistant mutants may persist for indefinite periods after initial infection;
- these viral variants may be detectable by standard assays used in clinical practice;
- the prevalence of resistance in antiretroviral-naïve patients is increasing; and
- previous resistance may be associated with adverse virologic outcomes *[1-8]*.

For these reasons, resistance testing is now recommended for all pregnant women prior to initiating antiretroviral drugs for treatment or prophylaxis of mother-to-child transmission of HIV *[9-10]*.

Resistance testing should also be performed before initiation of therapy or prophylaxis in pregnant women who received prophylaxis in previous pregnancies and are now restarting antiretroviral drugs for prevention of perinatal transmission. There are no data currently addressing the utility of resistance testing in the setting of pregnancy, when short-term prophylactic therapy is often initiated in women who do not yet need treatment for their own disease, and women who have multiple pregnancies may undergo several periods of antiretroviral prophylaxis to prevent mother-to-child transmission. The identification of baseline resistance mutations may allow selection of more effective and more durable antiretroviral regimens in women needing treatment and greater preservation of future treatment options in women receiving antiretroviral therapy only for perinatal prophylaxis. However, there is no evidence that baseline resistance testing in pregnancy is associated with a reduction in perinatal transmission rates.

For pregnant women already receiving antiretroviral therapy at the time they present for obstetrical care or are seen for follow-up after initiation of therapy, resistance testing is indicated if there is suboptimal initial viral suppression following initiation of antiretroviral therapy or virologic failure on the current regimen as signified by persistently detectable HIV RNA levels.

In most settings, the results of resistance testing guide selection of the initial antiretroviral regimen. However, in some clinical situations, the clinician may choose to initiate empiric antiretroviral therapy or prophylaxis before resistance testing results are available in order to maximize prevention of perinatal transmission. Once resistance test results are obtained, the antiretroviral drug regimen may be modified as needed. Such situations

include when women have initial resistance testing in the third trimester and test results may not be back in time to allow effective reduction of viral load before delivery. If results of resistance testing performed in the latter half of a woman's pregnancy cannot be obtained within 7 days, most experts believe that the benefits of immediate initiation of antiretroviral drugs—taking into account a woman's previous antiretroviral history—outweigh the possible risk of initiating a regimen that could be suboptimal due to pre-existing resistance.

Significance of Antiretroviral Drug Resistance in Pregnancy

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV-infected persons. Resistant viral variants emerge under selective pressure, especially with incompletely suppressive regimens, because of the mutation-prone process of reverse transcription in viral replication. Although specific resistance mutations may become undetectable when selective drug pressure is removed, resistant viral variants are believed to be archived permanently in latent HIV reservoirs and can re-emerge with re-exposure to drugs to which decreased susceptibility had been established *[11]*. The administration of combination antiretroviral regimens with maximal suppression of viral replication to undetectable levels limits the development of antiretroviral resistance in both pregnant and nonpregnant persons.

In addition to the concerns about development of drug resistance in the general population, pregnancy presents some special concerns related to the development of drug resistance. Pre-existing resistance to a drug in an antiretroviral prophylaxis regimen may diminish efficacy of that regimen in preventing perinatal transmission. 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 future pregnancies. Additionally, if maternal resistance is present or develops and resistant virus is transmitted, infant treatment options may be limited.

Several factors unique to pregnancy may increase the chance of development of resistance. Antiretroviral drugs may be used during pregnancy solely for prophylaxis of perinatal transmission and discontinued after delivery in women who do not require therapy for their own health. If regimens used for prophylaxis include drugs with significant differences in half-life, such as nevirapine or efavirenz combined with two nucleoside analogue drugs, discontinuation of all regimen components simultaneously postpartum may result in persistent subtherapeutic drug levels and increase the risk of development of 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 antiretroviral treatment.

Prevalence of Antiretroviral Drug Resistance

General Population

The reported prevalence of antiretroviral drug resistance varies depending on several factors, including characteristics of the population studied (e.g., newly infected versus chronically infected), prior and current exposure to antiretroviral drugs and type of regimen (HAART versus non-HAART), geographic area, and type of resistance assay used (genotypic versus phenotypic). In genotypic resistance surveys of newly infected, therapy-naïve persons conducted in the United States and Europe, rates of primary resistance mutations appear to be increasing over time and have been reported as high as 23% *[5, 12-13]*. The presence of high-level phenotypic resistance (>10-fold increase in 50% inhibitory concentration [IC50]) increased from 3.4% in 1995–1998 to 12.4% in 1999–2000 in a retrospective analysis from 10 U.S. cities and was associated with longer time to viral suppression and shorter time to virologic failure *[12]*.

Other studies have examined antiretroviral drug resistance in treatment-naïve persons with newly diagnosed HIV infection of unknown duration. In this population more typical of patients presenting for initial evaluation and care, 8.3% to 10.8% of patients had HIV with genotypic mutations associated with reduced antiretroviral

susceptibility, with prevalence increasing over time *[4-5]*. The highest rates of antiretroviral drug resistance have been reported in antiretroviral treatment-experienced individuals, with resistance rates as high as 88% reported in viremic individuals currently receiving therapy and 30% in individuals with a past history of treatment *[14]*.

Pregnancy

Data about the prevalence of antiretroviral drug resistance in pregnant women are limited. The available data suggest that rates of resistance are similar in pregnant women and in nonpregnant individuals, with antiretroviral drug resistance more frequent among antiretroviral-experienced women. A study from a university hospital in St. Louis found that 3 (17%) of 18 antiretroviral-naïve pregnant women followed at the hospital had primary genotypic resistance to NNRTI drugs, which was equal to the overall prevalence of such resistance in the antiretroviral-naïve population in the same city *[15]*. In a retrospective review of 45 consecutive HIV-infected pregnant women with amplifiable virus presenting for care in New York, 0 of 22 antiretroviral-naïve pregnant women and 11 (48%) of 23 antiretroviral-experienced women had major drug resistance mutations *[16]*. Among 220 pregnant antiretroviral-experienced women in the Perinatal AIDS Collaborative Transmission Study (PACTS), all of whom had prior zidovudine exposure in pregnancy from 1991 to 1997, 17.3% had zidovudine-associated mutations *[17]*. In a substudy of the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 316, an international, multi-center clinical trial comparing single-dose nevirapine with placebo in HIV-infected pregnant women receiving standard antiretroviral therapy, 7 (3.2%) of 217 women with detectable HIV RNA had mutations associated with nevirapine resistance at 6 weeks postpartum, despite no history of prior exposure to non-nucleoside drugs or receipt of nevirapine at delivery *[18]*. Additionally, more than 60% of women receiving combination therapy (either dual nucleosides or combinations containing a PI) had the M184V mutation conferring resistance to lamivudine, and 25 (11%) of 217 women had primary or secondary protease mutations.

Despite the increasing prevalence of drug resistance in treatment-naïve and -experienced individuals, there is currently no evidence to indicate on a population basis that antiretroviral drug resistance in HIV-infected pregnant women is compromising the efficacy of perinatal HIV prevention efforts in North America or Europe, where mother-to-child transmission rates remain less than 2% *[19-20]*.

Incidence of Antiretroviral Resistance with Perinatal Prophylactic Regimens

The presence of mutations conferring resistance to nucleoside analogue drugs appears to be correlated with more advanced maternal disease and duration of prior or current exposure to these drugs *[17, 21-23]*. Development of zidovudine drug resistance when zidovudine is used alone appears uncommon in women with higher CD4 count and low viral load *[24-25]* but is more of a concern in women who have more advanced disease and lower CD4 count *[21]*.

Nevirapine also has a low genetic barrier to resistance, with 1 point mutation conferring resistance to nevirapine and to other 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 risk of resistance *[26]*. Factors associated with increased risk of resistance following single-dose nevirapine exposure include high baseline viral load, low baseline CD4 cell count, viral subtype, and number of maternal doses. The rate of genotypic resistance after exposure to single-dose nevirapine has varied in studies, ranging from 15% to 75% *[18, 27-36]*. 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 *[35-38]*. However, these studies demonstrate that although resistance occurs in the first few weeks post-exposure in the majority of women exposed to single-dose nevirapine, 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; additionally, archiving of resistance in cellular provirus may be infrequent. 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. The K103N mutation was found in cellular DNA in only 4.2% of women at 12 months post-exposure *[38]*. A recent study has examined the presence of resistant mutations in HIV-1-infected women receiving antiretrovirals limited to pregnancy. All women evaluated received zidovudine and lamivudine with 76% receiving nelfinavir and 8% nevirapine. In women receiving dual or triple prophylaxis, postpartum rates of the M184V/I mutations were 65% and 29%, respectively. NNRTI resistance was identified postpartum among 38% of nevirapine recipients, whereas only 1% of PI recipients developed resistance *[39]*.

Addition of single-dose nevirapine to other background regimens (77% of women received antenatal combination antiretroviral therapy) still resulted in nevirapine resistance in 14 of 95 (15%; 95% CI, 8%–23%) women in the PACTG 316 study *[18]*. Because PACTG 316 demonstrated that the addition of single-dose nevirapine in situations where combination antiretroviral therapy is being received did not provide any additional efficacy in prevention of mother-to-child transmision, and because there is a risk of nevirapine resistance, this approach is not recommended.

Impact of Resistance in Pregnancy

Perinatal Transmission

Although perinatal transmission of resistant virus has been reported, it appears to be unusual, and there is little evidence that the presence of resistant mutations increases the risk of transmission when current recommendations for antiretroviral management in pregnancy are followed. A substudy of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV disease in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count *[21]*; however, women in this cohort had characteristics that would indicate treatment with combination antiretroviral therapy under the current 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 found in the infant *[40]*, and other studies have suggested that drug resistance mutations may diminish the fitness of the virus *[41]*, possibly leading to a decrease in transmissibility. The prevalence of antiretroviral drug resistance was examined among HIV-infected newborns in New York State. Eleven (12.1%) of 91 infants born in 1989–1999 and 8 (19%) of 42 infants born in 2001–2002 had mutations associated with decreased drug susceptibility. However, perinatal antiretroviral exposure was not found to be a significant risk factor for the presence of resistance in either time period *[42-43]*. 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 *[44-45]*.

Maternal Response to Subsequent Treatment Regimens

Because nevirapine resistance mutations can be detected in the postpartum period in a significant proportion of women receiving single-dose intrapartum/infant nevirapine prophylaxis, the response to non-nucleoside-based combination therapy when later required for maternal health reasons has been a concern *[30, 38, 44-47]*. The Optimal Combination Therapy After Nevirapine Exposure (OCTANE)/A5208 trial conducted in Africa compared nevirapine versus 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 higher risk of viral failure with nevirapine-based therapy compared to lopinavir/ritonavir-based therapy. In this study, significantly more women in the nevirapine arm (29, 24%) failed to achieve undetectable viral load (25) or died (4) compared to women in the lopinavir/ritonavir arm (8, 7%; 7 virologic failures and 1 death; $p < 0.0005$). Of those women with documented nevirapine resistance at the start of therapy, 38% (5 of 13) either had detectable virus or died. One caveat to the OCTANE study, however, is that the women who received lopinavir/ritonavir had a 93%

rate of viral suppression, a percentage substantially greater than that found in comparable studies. However, this study further supports 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) *[48]*.

There are few data evaluating response to subsequent therapy in women who receive current combination drug regimens for prophylaxis and discontinue the drugs postpartum. However, if the regimen that was discontinued had fully suppressed viral replication, theoretically, resistance should not occur. Issues relating to discontinuation of nevirapine-based combination therapy are discussed in the section **Prevention of Antiretroviral Drug Resistance**.

Management of Antiretroviral Drug Resistance during Pregnancy

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 regimens and postnatal oral zidovudine for their infants (AII). For women who are receiving a stavudine-containing regimen, stavudine should be discontinued during labor while intravenous zidovudine is being administered (see Intrapartum Care).***
- ***The optimal prophylactic regimen for newborns of women with antiretroviral resistance is unknown (see Infant Antiretroviral Prophylaxis). Therefore, antiretroviral 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, antiretroviral regimens used during pregnancy for treatment or prophylaxis should be chosen based on the results of antiretroviral resistance testing. However, antiretroviral drugs are also used during pregnancy for prevention of mother-to-child transmission. Although most transmission occurs during the intrapartum period, 30% to 35% of transmission may occur *in utero [49-51]*; the majority of *in utero* infection is thought to occur later in pregnancy *[49]* and may be more likely in women with advanced HIV disease and/or high viral load *[50-51]*. Therefore, delay in initiation of an antiretroviral 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 antiretroviral prophylaxis may be warranted to maximize prevention of perinatal transmission, with the regimen modified if needed once resistance testing results become available.

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, intravenous zidovudine during labor should still be administered whenever possible (see **Intrapartum Care**). If the woman's antepartum regimen includes stavudine, which may be antagonistic to zidovudine, stavudine should be stopped during the intrapartum period and restarted after delivery (see **Intrapartum Care**). Other antiretrovirals should be continued orally during labor to the extent possible. Zidovudine should also be administered orally to the infant for 6 weeks. For an infant born to a woman with known zidovudine-resistant virus, many clinicians would choose to provide additional antiretroviral agents to the infant in combination with zidovudine (see **Infant Antiretroviral Prophylaxis**). Such a decision must be accompanied by a discussion with the woman of the potential benefits and risks of this approach and the lack of data to address its efficacy and safety. The optimal prophylactic regimen for newborns of women with antiretroviral drug-resistant virus is unknown. Therefore, antiretroviral prophylaxis for the infant born to a woman with known or suspected drug-resistant virus should be determined with a pediatric HIV specialist, preferably before delivery.

The rationale for including zidovudine intrapartum and to the infant when a woman is known to harbor virus with zidovudine resistance is based on several factors. Data thus far have suggested that when mothers have mixed populations of wild-type virus and virus with low-level zidovudine resistance, only wild-type virus is

found in the infant *[40]*. Other studies have suggested that drug resistance mutations may diminish viral fitness and possibly decrease transmissibility *[41]*. Efficacy of the zidovudine prophylaxis appears to be based not only on reduction of HIV levels in the mother but also on pre- and post-exposure prophylaxis in the infant *[52-54]*. Zidovudine crosses the placenta readily and has one of the highest maternal-to-cord blood ratios among the nucleoside analogue agents. Additionally, zidovudine is metabolized to the active triphosphate within the placenta *[55-56]*, 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) *[57-58]*. In addition, zidovudine has been shown to reduce genital HIV RNA levels, and genital viral levels have been shown to correlate with perinatal transmission *[59]*. Data on levels of other nucleoside analogues in the genital tract are more limited, and it is unknown if other nucleoside analogue agents will provide a similar reduction in genital tract HIV RNA levels *[60-62]*. Zidovudine has better penetration into the central nervous system (CNS) compared to other nucleoside analogues with the exception of stavudine, whose CNS penetration is similar; this may help to eliminate a potential reservoir for transmitted HIV in the infant *[63-64]*. Thus, intravenous intrapartum and oral zidovudine for the infant should be included even in the presence of known zidovudine resistance because of the unique characteristics of zidovudine and its proven record in reducing perinatal transmission.

Prevention of Antiretroviral Drug Resistance

Panel's Recommendations:

- ***HIV-infected pregnant women should use combination antiretroviral drug regimens to maximally suppress viral replication; this is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission (AII).***
- ***All pregnant women should be counseled about the importance of adherence to prescribed antiretroviral medications to reduce the potential for development of resistance (AII).***
- ***For pregnant women receiving an NNRTI-based combination antiretroviral therapy regimen for prophylaxis only, with plans to discontinue therapy after delivery, the nucleoside analogue agents should be given for at least 7 days after stopping the NNRTI to minimize the risk of resistance (AI). An alternative strategy is to substitute a PI for the NNRTI prior to the interruption and to continue the PI with dual NRTIs. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days. (CIII) (See Stopping Antiretroviral Therapy during Pregnancy and Postpartum Follow-Up of HIV-Infected Women.)***
- ***The addition of single-dose maternal/infant nevirapine to an ongoing combination antiretroviral treatment or prophylaxis regimen does not provide additional 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 antiretroviral drug resistance in pregnancy is to use and adhere to an effective combination of antiretroviral drugs to achieve maximal viral suppression. Selection of a regimen should take into account prior antiretroviral treatment history, including documented clinical, immunologic, or virologic failure with or without genotypic or phenotypic resistance testing; history of nonadherence; and problems with intolerance.

When nevirapine or other NNRTI drugs are used as part of a prophylactic combination antiretroviral regimen that is stopped after delivery, there is a risk of development of NNRTI resistance because of the drug's prolonged half-life, leading to a period of persistent subtherapeutic levels of a single drug if all drugs are discontinued at once. Studies in South Africa and Cote d'Ivoire have shown that the development of

nevirapine resistance following exposure to single-dose intrapartum nevirapine (given alone or in combination with antenatal antiretroviral therapy) was significantly decreased (but not eliminated) if zidovudine/lamivudine was given intrapartum and administered for 3 to 7 days postpartum after intrapartum nevirapine *[65-66]*. In a cohort of 39 women who initiated combination antiretroviral therapy in pregnancy and had genotypic testing performed at 6 weeks postpartum, 5 (13%) had primary mutations detected *[31]*. All 5 were on combination regimens that included nevirapine, were treatment naïve prior to pregnancy, and had staggered drug discontinuation after delivery (the dual nucleoside component of the regimen was continued for 5 days after stopping nevirapine). It is not known whether the incidence of resistance would have been significantly higher if drug discontinuation had not been staggered. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time *[67]*. The optimal duration needed to continue either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is not known. NNRTI drugs have long half-lives, and drug levels can persist for up to 1 to 3 weeks after stopping the drug; efavirenz levels persist longer than nevirapine levels *[26, 68]*. Further 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 following discontinuation of NNRTI-based therapy. Many experts will stop the NNRTI drug and continue the other antiretroviral drugs for at least 7 days, although other experts would recommend up to 30 days, particularly if an efavirenz-based regimen is being stopped.

References

1. Pao D, Andrady U, Clarke J, et al. Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. *J Acquir Immune Defic Syndr.* 2004;37(5):1570-1573.
2. Barbour JD, Hecht FM, Wrin T, et al. Persistence of primary drug resistance among recently HIV-1-infected adults. *AIDS.* 2004;18(12):1683-1689.
3. Ghosn J, Pellegrin I, Goujard C, et al. HIV-1 resistant strains acquired at the time of primary infection massively fuel the cellular reservoir and persist for lengthy periods of time. *AIDS.* 2006;20(2):159-170.
4. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):468-474.
5. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistence among drug-naïve HIV-1 infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
6. Wensing AM, van de Vijver D, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
7. Metzner KJ, Rauch P, Walter H, et al. Detection of minor populations of drug-resistant HIV-1 in acute seroconverters. *AIDS.* 2005;19(16):1819-1825.
8. Derdelinckx I, Van Laethem K, Maes B, et al. Current levels of drug resistance among therapy-naïve patients have significant impact on treatment response. *J Acquir Immune Defic Syndr.* 2004;37(5):1664-1666.
9. Hecht FM, Grant RM. Resistance testing in drug-naïve HIV-infected patients: is it time? *Clin Infect Dis.* 2005;41(9):1324-1325.
10. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naïve HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis.* 2005;41(9):1316-1323.
11. Siliciano JD, Siliciano RF. A long-term latent reservoir for HIV-1: discovery and clinical implications. *J Antimicrob Chemother.* 2004;54(1):6-9.
12. Little SJ, Holte S, Routy JP, et al. Antiretroviral drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002;347(6):385-394.
13. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA.* 1999;282(12):1135-1141.
14. Richman DD, Morton SC, Wrin T, et al. The prevalence of antiretroviral drug resistance in the United States. *AIDS.* 2004;18(10):1393-1401.
15. Juethner SN, Williamson C, Ristig MB, et al. Nonnucleoside reverse transcriptase inhibitor resistance among antiretroviral-naive HIV-positive pregnant women. *J Acquir Immune Defic Syndr.* 2003;32(2):153-156.

16. Shah SS, Crane M, Monaghan K, et al. Genotypic resistance testing in HIV-infected pregnant women in an urban setting. *Int J STD AIDS.* 2004;15(6):384-387.
17. Palumbo P, Holland B, Dobbs T, et al. Antiretroviral resistance mutations among pregnant human immunodeficiency virus type 1-infected women and their newborns in the United States: vertical transmission and clades. *J Infect Dis.* 2001;184(9):1120-1126.
18. Cunningham CK, Chaix ML, Rekacewica C, et al. Development of resistance mutations in women on standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal HIV-1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis.* 2002;186(2):181-188.
19. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
20. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):458-465.
21. Welles SL, Pitt J, Colgrove R, et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal-infant transmission in the Women and Infants Transmission Study Group. *AIDS.* 2000;14(3):263-271.
22. Kully C, Yerly S, Erb P, et al. Codon 215 mutations in human immunodeficiency virus-infected pregnant women. *J Infect Dis.* 1999;179(3):705-708.
23. Sitnitskaya Y, Rochford G, Rigaud M, et al. Prevalence of the T215Y mutation in human immunodeficiency virus type 1-infected pregnant women in a New York cohort, 1995-1999. *Clin Infect Dis.* 2001;33(1):e3-7.
24. Eastman PS, Shapiro DE, Coombs RW, et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in Pediatric AIDS Clinical Trial Group Protocol 076. *J Infect Dis.* 1998;177(3):557-564.
25. Larbalestier N, Mullen J, O'Shea S, et al. Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS.* 2003;17(18):2665-2671.
26. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
27. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS.* 2001;15(15):1951-1957.
28. Eshleman SH, Guay LA, Mwatha A, et al. Characterization of nevirapine resistance mutations in women with subtype A vs. D HIV-1 6-8 weeks after single-dose nevirapine (HIVNET 012). *J Acquir Immune Defic Syndr.* 2004;35(2):126-130.
29. Sullivan J. South African Intrapartum Nevirapine Trial: selection of resistance mutations. Paper presented at: XIV International Conference on AIDS; July 7-12, 2002; Barcelona, Spain.
30. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
31. Lyons FE, Coughlan S, Byrne CM, et al. Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *AIDS.* 2005;19(1):63-67.
32. Eshleman SH, Becker-Pergola G, Deseyve M, et al. Impact of human immunodeficiency virus type 1 (HIV-1) subtype on women receiving single-dose nevirapine prophylaxis to prevent HIV-1 vertical transmission (HIV network for prevention trials 012 study). *J Infect Dis.* 2001;184(7):914-917.
33. Servais J, Lambert C, Karita E, et al. HIV type 1 pol gene diversity and archived nevirapine resistance mutation in pregnant women in Rwanda. *AIDS Res Hum Retroviruses.* 2004;20(3):279-283.
34. Eshleman SH, Guay LA, Mwatha A, et al. Comparison of nevirapine (NVP) resistance in Ugandan women 7 days vs. 6-8 weeks after single-dose nvp prophylaxis: HIVNET 012. *AIDS Res Hum Retroviruses.* 2004;20(6):595-599.
35. Eshleman SH, Hoover DR, Chen S, et al. Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *J Infect Dis.* 2005;192(1):30-36.
36. Johnson JA, Li JF, Morris L, et al. Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *J Infect Dis.* 2005;192(1):16-23.

37. Flys T, Nissley DV, Claasen CW, et al. Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012. *J Infect Dis.* 2005;192(1):24-29.
38. Loubser S, Balfe P, Sherman G, et al. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother to child HIV transmission. *AIDS.* 2006;20(7):995-1002.
39. Paredes R, Cheng I, Kuritzkes DR, et al. Postpartum antiretroviral drug resistance in HIV-1-infected women receiving pregnancy-limited antiretroviral therapy. *AIDS.* 2010;24(1):45-53.
40. Colgrove RC, Pitt J, Chung PH, et al. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS.* 1998;12(17):2281-2288.
41. Nijhuis M, Deeks S, Boucher C. Implications of antiretroviral resistance on viral fitness. *Curr Opin Infect Dis.* 2001;14(1):23-28.
42. Parker M, Wade N, Lloyd RM, Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *J Acquir Immune Defic Syndr.* 2003;32(3):292-297.
43. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr.* 2006;42(5):614-619.
44. McConnell M, Bakaki P, Eure C, et al. Effectiveness of repeat single-dose nevirapine for prevention of mother-to-child transmission of HIV-1 in repeat pregnancies in Uganda. *J Acquir Immune Defic Syndr.* 2007;46(3):291-296.
45. Martinson NA, Ekouevi DK, Dabis F, et al. Transmission rates in consecutive pregnancies exposed to single-dose nevirapine in Soweto, South Africa and Abidjan, Côte d'Ivoire. *J Acquir Immune Defic Syndr.* 2007;45(2):206-209.
46. Coovadia A, Marais B, Abrams E, et al. Virologic response to NNRTI-treatment among women who took single-dose nevirapine 18-36 months later. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; February 2006; Denver, Co. Abstract 641.
47. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
48. Lockman S and the A5208/OCTANE Study Team. Lopinavir/ritonavir + tenofovir/emtricitabine is superior to nevirapine + tenofovir/emtricitabine for women with prior exposure to single-dose nevirapine: A5208 ("OCTANE"). Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada.
49. Rouzioux C, Costagliola D, Burgard M, et al. Estimated timing of mother to child human immunodeficiency virus type 1 (HIV-1) transmission by use of a Markov model. *Am J Epidemiol.* 1995;142(12):1330-1337.
50. Kuhn L, Steketee RW, Weedon J, et al. Distinct risk factors for intrauterine and intrapartum human immunodeficiency virus transmission and consequences for disease progression in infected children. *J Infect Dis.* 1999;179(1):52-58.
51. Magder LS, Mofenson LM, Paul ME, et al. Risk factors for in utero and intrapartum transmission of HIV. *J Acquir Immune Defic Syndr.* 2005;38(1):87-95.
52. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1996;335(22):1621-1629.
53. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
54. Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14(3):232-236.
55. Qian M, Bui T, Ho RJY, Unadkat JD. Metabolism of 3'-azido-3'-deoxythymidine (AZT) in human placental trophoblasts and hofbauer cells. *Biochem Pharmacol.* 1994;48(2):383-389.
56. Sandberg JA, Binienda Z, Lipe G, et al. Placental transfer and fetal disposition of 2',3'-dideoxycytidine and 2',3'-dideoxyinosine in the rhesus monkey. *Drug Metab Dispos.* 1995;23(8):881-884.
57. Dancis J, Lee JD, Mendoza S, Liebes L. Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1993;6(1):2-6.
58. Sandberg JA, Binienda Z, Lipe G, Slikker Jr W. Placental transfer and fetal disposition of dideoxycytidine (ddC) and dideoxyinosine (ddI) [Abstract]. *Toxicologist.* 1994;14:434.
59. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. *J Infect Dis.* 2000;181(1):99-106.

60. Si-Mohamed A, Kazatchkine MK, Heard I, et al. Selection of drug-resistant variants in the female genital tract of human immunodeficiency virus type 1-infected women receiving antiretroviral therapy. *J Infect Dis.* 2000;182(1):112-122.
61. Dumond J, Yeh R, Corbett A, et al. First dose and steady state genital tract pharmacokinetics of ten antiretroviral drugs in HIV-infected women: implications for pre- and post-exposure prophylaxis. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Co. Abstract 129.
62. Vourvahis M, Tappouni H, Patterson K, et al. A pharmacologic basis for the use of tenofovir in pre- and post-exposure prophylaxis: intra- and extra-cellular genital tract pharmacokinetics and pharmacodynamics from first dose to steady state in HIV-1-infected men and women. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Co. Abstract 569.
63. Strazielle N, Belin MF, Ghersi-Egea JF. Choroid plexus contrals brain availability of anti-HIV nucleoside analogs via pharmacologically inhibitable organic anion transporters. *AIDS.* 2003;17(10):1473-1485.
64. Thomas SA. Anti-HIV drug distribution to the central nervous system. *Curr Pharmaceut Des.* 2004;10(12):1313-1324.
65. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med. 2009;6(10):e1000172.
66. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487. Epub 2006 Jan 2011.
67. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.
68. Sadiq ST, Fredericks S, Khoo SH, et al. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS.* 2005;19(15):1716-1717.

Intrapartum Care (Updated May 24, 2010)

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 treatment regimen should continue this regimen on schedule as much as possible during labor and prior to scheduled cesarean delivery (AIII).***
- ***Women receiving fixed-dose combination regimens that include zidovudine should have zidovudine administered intravenously during labor while other antiretroviral components are continued orally (AIII).***
- ***For women who have received antepartum antiretroviral drugs but have suboptimal viral suppression near delivery (i.e., >1,000 copies/mL), scheduled cesarean delivery is recommended (AI). The addition of single-dose intrapartum/newborn nevirapine is generally not recommended (AI).***
- ***Women of unknown HIV status who present in labor should have rapid HIV antibody testing performed (AII). If the test is positive, a confirmatory HIV test should be sent as soon as possible and maternal/infant antiretroviral drugs should be initiated without waiting for results of the confirmatory test (AII). If the confirmatory HIV test is positive, antiretroviral drugs should be continued in the infant for 6 weeks (see Neonatal Postnatal Care) (AI); if the test is negative, the infant antiretroviral drugs should be stopped.***
- ***For HIV-infected women in labor who have not received antepartum antiretroviral drugs, intravenous zidovudine during labor and 6 weeks of infant zidovudine are recommended (AII). Some experts would combine the intravenous intrapartum/6-week newborn zidovudine regimen with single-dose intrapartum/newborn nevirapine (CIII).***
- ***If single-dose intrapartum/newborn nevirapine is given, an antiretroviral "tail" should be administered to reduce development of nevirapine resistance (AII).***

Table 7 shows dosing for intravenous intrapartum zidovudine given in continuous infusion during labor and neonatal zidovudine dosing; Table 8 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

The PACTG 076 results and subsequent epidemiologic studies have proven the efficacy of the three-part zidovudine chemoprophylaxis regimen alone or in combination with other antiretroviral 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). Therefore, intravenous zidovudine during the intrapartum period should be discussed with and recommended to all HIV-infected pregnant women. For a scheduled cesarean delivery, intravenous zidovudine should begin 3 hours before surgery, according to standard dosing recommendations. Women receiving fixed-dose combination regimens that include zidovudine (e.g., the zidovudine/lamivudine combination) should have zidovudine administered intravenously during labor while other antiretroviral components are continued orally (e.g., if a woman is receiving zidovudine/lamivudine during pregnancy, zidovudine should be given intravenously and lamivudine should be given orally during labor).

If known or suspected zidovudine resistance or toxicity has precluded antenatal use of zidovudine, intrapartum zidovudine according to the PACTG 076 protocol should still be recommended unless a woman has a documented history of hypersensitivity. This intrapartum use of the drug is recommended due to the unique characteristics of zidovudine and its proven record in reducing perinatal transmission (see **Management of Antiretroviral Drug Resistance during Pregnancy**). There is a pharmacologic antagonism between zidovudine and stavudine, and therefore these drugs should not be coadministered during labor. Women who are receiving an antepartum stavudine-containing regimen should discontinue stavudine during labor while intravenous zidovudine is being administered, with other components of the regimen continued orally.

Continuation of Antenatal Antiretroviral Drugs during Labor and Postpartum

Women who are receiving an antepartum combination antiretroviral treatment regimen should continue this 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 may be continued preoperatively with sips of water. Medications requiring food ingestion for absorption could be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist in the preoperative period. If maternal antiretroviral therapy must be interrupted temporarily (i.e., for less than 24 hours) in the peripartum period, all drugs (except for intrapartum intravenous zidovudine) should be stopped and reinstituted simultaneously to minimize the chance of resistance developing.

Women Who Have Received Antepartum Antiretroviral Drugs but Have Suboptimal Viral Suppression near Delivery

Women who have received antiretroviral therapy may not achieve complete viral suppression by the time of delivery due to 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 antiretroviral 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 but was associated with the development of nevirapine resistance in 15% of women with detectable HIV RNA postpartum *[1-2]*. However, the number of women with detectable HIV RNA at delivery, and especially with HIV RNA greater than

10,000 copies/mL, was small and may have been insufficient to allow assessment of a possible benefit of single-dose nevirapine in this subgroup. Given the risk of development of resistance and the lack of data to suggest added efficacy, addition of single-dose nevirapine when a woman has received antepartum drugs is generally not recommended. However, single-dose nevirapine use may be considered in special circumstances, such as in women with high HIV RNA levels at or near the time of delivery, especially if delivery is vaginal rather than a scheduled cesarean delivery. If single-dose nevirapine is administered, the use of maternal postpartum zidovudine/lamivudine for at least 7 days is suggested to prevent the development of nevirapine resistance (see **Choice of Intrapartum/Postpartum Antiretroviral Regimen for Women without Antepartum Antiretroviral Therapy**).

Women Who Have Not Received Antepartum Antiretroviral Drugs

Women Who Present in Labor with No Documentation of HIV Status

Any woman without documented HIV status at the time of labor should be screened with rapid HIV testing unless she declines (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 increasing risk of infection may include diagnosis of an STD, illicit drug use or exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of HIV infection, signs/symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age without a repeat HIV test 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 should also be available at all facilities with a maternity service and/or neonatal intensive care unit.

A woman with a positive rapid antibody test should be presumed to be infected until standard HIV antibody confirmatory testing clarifies her infection. Along with confirmatory HIV antibody testing, the woman should have appropriate assessments (e.g., CD4 count and HIV RNA copy number) as soon as possible to determine maternal health status and whether antiretroviral therapy is recommended for her own health. Arrangements for establishing HIV care and providing ongoing psychosocial support after discharge should also be provided. All women with a positive rapid HIV test in labor should have intravenous zidovudine started immediately 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 antiretroviral therapy should have intravenous zidovudine started immediately to prevent perinatal transmission of HIV (see **Table 7** for dosing information). Although intrapartum/neonatal antiretroviral 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 the mother a drug that rapidly crosses the placenta to produce systemic antiretroviral drug levels in the fetus during intensive exposure to HIV in maternal genital secretions and blood during birth. In general, zidovudine and other NRTI drugs as well as NNRTI drugs cross the placenta well, although PI drugs do not (see **Table 4**).

Epidemiologic data indicate that intravenous maternal intrapartum zidovudine followed by oral zidovudine for 6 weeks for the infant significantly reduces transmission compared to 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]*.

Whether the addition of other antiretroviral drugs to the intravenous intrapartum/newborn zidovudine regimen when no maternal antepartum drugs have been received increases efficacy in preventing perinatal transmission has not been directly studied. Several intrapartum/neonatal prophylaxis regimens have been found to be effective in international studies. These include oral zidovudine/lamivudine during labor followed by 1 week of oral zidovudine/lamivudine to the infant and single-dose intrapartum/newborn nevirapine *[5-6]*. However, none of these regimens has been compared to intravenous zidovudine combined with 6 weeks of infant zidovudine prophylaxis.

An ongoing study in the United States, Brazil, Argentina, and South Africa is assessing whether adding drugs to the intravenous intrapartum/newborn zidovudine regimen will enhance efficacy in reducing perinatal transmission. In the absence of data, some experts feel additional drugs may be warranted. One option is to add the single-dose intrapartum/newborn nevirapine regimen to the intravenous/6-week infant zidovudine regimen. Although single-dose nevirapine did not provide additional efficacy when added to antepartum combination antiretroviral regimens in PACTG 316, in this situation, no maternal antepartum therapy has been given. Theoretical advantages of combining the zidovudine and nevirapine intrapartum/neonatal regimens include the known short-term safety of each regimen alone, excellent transplacental passage of both drugs, greater antiviral activity of nevirapine compared to zidovudine, as well as the activity of nevirapine against extracellular and intracellular virus *[7-8]*, and the known synergy of zidovudine and nevirapine in inhibiting HIV replication *in vitro [9]*.

However, single-dose nevirapine is associated with the development of nevirapine -resistant virus (see **Incidence of Antiretroviral Resistance with Perinatal Prophylactic Regimens**) *[2, 10-12]*. Studies have shown that nevirapine resistance after intrapartum administration of single-dose nevirapine can be substantially reduced (but not eliminated) by using a short postpartum course of antiretroviral agents from alternate classes (a “tail”). There is no current consensus about the exact duration or composition of the antiretroviral tail. Several trials in Africa have found 3–7 days of maternal/infant postpartum zidovudine/lamivudine to be effective *[13-15]* (See **Table 8** for dosing information.) Development of resistance to zidovudine or lamivudine given for a short period in this setting is rare *[16-17]*. More recent studies have found that 7 days of tenofovir/emtricitabine *[18]*, 7 days of zidovudine/didanosine/lopinavir-ritonavir *[19]*, and 30 days of zidovudine/didanosine or zidovudine/didanosine/lopinavir-ritonavir *[19-20]* all appear to be effective at reducing the development of nevirapine resistance. In the United States the use of maternal postpartum zidovudine/lamivudine for at least 7 days is suggested as a reasonable tail after intrapartum single-dose nevirapine use (see **Neonatal Postnatal Care** section for discussion of infant regimens). Other tail options may also be considered.

References:

1. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA.* 2002;288(2):189-198.
2. Cunningham CK, Chaix ML, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis.* 2002;186(2):181-188.
3. Centers for Disease Control and Prevention (CDC). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006;55(RR-14):1-17; quiz CE11-14.

4. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
5. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
6. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868.
7. Zhang H, Dornadula G, Wu Y, et al. Kinetic analysis of intravirion reverse transcription in the blood plasma of human immunodeficiency virus type 1-infected individuals: direct assessment of resistance to reverse transcriptase inhibitors in vivo. *J Virol.* 1996;70(1):628-634.
8. Musoke P, Guay L, Bagenda D, et al. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). *AIDS.* 1999;13(4):479-486.
9. Koup RA, Brewster F, Grob P, et al. Nevirapine synergistically inhibits HIV-1 replication in combination with zidovudine, interferon or CD4 immunoadhesin. *AIDS.* 1993;7(9):1181-1184.
10. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS.* 2001;15(15):1951-1957.
11. Eshleman SH, Guay LA, Mwatha A, et al. Characterization of nevirapine resistance mutations in women with subtype A vs. D HIV-1 6-8 weeks after single-dose nevirapine (HIVNET 012). *J Acquir Immune Defic Syndr.* 2004;35(2):126-130.
12. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
13. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
14. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487.
15. Farr S, Nelson J, Ng'ombe3 T, et al. Addition of 7 Days of Zidovudine + Lamivudine to Peripartum Single-dose Nevirapine Effectively Reduces Nevirapine Resistance at 2 and 6 Weeks Post-partum in HIV-infected Mothers: Lilongwe, Malawi. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 958b.
16. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
17. Sullivan J. South African Intrapartum Nevirapine Trial: selection of resistance mutations. Paper presented at: XIV International Conference on AIDS; July 7-12, 2002; Barcelona, Spain. Abstract LbPeB9024.
18. TEmAA ANRS 12109 Study Group. Tolerance and viral resistance after single-dose nevirapine with tenofovir and emtricitabine to prevent vertical transmission of HIV-1. *AIDS.* 2009;23(7):825-833.
19. Van Dyke R, Jourdain G, Shapiro D, et al. A Phase II Study of the Incidence of Nevirapine Resistance Mutations in HIV-infected Thai Women Receiving a Single Intrapartum Dose of NVP followed by a Postpartum Tail of ZDV/ddI or ZDV/ddI/LPV/r: IMPAACT P1032. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 95aLB.
20. Lallemant M, Ngo-Giang-Huong N, Jourdain G, et al. Efficacy and safety of 1-month postpartum zidovudine-didanosine to prevent HIV-resistance mutations after intrapartum single-dose nevirapine. *Clin Infect Dis.* 2010;50(6):898-908.

Table 7. Intrapartum Maternal and Neonatal Zidovudine (ZDV) Dosing for Prevention of Mother-to-Child Transmission of HIV

Maternal Intrapartum		
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		
Drug	**Dosing**	**Duration**
ZDV	>35 weeks gestation: 2 mg per kg body weight per dose given orally [1, 2] (or 1.5 mg per kg body weight per dose given intravenously) started within 6–12 hours of delivery, then every 6 hours	Birth to 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 given intravenously) started within 6–12 hours of delivery, then every 12 hours, advanced to every 8 hours at 2 weeks of age	Birth to 6 weeks
ZDV	<30 weeks gestation: 2 mg per kg body weight per dose given orally (or 1.5 mg/kg/dose given intravenously) started within 6–12 hours of delivery, then every 12 hours, advanced to every 8 hours at 4 weeks of age	Birth to 6 weeks

[1] Zidovudine dosing of 4 mg per kg body weight per dose given every 12 hours has been used for infant prophylaxis in some international perinatal studies. Although there are no definitive data to show equivalent pharmacokinetic parameters or efficacy in preventing transmission, a regimen of zidovudine 4 mg per kg body weight per dose given orally twice daily instead of 2 mg per kg body weight per dose given orally 4 times daily may be considered when there are concerns about adherence to drug administration to the infant.

[2] A simplified zidovudine dosing regimen has been developed for use in low resource settings. This regimen consists of 10 mg orally 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. See discussion in **Neonatal Postnatal Care: Infant Antiretroviral Prophylaxis**. This regimen could be considered for infants in higher resource settings born after 35 weeks gestation if simplicity in zidovudine dosing and administration is of prime importance.

Table 8. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs to be Considered Only in Selected Circumstances

*(See **Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants** and **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy** for further discussion.)*

Maternal Intrapartum/Postpartum		
Drug	**Dosing**	**Duration**
NVP (as single dose intrapartum)[1]	200 mg given orally as single dose	Single dose at onset of labor
ZDV + 3TC (given with single dose NVP as "tail" to reduce NVP resistance)	ZDV: intravenously intrapartum as per **Table 7**, then after delivery 300 mg orally twice daily 3TC: 150 mg orally twice daily starting at onset of labor	Through 1 week postpartum
Neonatal		
Drug	**Dosing**	**Duration**
NVP (as single dose)[2]	2 mg per kg body weight given orally as single dose	Single dose between birth and 72 hours of age. If maternal dose is given ≤ 2 hours before delivery or not received, infant dose should be administered as soon as possible following birth.[3]
ZDV + 3TC (given with single dose NVP as "tail" to reduce NVP resistance)	ZDV: neonatal dosing as per **Table 5** 3TC: 2 mg per kg body weight given orally twice daily	ZDV: Birth to 6 weeks 3TC: Birth to 1 week

Key to Abbreviations: NVP = nevirapine, ZDV = zidovudine, 3TC = lamivudine

[1] Given *in addition* to intravenous intrapartum ZDV; if intrapartum single-dose NVP is given to mother, administration of intrapartum oral 3TC followed by administration of ZDV and 3TC for at least 7 days postpartum to reduce development of NVP-resistant virus is recommended.

[2] Given *in addition* to 6 weeks of infant ZDV; addition of at least 7 days of 3TC may be considered to reduce development of NVP-resistant virus.

[3] Some experts recommend a second NVP dose at 48–72 hours of life to babies born in this circumstance.

TRANSMISSION AND MODE OF DELIVERY

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 (whether receiving or not receiving antepartum antiretroviral drugs) and for women with unknown HIV RNA levels near the time of delivery (AII).***
- ***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 antiretroviral therapy, and other clinical factors (BII).***
- ***Data are insufficient to evaluate the potential benefit of cesarean delivery for prevention of perinatal transmission in pregnant women receiving combination antiretroviral drugs with plasma HIV RNA levels <1,000 copies/mL near the time of delivery. Given the low rate of transmission among this group, it is unclear whether scheduled cesarean delivery would confer additional benefit in reduction of transmission. Decisions should be individualized based on discussion between the obstetrician and the mother (BII).***
- ***Among HIV-infected women, use of prophylactic antibiotics at the time of cesarean delivery is recommended (AII).***
- ***Women should be informed of the risks associated with cesarean delivery; the risk 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 ruptured 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 the findings from a multi-center randomized clinical trial *[2]* and a large individual patient data meta-analysis *[3]*. These two studies were conducted at a time when the majority of women received no antiretroviral medications or zidovudine as a single drug and before the availability of viral load information. However, study results have been extrapolated to make recommendations regarding the mode of delivery in an era when combination antiretroviral therapy during pregnancy is recommended and viral load information is readily available. In the randomized clinical trial, 1.8% of infants born to women randomized to undergo cesarean delivery were HIV infected compared to 10.5% of infants born to women randomized to deliver vaginally ($p<0.001$). When adjusted for antiretroviral use in pregnancy (zidovudine alone), scheduled cesarean delivery lowered the risk of HIV transmission by 80%, although the results were no longer statistically significant (OR 0.2, 95% CI 0–1.7). When the data were analyzed by the actual mode of delivery, rather than to what group women were allocated, there was still a protective effect of scheduled cesarean delivery (adjusted odds ratio [OR] 0.3; 95% CI 0.1–0.8) but not with emergency cesarean delivery (adjusted OR 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 a benefit of scheduled cesarean delivery with a 50% reduction in risk *[3]*. Primarily based on these data, the American College of

Obstetricians and Gynecologists (ACOG) 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 Cesarean Delivery

The original ACOG committee opinion was updated in 2000 to include further refinements based on HIV RNA levels *[1]*. Currently, ACOG *[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 occurred among infants born to women with low viral loads. In an analysis of 957 women with plasma viral loads of <1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal antiretroviral therapy, primarily zidovudine alone as prophylaxis (adjusted OR 0.30; p=0.022) *[6]*. Overall, the transmission rate among women with HIV RNA <1,000 copies/mL receiving antiretroviral therapy was 8 (1%) of 834. 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]*. These later studies document 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 reduction of transmission. Therefore, 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.

Cesarean Delivery in the HAART Era

In surveillance data from the United Kingdom and Ireland, pregnant women receiving combination antiretroviral drugs regimens (e.g., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery. Pregnant women with undetectable HIV viral load (< 50 copies/mL) had transmission rates of about 0.1% *[7]*. Given the low transmission rates achievable with use of maternal combination antiretroviral therapy or prophylaxis, 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 antiretrovirals 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 antiretroviral 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 antiretroviral therapy (none vs. any), the effect was no longer significant (adjusted OR 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 (adjusted OR 1.24; 95% CI 0.34–4.5) among women on combinational antiretroviral therapy or prophylaxis *[7]*. The transmission rate among all women who received at least 14 days of antiretroviral therapy 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 antiretroviral therapy for several weeks.

Women Presenting Late in Pregnancy

HIV-infected women who present in late pregnancy and are not receiving antiretroviral 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 antiretroviral therapy were begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the baseline RNA level *[9]*. In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing risk of perinatal transmission of HIV for women with unknown HIV RNA levels near the time of delivery.

Timing of Scheduled Cesarean Delivery

In general, for women without HIV infection, ACOG recommends that scheduled cesarean delivery not be performed before 39 weeks gestation due to the risk of iatrogenic prematurity *[10-11]*. However, in cases of cesarean delivery performed to prevent HIV transmission, ACOG recommends scheduling cesarean delivery at 38 weeks gestation in order to decrease the likelihood of onset of labor or rupture of membranes before delivery *[1]*. Among all women undergoing repeat cesarean delivery, the risk of any neonatal adverse event, which includes 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]*. 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. Furthermore, gestational age should be determined by last menstrual period and ultrasonography because amniocentesis to document lung maturity should be avoided when possible *[1]*.

Risk of Maternal Complications

Because maternal infectious morbidity is increased with cesarean delivery even among women without HIV infection, use of peri-operative 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 to HIV-uninfected women and that the risk of complications is related to the degree of immunosuppression *[12-17]*. 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 *[18]*. Complication rates in most studies *[2, 19-23]* 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 antiretroviral therapy.

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 the risk of transmission with cesarean delivery done after labor and membrane rupture for obstetric indications to be similar to that with vaginal delivery. In one study, the HIV transmission rate among women undergoing emergency cesarean delivery was similar to women delivering vaginally (1.6% vs. 1.9%, respectively) *[7]*. A meta-analysis of women mostly on zidovudine as a single drug or no antiretroviral therapy demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes *[24]*. However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost *[25]*. 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 antiretroviral therapy or prophylaxis status. When membrane rupture occurs prior to 37 weeks gestation, decisions about delivery should be based on gestational age, HIV RNA level, current antiretroviral regimen, and evidence of acute infection (e.g., chorioamnionitis); consultation with an expert is recommended. The antiretroviral drug regimen should be continued and consideration given to initiating intravenous zidovudine if imminent delivery seems possible. There are no data to suggest that use of steroids to accelerate fetal lung maturity should be altered among HIV-infected women.

Table 9 provides a summary of recommendations regarding mode of delivery for different clinical scenarios.

Table 9. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV

Clinical Scenario	Recommendations
HIV-infected woman presenting in late pregnancy (after about 36 weeks gestation), known to be HIV-infected but not receiving antiretroviral therapy, and who has HIV RNA level and CD4 count pending but unlikely to be available before delivery.	• The woman should be started on antiretroviral therapy as per **Table 6**. • The woman should be counseled that scheduled cesarean delivery is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean delivery, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. • If cesarean delivery is chosen, the procedure should be scheduled at 38 weeks gestation based on the best available clinical information. • When scheduled cesarean delivery is performed, the woman should receive continuous intravenous zidovudine infusion beginning 3 hours before surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is generally recommended. • Options for continuing or initiating combination antiretroviral therapy after delivery should be discussed with the woman as soon as her viral load and CD4 count results are available. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).
HIV-infected woman who initiated prenatal care early in the third trimester, is receiving a combination antiretroviral regimen, and has an initial virologic response but has HIV RNA levels that remain substantially greater than 1,000 copies/mL at 36 weeks gestation.	• The current combination antiretroviral regimen should be continued because the HIV RNA level is dropping appropriately. • The woman should be counseled that although she is responding to the antiretroviral therapy, it is unlikely that her HIV RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean delivery may provide additional benefit in preventing intrapartum transmission of HIV. She should also be informed of the increased risks to her of cesarean delivery, including risks related to anesthesia and surgery and increased rates of postoperative infection. • If the woman chooses scheduled cesarean delivery, the procedure should be performed at 38 weeks gestation as determined by last menstrual period and ultrasonography. Intravenous zidovudine should be started at least 3 hours before surgery. • Other antiretroviral medications should be continued on schedule as much as possible before and after surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is generally recommended. • The importance of adhering to therapy after delivery for the woman's health should be emphasized. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).
HIV-infected woman on a combination antiretroviral regimen with an undetectable HIV RNA level at 36 weeks gestation.	• The woman should be counseled that her risk of perinatal transmission of HIV with a persistently undetectable HIV RNA level is low, probably 1% or less, even with vaginal delivery. There is currently no evidence that performing a scheduled cesarean delivery will lower her risk further. • Cesarean delivery has an increased risk of complications for the woman compared to vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean delivery in this case. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).

Clinical Scenario	Recommendations
HIV-infected woman who has elected scheduled cesarean delivery but presents after rupture of membranes at >37 weeks gestation.	• Intravenous zidovudine should be started immediately. • Decision regarding mode of delivery should be individualized and based on clinical factors such as duration of rupture, anticipated progress of labor, plasma RNA level, and current antiretroviral therapy. • If the decision is made to proceed with vaginal delivery, 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. • If the decision is made to proceed with cesarean delivery, administration of the loading dose of intravenous zidovudine should be completed prior to cesarean delivery. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).

References

1. American College of Obstetricians and Gynecologists. ACOG committee opinion scheduled Cesarean delivery and the prevention of vertical transmission of HIV infection. Number 234, May 2000 (replaces number 219, August 1999). *Int J Gynaecol Obstet.* 2001;73(3):279-281.
2. European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. The European Mode of Delivery Collaboration. *Lancet.* 1999;353(9158):1035-1039.
3. International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. The International Perinatal HIV Group. *N Engl J Med.* 1999;340(13):977-987.
4. American College of Obstetricians and Gynecologists. ACOG committee opinion. Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. Number 219, August 1999. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet.* 1999;66(3):305-306.
5. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med.* 1999;341(6):394-402.
6. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis.* 2001;183(4):539-545.
7. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981.
8. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):458-465.
9. European Collaborative Study, Patel D, Cortina-Borja M, et al. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis.* 2007;44(12):1647-1656.
10. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 97: Fetal lung maturity. *Obstet Gynecol.* 2008;112(3):717-726.
11. Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med.* 2009;360(2):111-120.
12. Grubert TA, Reindell D, Kastner R, et al. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. *Lancet.* 1999;354(9190):1612-1613.
13. Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, et al. Post-cesarean section morbidity in HIV-positive women. *Acta Obstet Gynecol Scand.* 1999;78(9):789-792.

14. Rodriguez EJ, Spann C, Jamieson D, et al. Postoperative morbidity associated with cesarean delivery among human immunodeficiency virus-seropositive women. *Am J Obstet Gynecol.* 2001;184(6):1108-1111.
15. Semprini AE, Castagna C, Ravizza M, et al. The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS.* 1995;9(8):913-917.
16. Urbani G, de Vries MM, Cronje HS, et al. Complications associated with cesarean section in HIV-infected patients. *Int J Gynaecol Obstet.* 2001;74(1):9-15.
17. Vimercati A, Greco P, Loverro G, et al. Maternal complications after caesarean section in HIV infected women. *Eur J Obstet Gynecol Reprod Biol.* 2000;90(1):73-76.
18. Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database Syst Rev.* 2005(4):CD005479.
19. Faucher P, Batallan A, Bastian H, et al. [Management of pregnant women infected with HIV at Bichat Hospital between 1990 and 1998: analysis of 202 pregnancies]. *Gynecol Obstet Fertil.* 2001;29(3):211-225.
20. Fiore S, Newell ML, Thorne C. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS.* 2004;18(6):933-938.
21. Marcollet A, Goffinet F, Firtion G, et al. Differences in postpartum morbidity in women who are infected with the human immunodeficiency virus after elective cesarean delivery, emergency cesarean delivery, or vaginal delivery. *Am J Obstet Gynecol.* 2002;186(4):784-789.
22. Read JS, Tuomala R, Kpamegan E, et al. Mode of delivery and postpartum morbidity among HIV-infected women: the women and infants transmission study. *J Acquir Immune Defic Syndr.* 2001;26(3):236-245.
23. Watts DH, Lambert JS, Stiehm ER, et al. Complications according to mode of delivery among human immunodeficiency virus-infected women with CD4 lymphocyte counts of < or = 500/microL. *Am J Obstet Gynecol.* 2000;183(1):100-107.
24. The International Perinatal HIV Group. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS.* 2001;15(3):357-368.
25. Jamieson DJ, Read JS, Kourtis AP, et al. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S96-100.

OTHER INTRAPARTUM MANAGEMENT CONSIDERATIONS

Panel's Recommendations:

- ***Artificial rupture of membranes should generally be avoided because of a small but 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 (BIII).***
- ***Operative delivery with forceps or the vacuum extractor and episiotomy should be performed only in select circumstances (BIII).***
- ***When uterine atony results in excessive postpartum bleeding in women receiving a protease inhibitor or efavirenz, methergine should not be used unless alternative treatments for postpartum hemorrhage are not available and if the need for pharmacologic treatment outweighs the risks. If used, methergine should be administered in the lowest effective dose for the shortest duration possible (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. For women who present in labor and the decision is made to proceed with vaginal delivery despite detectable viral load, artificial rupture of membranes should be avoided and employed only for a clear obstetric indication. For women with nondetectable viral load and planned vaginal delivery, data are limited, but artificial rupture of membranes should generally still be avoided and be performed only for clear obstetrical indications in order to avoid the small but potential increased risk of HIV transmission.

Obstetric procedures increasing 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 *[1-4]*. Although data are limited, the routine use of fetal scalp electrodes in labor should be avoided in the setting of maternal HIV infection because of the potential risk of disruption of fetal skin.

Operative vaginal delivery with forceps or the vacuum extractor and/or use of episiotomy theoretically may increase the risk of transmission but should not be delayed if there are clear obstetric indications *[2, 4]*.

Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use

Women experiencing postpartum hemorrhage due to uterine atony are often managed with oral or parenteral methergine or other ergot alkaloids as a first-line agent. However, methergine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors. The concomitant use of ergotamines (e.g., methergine) and protease inhibitors has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving protease inhibitors or efavirenz as a component of an antiretroviral regimen, methergine should not be used unless alternative treatments (e.g., prostaglandin F 2 alpha, misoprostol, or oxytocin) are not available. If there are no alternative medications available and the need for pharmacologic treatment outweighs the risks, methergine should be used in as low a dosage and for as short a duration as possible. When other antiretroviral agents are used that are CYP3A4 inducers, there is the potential for decreased methergine levels and inadequate treatment effect; therefore, additional uterotonic agents may be needed.

References

1. Boyer PJ, Dillon M, Navaie M, et al. Factors predictive of maternal-fetal transmission of HIV-1. Preliminary analysis of zidovudine given during pregnancy and/or delivery. *JAMA.* 1994;271(24):1925-1930.
2. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol.* 1996;175(3 Pt 1):661-667.
3. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
4. Shapiro DE, Sperling RS, Mandelbrot L, et al. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol.* 1999;94(6):897-908.

Postpartum Care (Updated May 24, 2010)

POSTPARTUM FOLLOW-UP OF HIV-INFECTED WOMEN

Panel's Recommendations:

• The decision to continue antiretroviral therapy after delivery should be based on the nadir CD4 count, clinical symptoms/disease stage, presence of other indications for antiretroviral therapy, and patient and provider preference (AI).

• The immediate postpartum period poses unique challenges for adherence; new or continued supportive services should be assured prior to hospital discharge (AII).

• Women with a positive rapid HIV antibody test during labor require comprehensive follow-up, including confirmation of HIV infection and, if infection is confirmed, a full health assessment including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of need for antiretroviral therapy and opportunistic infection prophylaxis (AII).

• Breastfeeding is not recommended for HIV-infected women in the United States (AI).

• Contraceptive counseling should be included as a critical aspect of postpartum care (AIII).

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 the individual woman's needs and may include case management, child care, respite care, assistance with basic life needs (e.g., housing, food, transportation), peer counseling, and legal and advocacy services. Ideally, this care should begin before pregnancy and should be continued throughout pregnancy and the postpartum period.

Maternal medical services during the postpartum period must be coordinated between obstetric care providers and HIV specialists. It is especially critical to ensure continuity of antiretroviral treatment when such treatment is required for the woman's health. The decision whether to continue antiretroviral therapy after delivery will depend on the woman's nadir CD4 count; clinical symptoms/disease stage; presence of other indications for antiretroviral therapy, such as chronic hepatitis B; and patient and provider preference. Ideally, a discussion of these factors should occur well before delivery.

Concerns have been raised about adherence to antiretroviral regimens during the postpartum period. Women should be counseled that the physical and psychological changes of the postpartum period, as well as the stresses and demands of caring for a new baby, might make adherence more difficult and that additional support may be needed to maintain good adherence during this period *[1-3]*. The health care provider should

be vigilant for signs of depression and illicit drug or alcohol use, which may require assessment and treatment and which may interfere with adherence. Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of antiretroviral therapy *[4-6]*. Efforts to maintain adequate adherence during the postpartum period might 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***.

Women with nadir CD4 counts less than the currently recommended threshold for institution of antiretroviral therapy *[7]* and/or symptomatic HIV infection should be encouraged to continue their antiretroviral regimens postpartum with no interruption. For women who began antiretroviral drugs for prophylaxis of transmission with a nadir CD4+ cell count greater than that currently recommended for treatment *[7]*, the decision of whether to continue therapy after delivery should be made in consultation with the HIV provider, taking into account current and nadir CD4+ lymphocyte counts and trajectory, HIV RNA levels, and patient preference.

For women whose antepartum regimen included an NNRTI and who plan to stop antiretroviral prophylaxis after delivery, consideration should be given to stopping the NNRTI and continuing the other antiretroviral drugs or switching from an NNRTI to a PI prior to interruption and continuing the PI with the other antiretroviral drugs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days. (See **Stopping Antiretroviral Therapy during Pregnancy** and **Prevention of Antiretroviral Drug Resistance**).

Among women with indications for continued antiretroviral therapy postpartum, planned interruption of antiretroviral therapy for several weeks or months has not been studied prospectively and cannot be recommended. However, women may be at increased risk of decreased adherence during the postpartum period. Intermittent adherence increases the risk of developing HIV resistance, so every effort should be made to maximize adherence. Simplification of an antiretroviral regimen (for example, to once-daily medications) could be considered. If a woman is unable to adhere to her regimen, it may be preferable to temporarily interrupt antiretroviral therapy while she works with her provider on strategies to improve adherence.

Data on follow-up of women from PACTG 076 who received antepartum and intrapartum zidovudine prophylaxis with discontinuation of the drug after delivery (median follow-up 4 years) demonstrated no difference in clinical, immunologic, virologic, and resistance status compared to women who received placebo *[8]*. Among women with CD4 cell counts >350 cells/mm^3 followed in the Women and Infants Transmission Study (WITS) cohort, there were no significant differences in CD4 count or disease progression among those who did or did not continue antiretroviral treatment after delivery *[9]*. However, for women receiving current combination antiretroviral prophylaxis regimens with no indication to continue antiretroviral therapy postpartum, the effect of limited-duration, fully suppressive antiretroviral prophylaxis in pregnancy on future treatment efficacy is unknown, and further research is needed. Such women may eventually require antiretroviral therapy again in the context of subsequent pregnancies or for advancing HIV disease.

Women with a positive rapid HIV antibody test during labor or at delivery require comprehensive medical assessment, counseling, and follow-up. Confirmatory HIV antibody testing should be performed as soon as possible after an initial positive rapid test to minimize the delay for definitive diagnosis *[10]*. Women with a positive rapid HIV antibody test should not breastfeed unless the 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 antiretroviral therapy and opportunistic infection prophylaxis as indicated. Her other children and partner(s) should be referred for HIV testing.

In the United States and other parts of the world where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, breastfeeding by HIV-infected women (including those receiving antiretroviral drugs) is

not recommended. Postpartum HIV transmission via breast milk is well documented and the risk of transmission is related to a variety of factors, including maternal health status and breast milk cell-free and cell-associated viral load *[11]*. There are no safe methods to treat breast milk that will completely eliminate the risk of HIV transmission associated with breastfeeding. Data are limited regarding the penetration of antiretroviral drugs into breast milk. The available data indicate that there is differential penetration of drugs into milk, with some drugs having high levels while others may have low or undetectable levels in breast milk, which raises concerns regarding both infant toxicity and selection of drug-resistant virus within breast milk *[12-13]*. Three studies have found multi-class drug resistance in breastfeeding infants who have become infected despite maternal triple antiretroviral drug prophylaxis *[14-16]*. Additionally, drug levels in the neonate from ingested breast milk may be subtherapeutic and cannot be relied on to interrupt transmission of HIV via breast milk.

Contraceptive counseling is a critical aspect of postpartum care. Although condoms are universally recommended for prevention of STD/HIV transmission, the unintended pregnancy rate even with consistent condom use alone is estimated at 10%–15% annually. Women should be educated about the risk of unintended pregnancy when condoms are the sole contraceptive method used. If another pregnancy is not desired in the near future and/or if the antiretroviral regimen contains potentially teratogenic agents such as efavirenz, women should be offered dual-method contraception *[17]*. Reversible options include intrauterine devices, which have been shown to be safe and effective in HIV-infected women *[18]*, and hormonal methods. Emergency contraception should not be recommended for routine use as a form of contraception but should be provided for use within 72 hours after an episode of unprotected intercourse or broken condom for women declining additional contraception.

Drug interactions have been documented between oral contraceptives and many antiretrovirals (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***, Tables 13, 14a, and 14b) *[7]*. These interactions do not necessarily rule out the use of hormonal contraceptive methods because there is no clear evidence of an effect on contraceptive or antiretroviral efficacy or toxicity. However, amprenavir/fosamprenavir levels are significantly lowered by oral contraceptives and co-administration is not recommended; it is not known if low-dose ritonavir boosting raises amprenavir levels sufficiently to allow co-administration. Depot medroxyprogesterone acetate (Depo-Provera, DMPA) pharmacokinetics are not significantly affected by nevirapine, efavirenz, or nelfinavir, and levels of these drugs were not significantly altered by DMPA *[19]*. Potential interactions between antiretroviral agents and the transdermal contraceptive patch, vaginal ring, and other implantable forms of contraception have not yet been defined. Permanent sterilization is an appropriate option only for those women who are certain they do not desire future childbearing. Advance counseling and discussion about sterilization is strongly encouraged in order to enable the woman to make a well-informed choice.

The postpartum period provides an opportunity to review and optimize women's health care; this should include cervical cancer screening and routine immunizations. This period also provides an opportunity to assess the need for behavioral health interventions; this should include mental health screening, including an assessment for signs of postpartum depression, and substance abuse treatment as indicated. Providers should also re-emphasize the importance of safer sex practices.

References

1. Cohn SE, Umbleja T, Mrus J, et al. Prior illicit drug use and missed prenatal vitamins predict nonadherence to antiretroviral therapy in pregnancy: adherence analysis A5084. *AIDS Patient Care STDS.* 2008;22(1):29-40.
2. Ickovics JR, Wilson TE, Royce RA, et al. Prenatal and postpartum zidovudine adherence among pregnant women with HIV: results of a MEMS substudy from the Perinatal Guidelines Evaluation Project. *J Acquir Immune Defic Syndr.* 2002;30(3):311-315.

3. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr.* 2008;48(4):408-417.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
5. Le Moing V, Chene G, Carrieri MP, et al. Clinical, biologic, and behavioral predictors of early immunologic and virologic response in HIV-infected patients initiating protease inhibitors. *J Acquir Immune Defic Syndr.* 2001;27(4):372-376.
6. Murri R, Ammassari A, Gallicano K, et al. Patient-reported nonadherence to HAART is related to protease inhibitor levels. *J Acquir Immune Defic Syndr.* 2000;24(2):123-128.
7. 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. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
8. Bardeguez AD, Shapiro DE, Mofenson LM, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *J Acquir Immune Defic Syndr.* 2003;32(2):170-181.
9. Watts DH, Lu M, Thompson B, et al. Treatment interruption after pregnancy: effects on disease progression and laboratory findings. *Infect Dis Obstet Gynecol.* 2009;2009:456717.
10. Centers for Disease Control and Prevention (CDC). Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: a practical guide and model protocol. 2004; www.cdc.gov/hiv/topics/testing/resources/guidelines/pdf/Labor&DeliveryRapidTesting.pdf.
11. Rousseau CM, Nduati RW, Richardson BA, et al. Longitudinal analysis of human immunodeficiency virus type 1 RNA in breast milk and of its relationship to infant infection and maternal disease. *J Infect Dis.* 2003;187(5):741-747.
12. Shapiro RL, Holland DT, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. *J Infect Dis.* 2005;192(5):720-727.
13. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother.* 2009;53(3):1170-1176.
14. Lidstrom J, Kumwenda N, Kafulafula G, et al. Antiretroviral treatment of HIV-infected women can induce multi-class drug resistance in their breastfeeding infants. *Antiviral Ther.* 2009;14 Suppl 1:A158.
15. Lidstrom J, Guay L, Musoke P, et al. Multi-class drug resistance arises frequently in HIV-infected breastfeeding infants whose mothers initiate HAART postpartum. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 920.
16. Zeh C, Weidle P, Nafisa L, et al. Emergence of HIV-1 Drug Resistance among Breastfeeding Infants Born to HIV-infected Mothers Taking Antiretrovirals for Prevention of Mother-to-Child Transmission of HIV: The Kisumu Breastfeeding Study, Kenya. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 84LB.
17. Cates W, Jr., Steiner MJ. Dual protection against unintended pregnancy and sexually transmitted infections: what is the best contraceptive approach? *Sex Transm Dis.* 2002;29(3):168-174.
18. Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. *Am J Obstet Gynecol.* 2007;197(2):144 e141-148.
19. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther.* 2007;81(2):222-227.

Neonatal Postnatal Care (Updated May 24, 2010)

INFANTS BORN TO MOTHERS WITH UNKNOWN HIV INFECTION STATUS

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 initiation of infant antiretroviral prophylaxis immediately if the rapid test is positive (AII).***
- ***If the rapid HIV antibody test is positive, standard antibody confirmatory testing (e.g., Western blot) should be performed on the mother (or her infant) as soon as possible. If the confirmatory test is negative, antiretroviral prophylaxis can be discontinued (AIII).***
- ***If the HIV antibody confirmatory test is positive, a newborn HIV DNA PCR should be obtained (AIII).***
- ***If the newborn HIV DNA PCR is positive, antiretroviral 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 (AI). The HIV-infected infant should also receive chemoprophylaxis against Pneumocystis jirovecci pneumonia (PCP) with oral trimethoprim-sulfamethoxazole according to guidelines (AII).***

If maternal HIV status is unknown and a rapid HIV antibody test was not performed on the mother during labor, rapid HIV antibody testing of the mother and/or infant is recommended as soon as possible after birth, with initiation of antiretroviral prophylaxis for the infant immediately if the rapid test is positive. 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 rapid antibody test on the mother or the infant 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 the mother (or her infant) as soon as possible after the initial positive rapid test *[1]*. A positive HIV antibody test in the infant indicates maternal but not necessarily infant HIV infection. Diagnosing HIV infection in infants <18 months of age requires virologic testing. If the confirmatory test on the mother (or infant) is negative, antiretroviral 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, antiretroviral prophylaxis should be promptly discontinued and the infant should receive treatment for HIV infection with standard combination antiretroviral therapy 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 (**http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf**). In addition, all newly diagnosed HIV-infected infants should receive chemoprophylaxis to prevent *Pneumocystis jirovecii* pneumonia (PCP) with oral trimethoprim-sulfamethoxazole beginning at 4–6 weeks of age *[2]*.

INFANT ANTIRETROVIRAL PROPHYLAXIS

Panel's Recommendations:

- ***The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal HIV transmission (AI).***
- ***Zidovudine should be initiated as close to the time of birth as possible, preferably within 6 to 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 <35 weeks than for infants ≥35 weeks (see text) (AII).***
- ***In the United States, the use of antiretroviral drugs other than zidovudine cannot be recommended in premature infants due to lack of dosing and safety data (BIII).***
- ***The use of intrapartum/neonatal zidovudine is recommended regardless of maternal zidovudine resistance history (BIII).***
- ***The decision to combine additional drugs with the 6-week zidovudine regimen should be accompanied by consultation with a pediatric HIV specialist and a discussion of the potential risks and benefits of this approach with the mother, preferably before delivery (BIII).***
- ***Some experts consider the use of zidovudine in combination with other antiretroviral drugs in certain situations, although the optimal prophylactic regimen for infants born to women in these circumstances is unknown (CIII).***
- ***Decisions regarding the use of additional drugs for the neonate will depend on the history of maternal past and current antiretroviral drug exposure, maternal HIV RNA level at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant. If additional drugs are used, choice of drugs and dosing recommendations should be determined in consultation with a pediatric HIV specialist (CIII).***
- ***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 antiretroviral drugs to reduce perinatal HIV transmission. The 6-week neonatal zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed infants *[3-4]*. **Table 7** shows dosing for intravenous intrapartum zidovudine given in continuous infusion during labor and neonatal zidovudine dosing. **Table 8** shows intrapartum and neonatal dosing for additional drugs to be considered in certain situations as delineated below.

The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 2 mg/kg body weight orally every 6 hours for the first 6 weeks of life, starting as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. If given intravenously, the dose is 1.5 mg/kg body weight every 6 hours. However, some international studies have used an oral infant zidovudine dose of 4 mg/kg body weight twice daily for prophylaxis *[5-9]*. Zidovudine is now approved for two or three times a day dosing when used for treatment of HIV-infected children aged 4 weeks or older and weighing 4 kg or greater. Although there are no definitive data to show pharmacokinetic equivalence of giving double the standard dose at a longer interval when using zidovudine for prophylaxis or whether such dosing has equivalent efficacy in reducing perinatal transmission, a regimen of dosing twice instead of four times daily may increase adherence to the regimen and could be considered when there are concerns about adherence to drug administration to the infant. However, there is inadequate hematologic safety data with administration of double the standard dose of zidovudine

twice daily in infants younger than 1 month of age. Frequent hematological monitoring is recommended in this instance.

A simplified zidovudine dosing regimen has been developed for use in low resource settings. This regimen consists of 10 mg given twice daily for infants weighing less than 2.5 kg at birth and 15 mg given twice daily for infants weighing more than 2.5 kg at birth. The advantage of this simplified regimen is that it avoids the need for dosing calculations and involves administration of either 1.0 or 1.5 mL of zidovudine syrup. The disadvantage of this dosing regimen is that, compared to mg-per-kg dosing, infants with birth weight greater than 3.75 kg will receive a smaller zidovudine dose and infants less than 3.75 kg will receive a larger zidovudine dose. This regimen could be used for infants in higher resource settings born after 35 weeks gestation if simplicity in zidovudine dosing and administration is of prime importance.

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 to older infants. Because premature infants have even greater immaturity in hepatic metabolic function than full-term infants, further prolongation of clearance is seen *[10-11]*. The recommended zidovudine dosage for infants <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 2 weeks of age if ≥30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.

A 4-week neonatal chemoprophylaxis regimen is recommended in the United Kingdom *[12-13]*. This approach may be considered if there are concerns about adherence or toxicity with the 6-week regimen. An observational study in Ireland, where 4 weeks of infant zidovudine post-exposure chemoprophylaxis is standard (given in combination with maternal antiretroviral prophylaxis), reported a transmission rate of 1% in 835 HIV-exposed infants, which may be similar to transmission rates observed in the United States where 6 weeks of infant zidovudine prophylaxis is standard *[13]*. However, the optimal duration of neonatal zidovudine chemoprophylaxis has not been established in clinical trials and in the United States, when there are not concerns about adherence or toxicity, the standard 6-week infant zidovudine regimen is recommended.

General Considerations for Choice of Infant Prophylaxis

In certain situations, some experts combine the 6-week infant zidovudine prophylaxis regimen with additional antiretroviral drugs. Whether combining zidovudine with other antiretroviral drugs provides additional efficacy for prevention of transmission has not been proven in clinical trials. Additionally, appropriate drug formulations and dosing regimens for neonates are incompletely defined and there are minimal data about 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***). Therefore, the use of combination antiretroviral prophylaxis for the infant involves balancing potential benefits (in terms of preventing perinatal HIV transmission) with risks (in terms of toxicity to the infant).

Infants born to mothers who have received standard antepartum and intrapartum antiretroviral prophylaxis and have undetectable viral load are at very low risk of HIV transmission. However, the risk of transmission is increased when the mother has high viral load at delivery or when the mother has not received the full antepartum and/or intrapartum prophylaxis regimen. In such situations, some experts feel that the potential benefit of combining zidovudine infant prophylaxis with additional antiretroviral drugs may exceed the risk of multiple drug exposure to the infant. These situations include:

a. infants born to mothers who received antepartum and intrapartum antiretroviral drugs but who had suboptimal viral suppression at delivery, particularly if the infant was delivered vaginally;

b. infants born to mothers who received only intrapartum antiretroviral drugs;

c. infants born to mothers who received no antepartum or intrapartum antiretroviral drugs; and

d. infants born to mothers with known antiretroviral drug-resistant virus.

In each of these situations, there is a spectrum of transmission risk that will depend on a number of maternal and infant factors (e.g., maternal viral load, mode of delivery, gestational age at delivery); the risks and benefits of infant exposure to antiretroviral drugs in addition to zidovudine will differ depending on where the mother/child falls in that risk spectrum. For example, an infant born vaginally to a mother with a delivery HIV RNA level of ≥100,000 copies/mL has a higher risk of acquiring HIV infection than an infant born by cesarean delivery to a mother with a delivery HIV RNA level of approximately 10,000 copies/mL. Thus, a generic recommendation regarding use of combination drug regimens in these situations cannot be made and each situation needs to be considered individually. There are no data evaluating the efficacy of specific combination regimens in this situation and the choice of drugs in the neonate is limited (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis**). Decisions to use combination infant antiretroviral prophylaxis should be made in consultation with a pediatric HIV specialist before delivery and should be accompanied by a discussion with the mother of the potential risks and benefits of this approach.

Antiretroviral combinations with the greatest experience in neonates are zidovudine in combination with single-dose nevirapine and the dual NRTI combination of zidovudine and lamivudine combined with and/or without the NNRTI nevirapine. Newborn and neonatal dosing information is not available for either nelfinavir or the currently available boosted PIs. Caution should be exercised when using ritonavir or boosted PIs in neonates because both ritonavir and lopinavir/ritonavir have been reported to cause heart block. Careful infant monitoring is needed if combination drugs are provided (see **Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants**).

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.

Infant Antiretroviral Prophylaxis Recommendations for Specific Clinical Situations

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

Infants born to women who received standard antiretroviral prophylaxis regimens during pregnancy and labor and had undetectable viral load at delivery, or born to mothers with low viral load at delivery and delivered by cesarean section, have a very small risk of HIV acquisition. For example, in PACTG 316, the infection rate in infants born to women receiving antepartum PI-based therapy was 0.7% of 269 infants if delivery HIV RNA was <400 copies/mL *[4]*. Such infants should receive the 6-week zidovudine infant prophylaxis regimen. The benefit of combining zidovudine with additional antiretroviral drugs in reducing transmission in this situation would be very limited and this combination is not recommended.

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 receiving antiretroviral drugs as well as in antiretroviral-naïve women *[14-16]*. Scheduled cesarean delivery is recommended for prevention of perinatal transmission for women who have received antepartum antiretroviral drugs but have detectable viremia near the time of delivery (i.e., HIV RNA >1,000 copies/mL) (see **Intrapartum Care** and **Transmission and Mode of Delivery**). In PACTG 316, transmission occurred in 0% of 17 infants when maternal delivery HIV RNA was >10,000 copies/mL and the infant was born by scheduled cesarean delivery *[4]*. However, not all women with detectable viremia near delivery will undergo cesarean delivery. Infants born to mothers with higher viral load near delivery, particularly if delivered vaginally, will have a greater risk

of HIV acquisition. There is a gradient of transmission risk based on HIV RNA levels as well as type of maternal antiretroviral therapy. In the Women and Infants Transmission Study, the risk of HIV transmission in women receiving triple combination antiretroviral prophylaxis was ≤1.8% in women with delivery HIV RNA <30,000 copies/mL and increased to 4.8% in women with HIV RNA ≥30,000 copies/mL *[16]*.

There are no data to address whether a more intensive combination infant prophylaxis regimen when the mother has detectable viremia near delivery provides further protection against transmission or at what level of viremia this risk becomes significant enough to outweigh the potential risks of infant combination antiretroviral exposure.

All infants should receive zidovudine for 6 weeks. As discussed earlier (see **Intrapartum Care**), in the PACTG 316 study, the addition of single-dose maternal/infant nevirapine did not reduce the risk of transmission among women who were receiving primarily combination therapy during pregnancy; there were no significant differences in transmission rates between the single-dose nevirapine or placebo groups in any HIV RNA subgroup, although only a small proportion (11%) of the women had HIV RNA levels >10,000 copies/mL at delivery. Given the lack of additional efficacy of single-dose nevirapine in this study and the risk of nevirapine resistance in the mother (and the infant should the infant become infected despite prophylaxis), addition of maternal/infant single-dose nevirapine is not recommended in this situation. Some experts would consider the use of dual or triple antiretroviral drug infant prophylaxis in selected circumstances (e.g., infants born vaginally to mothers with very high viral load near delivery).

Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs

All infants whose mothers have received only intrapartum antiretroviral drugs should be given zidovudine for 6 weeks. The post-exposure prophylaxis provided by the 6-week course of infant zidovudine treatment is a critical component of prevention when no maternal antepartum antiretroviral drugs have been received. The PETRA study demonstrated that intrapartum prophylaxis alone, without an infant post-exposure prophylaxis component, is not effective in reducing perinatal transmission *[5]*. Additionally, a study in Thailand indicated that when the mother has <4 weeks of antenatal zidovudine, longer infant zidovudine prophylaxis (6 weeks compared to 3 days) is required for optimal efficacy *[17]*.

As discussed in the **Intrapartum Care** section, in this situation, some experts would add maternal/infant single-dose nevirapine to the standard intravenous intrapartum/6-week infant zidovudine regimen. This situation differs from that studied in PACTG 316 because, in this circumstance, the mother has received no antepartum antiretroviral drugs. Nevirapine resistance can occur in infants exposed to single-dose nevirapine who become infected despite prophylaxis. The addition of at least 7 days of lamivudine to the 6-week infant zidovudine regimen may reduce the development of nevirapine resistance in such infants, similar to what is recommended for women receiving single-dose nevirapine (see **Intrapartum Care** and **Table 7**) *[18-19]*. However, although all HIV-infected mothers exposed to single-dose nevirapine are at risk of resistance, only a small proportion of infants exposed to single-dose nevirapine become infected and would benefit from the addition of lamivudine. Combination zidovudine/lamivudine may be associated with more severe hematologic toxicity than zidovudine alone (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis** and see **Table 8** for dosing information), and more frequent hematologic monitoring of infants receiving this combination is recommended, particularly if it is given for more than 1 week *[20]*.

Although controversial, other experts might consider use of dual or triple antiretroviral drug infant prophylaxis for 6 weeks in this situation because maternal viral load at delivery will not be known and no antenatal therapy has been administered.

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 antiretroviral drugs should be started on prophylactic zidovudine as soon as possible after delivery. Observational studies suggest that post-exposure prophylaxis to the infant alone may be helpful in preventing HIV transmission. Epidemiologic data from a New York State study indicate a decline in transmission when infants were given zidovudine for the first 6 weeks of life compared to no prophylaxis *[21]*. Transmission rates were 9% (95% CI = 4.1%–17.5%) with zidovudine prophylaxis of newborns only (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 *[22]*. Thus, when no maternal antepartum or intrapartum antiretroviral drugs have been received, the 6-week infant zidovudine prophylaxis regimen should be initiated as soon as possible after birth.

The interval during which post-exposure prophylaxis can be initiated and still be of benefit is undefined. When prophylaxis was delayed beyond 48 hours after birth in the New York State study, no efficacy could be demonstrated. Data from studies of animals indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, antiretroviral prophylaxis initiated 24 to 36 hours after exposure has usually not been effective for preventing infection, although later administration has been associated with decreased viremia *[23-25]*. Initiation of post-exposure prophylaxis after 2 days of age is not likely to be efficacious in preventing transmission and, by age 14 days, infection would already be established in most infants *[26]*.

Some clinicians view this situation as analogous to nosocomial post-exposure prophylaxis *[27]* and may decide to provide zidovudine in combination with one or more other antiretroviral agents. However, there are no clinical trial data to demonstrate increased efficacy of combination antiretroviral drugs with 6-week zidovudine for infant-only post-exposure prophylaxis in nonbreastfeeding populations, although there is a clinical trial ongoing in the United States, South America, and South Africa.

Data are not available to demonstrate that 6 weeks of infant zidovudine combined with infant single-dose nevirapine at birth is superior to 6 weeks of zidovudine alone. A clinical trial of infant post-exposure prophylaxis in breastfeeding infants in Malawi (see **Lessons from International Clinical Trials of Short-Course Regimens for Prevention of HIV Perinatal Transmission** and **Table 3**) showed that the addition of 1 week of zidovudine to single-dose infant nevirapine was 36% more effective in reducing perinatal transmission compared to single-dose infant nevirapine alone *[7]*. Although this situation is not analogous to adding nevirapine to 6 weeks of zidovudine, particularly in formula-fed infants, some experts would provide single-dose nevirapine at birth to the infant in this situation with the addition of at least 7 days of lamivudine to reduce the risk of nevirapine resistance should the infant become infected (see **Table 8** for dosing information).

Although controversial, other experts might consider use of triple drug combination therapy in the infant for the 6-week prophylaxis period, similar to occupational post-exposure prophylaxis.

Infants Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal prophylactic regimen for newborns of women with antiretroviral drug-resistant virus is unknown. Antiretroviral prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery.

Data from the Women and Infants Transmission Study (WITS) suggest that in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive rather than -resistant virus may be preferentially transmitted *[28-29]* (see **Table 7**). 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.

There have been some studies suggesting that antiretroviral drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility *[29]*. However, transmission of multi-drug resistant virus from mother to child has been reported *[30-32]*.

The use of zidovudine in combination with other antiretroviral drugs selected on the basis of maternal virus resistance testing may be considered for these newborns. The efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs. Decisions regarding use of additional drugs will depend on the history of maternal past and current antiretroviral drug exposure, HIV RNA level at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant. Additional antiretroviral drugs that can be added to zidovudine include lamivudine and nevirapine.

Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis

Short-term toxicity of infant zidovudine prophylaxis has been minimal, consisting primarily of transient hematologic toxicity, mainly anemia, which generally resolves by age 12 weeks. Data on the toxicity of multiple antiretroviral drug exposure for the infant are limited.

The latest information on neonatal dosing for antiretroviral drugs can be found in the ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***. Other than zidovudine, the NRTI with the most experience in use for neonatal prophylaxis is lamivudine, although neonatal exposure to combination zidovudine/lamivudine has generally been limited to 1 week *[5-6, 33]*. Six weeks of infant zidovudine/lamivudine exposure has been reported in a few studies; 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 where 6 weeks of zidovudine/lamivudine was provided for infant prophylaxis in infants who were also exposed to antepartum zidovudine/lamivudine, more severe anemia and neutropenia were observed than in a historical cohort exposed only to zidovudine; anemia was observed 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 *[34]*. Similarly, in a Brazilian study using 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 *[35]*. In a Phase I study of stavudine in pregnant women, infants received 6 weeks of zidovudine/lamivudine and a single dose of stavudine at age 1 and 6 weeks; 43% of 14 infants experienced grade 3 hematologic toxicity after birth (36% neutropenia and 7% anemia) *[36]*. Finally, in 3 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% to 62% of infants *[37-39]*. Experience with other NRTI drugs for neonatal prophylaxis is more limited *[40-41]*. Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs *[34, 42-45]*.

Nevirapine is the only NNRTI drug with a pediatric drug formulation and neonatal dosing information (see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***). Chronic, multiple-dose nevirapine can be rarely associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving single-dose nevirapine or in breastfeeding infants receiving 6 to 14 weeks of daily infant nevirapine prophylaxis to prevent transmission of HIV via breast milk *[46-47]*. However, nevirapine drug resistance may occur with exposure to single-dose nevirapine should the infant become infected despite prophylaxis (see **Table 7**). If multiple-dose daily nevirapine is used as part of a combination infant prophylaxis regimen, some experts would stop nevirapine first and continue the other drugs for a period of time (e.g., at least 7 days). This drug administration strategy is adopted because the prolonged half-life of nevirapine in infants results in a period of persistent subtherapeutic level of nevirapine if all drugs are stopped simultaneously, resulting in a risk of nevirapine resistance should the infant become infected

despite prophylaxis. Antiretroviral drug resistance testing is recommended prior to initiation of antiretroviral therapy in all HIV-infected infants (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. However, dosing information for newborn infants is available only for nelfinavir, which has highly variable levels in neonates and requires high doses (more than 45 mg/kg body weight twice daily and possibly as high as 75 mg/kg body weight twice daily) to achieve target levels (see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***) *[39, 41]*. Pharmacokinetic data for treatment of HIV-infected infants aged 2 to 6 weeks of age with lopinavir/ritonavir are available. Although the lopinavir area under the curve with dosing 300 mg lopinavir/75 mg ritonavir per meter^2 body surface area twice daily was significantly lower than observed for infants older than 6 weeks, treatment was well tolerated, and 80% of 10 infants had viral control at 6 months *[48]*. Although under study, data are not yet available for infants younger than 2 weeks of age. However, there have been 4 premature infants (2 sets of twins) started on lopinavir/ritonavir from birth who developed heart block that resolved following discontinuation of the drug *[49-50]*. 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.

Dosing for premature infants is only available for zidovudine (see **Table 7**), making use of additional antiretroviral drugs more problematic in this group. Renal and hepatic metabolism is immature in preterm infants, which increases the risk of overdosing and toxicity. Additionally, zidovudine is the only antiretroviral drug available in intravenous formulation. Therefore, the 6-week zidovudine prophylaxis regimen is recommended for preterm infants at gestational age-appropriate doses. Use of antiretroviral drugs other than zidovudine cannot be recommended in premature infants due to lack of dosing and safety data.

Initial Postnatal Management of the HIV-Exposed Neonate

Panel's Recommendations:

- ***A complete blood count (CBC) and differential should be performed on the newborn as a baseline evaluation (BIII).***
- ***Decisions about the timing of subsequent monitoring of the hematologic parameters in the infant will depend on baseline hematologic values, gestational age at birth, clinical condition of the infant, dose of zidovudine 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 during the first few weeks of life for infants exposed to combination antiretroviral therapy in utero or during the neonatal period (CIII).***
- ***If hematologic abnormalities are identified while the infant is receiving prophylaxis, decisions on whether to continue infant antiretroviral 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 of serum lactate may 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 at a minimum at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months (AII).***
- ***To prevent Pneumocystis jirovecci pneumonia (PCP), all infants born to women with HIV infection should begin PCP prophylaxis at age 4–6 weeks, after completion of the zidovudine 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) (AIII).***

A CBC and differential should be performed on the newborn as a baseline evaluation before administration of zidovudine. Anemia has been the primary complication of the 6-week zidovudine regimen in the neonate. In PACTG 076, infants in the zidovudine group had lower hemoglobin at birth than infants in the placebo group, with the maximal difference (1 gm/dL) occurring at age 3 weeks *[3]*. The lowest mean value for hemoglobin (10 gm/dL) occurred at 6 weeks of age in the zidovudine group. By 12 weeks of age, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed between groups.

Decisions about the timing of subsequent hematologic monitoring of infants following birth will depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the infant, dose of zidovudine being administered, receipt of concomitant medications, and maternal antepartum therapy. Some experts re-check hematologic values in healthy infants receiving zidovudine prophylaxis only if the child is symptomatic, although others re-check hemoglobin and neutrophil count after 4 weeks of zidovudine prophylaxis.

If hematologic abnormalities are found, decisions on whether to continue infant antiretroviral prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether the infant has related symptoms, duration of infant prophylaxis received, the risk of HIV infection in the infant (as assessed by whether the mother had received antiretroviral prophylaxis, her viral load near delivery, and mode of delivery), and availability of alternative interventions (e.g., erythropoietin, transfusion). Consideration may be given to reducing the duration of infant prophylaxis from 6 to 4 weeks. Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.

Data are limited concerning potential toxicities in infants whose mothers have received combination antiretroviral therapy or when the infant receives more than zidovudine prophylaxis. Some studies suggest a higher incidence of anemia and/or neutropenia in infants who receive zidovudine prophylaxis but are born to mothers who received combination therapy compared to infants born to mothers who received only zidovudine during pregnancy *[45, 51-52]*. In PACTG 316, where 77% of mothers received antenatal combination therapy, significant grade 3 or higher anemia was seen in 13% and neutropenia in 12% of infants. Additionally, as discussed earlier, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine combination prophylaxis than in those receiving zidovudine alone.

Thus, more intensive monitoring of hematologic values and serum chemistry and liver function assays during the first few weeks of life is advised for these infants, based on what is known about the side effects of the drugs. For example, because hepatic toxicity is observed with most of the antiretroviral drugs, measurement of baseline liver transaminase levels in infants with exposure to multiple antiretroviral drugs *in utero* or receiving infant combination drug prophylaxis might be considered. Hematologic toxicity appears to be more significant in infants who receive both zidovudine and lamivudine as infant prophylaxis for 6 weeks and who were exposed to antepartum zidovudine/lamivudine. More frequent monitoring of hematologic values in these infants versus in infants who receive only zidovudine prophylaxis might be considered *[34]*. Additionally, as previously stated, hematologic safety data with administration of double the standard dose of zidovudine twice daily in infants under a month of age are inadequate. More frequent hematological monitoring is also recommended in this instance.

Although hyperlactatemia has been reported in infants with *in utero* antiretroviral exposure, this appears transient and in most cases asymptomatic *[53-54]*. Routine measurement of serum lactate in asymptomatic neonates to assess for potential mitochondrial toxicity is not recommended because the clinical relevance is unknown and predictive value for toxicity appears poor *[53-54]*. However, should an infant develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms, obtaining serum lactate should be considered. If serum lactate is significantly abnormal (>5 mmol/L) in an infant with symptoms, antiretroviral prophylaxis should be discontinued and an expert in pediatric HIV infection should be consulted regarding potential alternate prophylaxis.

To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV infection should begin trimethoprim-sulfamethoxazole prophylaxis at age 6 weeks, after completion of the zidovudine prophylaxis, 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***) *[2]*.

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 18 months of age; therefore, standard antibody tests should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed at a minimum at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months *[55]*. Some experts also perform a virologic test at birth, especially if the woman has 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 *[3, 56]*. However, the effect of combination antiretroviral therapy in the mother or newborn 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 more optimal for diagnosing infection in the neonatal period.

HIV may be presumptively excluded with two or more negative tests with one at ≥14 days and another at ≥1 month of age. Definitive exclusion of HIV in nonbreastfed infants may be based on two negative virologic

tests at ≥1 month and ≥4 months of age. Many experts confirm HIV-negative status with an HIV antibody test at age 12 to 18 months. (Alternative algorithms exist for presumptive and definitive HIV exclusion *[55]*.)

Following birth, HIV-exposed infants should have a detailed physical examination and a thorough maternal history should be obtained. The HIV-infected mother may be coinfected with other pathogens that can be transmitted from mother to child, such as cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis. Infants born to mothers with such coinfections should undergo appropriate evaluation as indicated by maternal CD4 count and evidence of disease activity to rule out transmission of additional infectious agents. HIV-exposed infants born to HIV-infected mothers should follow the routine primary immunization schedule. Infants with known HIV infection may require modifications in the schedule for live virus vaccines (see ***USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children***).

Infant Feeding Practices and the 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. Postnatally, mothers should be advised that although antiretroviral therapy is likely to reduce free virus in the plasma, the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and may therefore continue to pose a transmission risk *[57]*.

Late HIV transmission events in infancy have recently been reported from three HIV-infected children. In each case HIV infection is suspected to have occurred as a result of infant consumption of premasticated food given to them from 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 *[58]*.

Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants

Panel's Recommendations:

- ***Children with in utero/neonatal antiretroviral exposure 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 antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of the nucleoside analogue antiretroviral drugs (CIII).***

Data remain insufficient to address the effect that exposure to zidovudine or other antiretroviral 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 *[59-61]*. As discussed earlier in the section on **NRTI Drugs and Mitochondrial Toxicity**, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Continued evaluation of early and late effects of *in utero* antiretroviral exposure is ongoing through several mechanisms, 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 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 therapy, 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 antiretroviral drugs. Information regarding such exposure should be part of the ongoing permanent medical record of the child, particularly for uninfected children. Children with *in utero* antiretroviral exposure who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction *[62-64]*. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. Long-term follow-up should include yearly physical examinations of all children exposed to antiretroviral drugs.

HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* antiretroviral exposure. To the extent permitted by federal law and regulations, data from these confidential registries can be used to compare with information from birth defect and cancer registries to identify potential adverse outcomes.

References

1. Centers for Disease Control and Prevention (CDC). Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: a practical guide and model protocol. 2004; www.cdc.gov/hiv/topics/testing/resources/guidelines/pdf/Labor&DeliveryRapidTesting.pdf.
2. Centers for Disease Control and Prevention (CDC). Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med.* 1994;331(18):1173-1180.
4. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV-1 transmission: a randomized trial. *JAMA.* 2002;288(2):189-198.
5. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
6. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* 2003;187(5):725-735.
7. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet.* 2003;362(9391):1171-1177.
8. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA.* 2004;292(2):202-209.
9. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS.* 2006;20(9):1281-1288.
10. Capparelli E, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* 2003;142(1):47-52.
11. Mirochnick M, Capparelli E, Connor J. Pharmacokinetics of zidovudine in infants: a population analysis across studies. *Clin Pharmacol Ther.* 1999;66(1):16-24.
12. de Ruiter A, Mercey D, Anderson J, et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med.* 2008;9(7):452-502.
13. Ferguson W, Good M, Walksh A, et al. Four weeks of neonatal antiretroviral therapy (ART) is sufficient to optimally prevent mother to child transmission (PMTCT) of HIV. 48th Annual ICAAC/IDSA 46th Annual Meeting, October 25-28, 2008; Washington, DC. Abstract H-459, page 400.

14. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
15. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med.* 1999;341(6):394-402.
16. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
17. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med.* 2000;343(14):982-991.
18. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487. Epub 2006 Jan 2011.
19. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
20. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
21. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
22. Wade NA, Birkhead GS, French PT. Short courses of zidovudine and perinatal transmission of HIV (letter). *N Engl J Med.* 1999;340(13):1040-1043.
23. Van Rompay KK, Otsyula MG, Marthas ML, et al. Immediate zidovudine treatment protects simian immunodeficiency virus-infected newborn macaques against rapid onset of AIDS. *Antimicrob Agents Chemother.* 1995;39(1):125-131.
24. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. *Science.* 1995;270(5239):1197-1199.
25. Bottiger D, Johansson NG, Samuelsson B, et al. Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. *AIDS.* 1997;11(2):157-162.
26. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS.* 1995;9(9):F7-11.
27. Panlilio AL, Cardo DM, Grohskopf LA, et al. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep.* 2005;54(RR-9):1-17.
28. Colgrove RC, Pitt J, Chung PH, et al. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS.* 1998;12(17):2281-2288.
29. Bauer GR, Colgrove RC, Larussa PS, et al. Antiretroviral resistance in viral isolates from HIV-1-transmitting mothers and their infants. *AIDS.* 2006;20(13):1707-1712.
30. 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;19(9):989-990.
31. Desai N, Mathur M. Selective transmission of multidrug resistant HIV to a newborn related to poor maternal adherence. *Sex Transm Infect.* 2003;79(5):419-421.
32. De Jose MI, Ramos JT, Alvarez S, et al. Vertical transmission of HIV-1 variants resistant to reverse transcriptase and protease inhibitors. *Arch Intern Med.* 2001;161(22):2738-2739.
33. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis.* 1998;178(5):1327-1333.
34. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
35. Lambert JS, Nogueira SA, Abreu T, et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. *Sex Transm Infect.* 2003;79(6):448-452.

36. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis.* 2004;190(12):2167-2174.
37. Zorrilla CD, Van Dyke R, Bardeguez A, et al. Clinical response and tolerability to and safety of saquinavir with low-dose ritonavir in human immunodeficiency virus type 1-infected mothers and their infants. *Antimicrob Agents Chemother.* 2007;51(6):2208-2210.
38. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother.* 2007;51(2):783-786.
39. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* 2005;39(2):189-194.
40. Gray G, Violari A, McIntyre J, et al. Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: its role in preventing HIV infection in infants. *J Acquir Immune Defic Syndr.* 2006;42(2):169-176.
41. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr.* 2002;29(5):455-463.
42. Torres SM, Walker DM, Carter MM, et al. Mutagenicity of zidovudine, lamivudine, and abacavir following in vitro exposure of human lymphoblastoid cells or in utero exposure of CD-1 mice to single agents or drug combinations. *Environ Mol Mutagen.* 2007;48(3-4):224-238.
43. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS.* 2003;17(14):2053-2061.
44. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis.* 2006;194(8):1089-1097.
45. Feiterna-Sperling C, Weizsaecker K, Bührer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr.* 2007;45(1):43-51.
46. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet.* 2008;372(9635):300-313.
47. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med.* 2008;359(2):119-129.
48. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
49. Lopriore E, Rozendaal L, Gelinck LB, et al. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565.
50. McArthur MA, Kalu SU, Foulks AR, et al. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129.
51. El Beitune P, Duarte G. Antiretroviral agents during pregnancy: consequences on hematologic parameters in HIV-exposed, uninfected newborn infant. *Eur J Obstet Gynecol Reprod Biol.* 2006;128(1-2):59-63.
52. Watson WJ, Stevens TP, Weinberg GA. Profound anemia in a newborn infant of a mother receiving antiretroviral therapy. *Pediatr Infect Dis J.* 1998;17(5):435-436.
53. Ekouevi DK, Touré R, Becquet R, et al. Serum lactate levels in infants exposed peripartum to antiretroviral agents to prevent mother-to-child transmission of HIV: Agence Nationale de Recherches Sur le SIDA et les Hépatites Virales 1209 study, Abidjan, Ivory Coast. *Pediatrics.* 2006;118(4):e1071-1077.
54. Noguera A, Fortuny C, Muñoz-Almagro C, et al. Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. *Pediatrics.* 2004;114(5):e598-603.
55. Centers for Disease Control and Prevention (CDC). Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
56. Kovacs A, Xu J, Rasheed S, et al. Comparison of a rapid nonisotopic polymerase chain reaction assay with four commonly used methods for the early diagnosis of human immunodeficiency virus type 1 infection in neonates and children. *Pediatr Infect Dis J.* 1995;14(11):948-954.

57. Gaillard P, Fowler MG, Dabis F, et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. *J Acquir Immune Defic Syndr.* 2004;35(2):178-187.
58. Gaur AH, Dominguez KL, Kalish ML, et al. Practice of feeding premasticated food to infants: a potential risk factor for HIV transmission. *Pediatrics.* 2009;124(2):658-666.
59. Culnane M, Fowler MG, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA.* 1999;281(2):151-157.
60. Hanson IC, Antonelli TA, Sperling RS, et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999;20(5):463-467.
61. Brogly S, Williams P, Seage G, 3rd,, et al. In utero nucleoside reverse transcriptase inhibitor exposure and cancer in HIV-uninfected children: an update from the pediatric AIDS clinical trials group 219 and 219C cohorts. *J Acquir Immune Defic Syndr.* 2006;41(4):535-536.
62. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354(9184):1084-1089.
63. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS.* 2003;17(12):1769-1785.
64. Spector SA, Saitoh A. Mitochondrial dysfunction: prevention of HIV-1 mother-to-infant transmission outweighs fear. *AIDS.* 2006;20(13):1777-1778.

Appendix: Financial Disclosure for Members of HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission – January 2010

Name	Panel Status*	Company	Relationship
Erika Aaron	M	Gilead Pharmaceuticals Tibotec	Research Support Research Support
Elaine Abrams	M	NONE	N/A
Jean Anderson	M	Abbott Tibotec	Honoraria, Funded printing of provider tool for preconception care Honoraria, Advisory Board
Dawn Averitt Bridge	M	Boehringer Ingelheim Bristol-Myers Squibb Gilead Merck Tibotec	Consultant Advisory Board, Consultant Advisory Board Advisory Board, Honoraria, Consultant Consultant
Rana Chakraborty	M	NONE	N/A
Susan E. Cohn		Tibotec	Advisory Board
Amanda Cotter	M	NONE	N/A
Susan Cu-Uvin	M	Bristol-Myers Squibb Family Health International (FHI) and the Contraceptive Research and Development Program (CONRAD)	Research Support Advisory Board
Judith Feinberg	M	Bristol-Meyers Squibb Glaxo Smith Kline Merck Pfizer Tibotec	Advisory Board, Research Support, Speakers' Bureau Speakers' Bureau Advisory Board, Speakers' Bureau Research Support, Speakers' Bureau Advisory Board, Research Support, Speakers' Bureau
Patricia Flynn	M	Tibotec	Clinical trials agreement
Mary Glenn Fowler	M	NONE	N/A
Robert Maupin	M	NONE	N/A
Howard Minkoff	M	NONE	N/A
Mark Mirochnick	M	NONE	N/A
Fatima Y. Prioleau	M	New York State Education	Stockholder
Stephen Spector	M	Pfizer Sanofi Pasteur	Stockholder Stockholder
Ruth Tuomala	M	NONE	N/A
Geoffrey A. Weinberg	M	Medimmune, Inc. Merck Vaccines Sanofi Pasteur Vaccines Glaxo Smith Kline Vaccines	Advisory Board Speaker's Bureau Speaker's Bureau Speaker's Bureau

Name	Panel Status*	Company	Relationship
Federal Government Representatives			
Songhai Barclift	GR	NONE	N/A
Brian Feit	GR	NONE	N/A
Edward Handelsman	GR	NONE	N/A
Denise Jamieson	GR	NONE	N/A
Lynne Mofenson	GR	NONE	N/A
Alan Shaprio	GR	NONE	N/A
Heather D. Watts	GR	NONE	N/A

* M = Member; GR = government representative; N/A = not applicable

Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

(Updated May 24, 2010)

Glossary of Terms for Supplement

Clastogenic: causing disruption or breakages of chromosomes

Mutagenic: inducing or capable of inducing genetic mutation

Genotoxic: damaging to genetic material (e.g., DNA, chromosomes)

Carcinogenic: producing or tending to produce cancer

Notes: (1) Some agents (e.g., certain chemicals or forms of radiation) are both mutagenic and clastogenic. (2) Genetic mutations and/or chromosome damage can contribute to cancer formation.

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Six nucleoside analogue reverse transcriptase inhibitors are currently approved (zalcitabine is no longer available in the United States). Data are available from clinical trials in human pregnancy for zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine. Tenofovir disoproxil fumarate is the first nucleotide analogue reverse transcriptase inhibitor. 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 only requires 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 FDA pregnancy category C.

- Animal carcinogenicity studies
  Abacavir is mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.
- Reproduction/fertility
  No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).
- Teratogenicity/developmental toxicity
  Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir

during organogenesis at doses of 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 treated with 500 mg/kg of abacavir beginning at embryo implantation and ending at weaning had an increased incidence of stillbirth and lower body weight 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. The prevalence of birth defects with first-trimester abacavir exposure was 3.0% (19/628, 95% CI: 1.8%–4.7%) comparedto total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention (CDC) surveillance of 2.7% *[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 to 12 weeks postpartum and to 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 recur within hours and may include life-threatening hypotension and death.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Best BM, Mirochnick M, Capparelli EV, et al. Impact of pregnancy on abacavir pharmacokinetics. *AIDS*, 2006. 20(4):553-60. http://www.ncbi.nlm.nih.gov/pubmed/16470119

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 to 1.7- and 3- times in mice and rats, respectively, 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 in pregnant rats and rabbits, respectively. Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 4.6% (17/370, 95% CI: 2.7%–7.3%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 monitored closely.

- Placental and breast milk passage
  Placental transfer of didanosine was limited in a Phase I/II safety and pharmacokinetic 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 regimen). At the time of delivery, cord-to-maternal blood ratio for didanosine (n=10) was 0.38 (range 0.0–2.00) and in 15/24 samples (62%), 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 to 36 weeks and treated through 6 weeks postpartum *[2]*. The drug was well tolerated during pregnancy by the women and the fetuses. Pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral 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 the combination of didanosine and stavudine (see **NRTI Drugs and Mitochondrial Toxicity** in Perinatal Guidelines). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis,* 1999. 180(5):1536-41. http://www.ncbi.nlm.nih.gov/pubmed/10515813
3. Chappuy H, Tréluyer JM, Jullien V, et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother,* 2004. 48(11):4332-6. http://www.ncbi.nlm.nih.gov/pubmed/15504861
4. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
5. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Inf,* 2002. 78(1):58-9. http://www.ncbi.nlm.nih.gov/pubmed/11872862
6. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS,* 2003. 17(2):272-3. http://www.ncbi.nlm.nih.gov/pubmed/12545093

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 the 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
  The incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice resulting 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. The prevalence of birth defects with first-trimester emtricitabine exposure was 2.9% (11/384, 95% CI: 1.4%–5.1%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 pharmacokinetics have been evaluated in 18 HIV-infected pregnant women receiving combination antiretroviral therapy including emtricitabine (200 mg once daily) at 30 to 36 weeks gestation and 6 to 12 weeks postpartum *[3]*. Emtricitabine exposure was modestly lower during the third trimester (8.6 µg*h/mL [5.2–15.9]) compared to the postpartum period (9.8 µg*h/mL [7.4–30.3]). Two-thirds (12/18) of pregnant women versus 100% (14/14) of postpartum women met the AUC target (10^{th} percentile in nonpregnant adults). Trough emtricitabine levels were also lower during pregnancy (C_{min} 52 ng/mL [14 – 180]) compared to 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, C_{max}, and C_{min} were 14.3 µg*h/mL; 1,680 ng/mL; and 76 ng/mL, respectively *[4]*.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Szczech GM, Wang LH, Walsh JP, et al. Reproductive toxicology of emtricitabine in mice and rabbits. Reproductive Toxicol 2003;17:95-108. *Reproductive Toxicol*, 2003. 17(1):95-108. http://www.ncbi.nlm.nih.gov/pubmed/12507664
3. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of emtricitabine in HIV-infected pregnant women and their neonates: TEmAA ANRS 12109. 15^{th} Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA Abstract 626. http://www.retroconference.org/2008/PDFs/626.pdf
4. Best B, Stek A, Hu C, et al. for the PACTG/IMPAACT P1026S team. High-dose lopinavir and standard-dose emtricitabine pharmacokinetics during pregnancy and postpartum. 15^{th} Conference on Retroviruses and Opportunistic Infections, February 3-8, 2008; Boston, MA. Abstract 629. http://www.retroconference.org/2008/PDFs/629.pdf

Lamivudine (Epivir, 3TC) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Lamivudine has weak mutagenic activity in 1 *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- to 70- times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the most commonly occurring birth defects (e.g., defects of the cardiovascular and genitourinary systems). No such increase in birth defects has been observed with lamivudine. The prevalence of birth defects with first-trimester lamivudine exposure was 2.9% (96/3,314, 95% CI: 2.3%–3.5%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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]*. Their infants, who only received lamivudine via breast milk, had a median plasma lamivudine concentration of 23 ng/mL (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 pharmacokinetics 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 for 1 week following birth to the infants*[2]*. The drug was well tolerated in the women at the recommended adult dose of 150 mg orally twice daily; pharmacokinetics were similar to those observed in nonpregnant adults, and no pharmacokinetic interaction with zidovudine was observed.

  Zidovudine and lamivudine, given in combination orally intrapartum, were 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 to 8 mg/kg/day for infants older than 3 months). There are currently no data on the pharmacokinetics of lamivudine between 2 and 6 weeks of age, and the exact age at which lamivudine clearance begins to approximate that in older children is not known.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*, 1998. 178(5):1327-33. http://www.ncbi.nlm.nih.gov/pubmed/9780252
3. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother*, 2009. 53(3):1170-6. http://www.ncbi.nlm.nih.gov/pubmed/19114673

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
  No effect of stavudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of stavudine 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. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the 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. The prevalence of birth defects with first-trimester stavudine exposure was 2.5% (19/771, 95% CI: 1.5%–3.8%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 pharmacokinetic study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants has been conducted (PACTG 332). Both drugs were well tolerated, with pharmacokinetics similar to those in nonpregnant adults *[4]*. Data from primate studies also indicated that pregnancy did not affect the pharmacokinetics of stavudine *[5]*.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral 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 the combination of didanosine and stavudine (see **NRTI Drugs and Mitochondrial Toxicity** in the Perinatal Guidelines). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

References

1. Toltzis P, Mourton T and Magnuson T. Comparative embryonic cytotoxicity of antiretroviral nucleosides. *J Infect Dis,* 1994. 169(5):1100-2. http://www.ncbi.nlm.nih.gov/pubmed/8169400

2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Odinecs A, Nosbisch C, Keller RD, et al. In vivo maternal-fetal pharmacokinetics of stavudine (2',3'-didehydro-3'-deoxythymidine) in pigtailed macaques (*Macaca nemestrina*). *Antimicrob Agents Chemother*, 1996. 40(1):196-202. http://www.ncbi.nlm.nih.gov/pubmed/8787905
4. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis*, 2004. 190(12):2167-74. http://www.ncbi.nlm.nih.gov/pubmed/15551216
5. Odinecs A, Pereira C, Nosbisch C, et al. Prenatal and postpartum pharmacokinetics of stavudine (2',3'-didehydro- 3'-deoxythymidine) and didanosine (dideoxyinosine) in pigtailed macaques (*Macaca nemestrina*). *Antimicrob Agents Chemother*, 1996. 40(10):2423-5. http://www.ncbi.nlm.nih.gov/pubmed/8891157
6. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
7. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Inf*, 2002. 78(1):58-9. http://www.ncbi.nlm.nih.gov/pubmed/11872862
8. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS*, 2003. 17(2):272-3. http://www.ncbi.nlm.nih.gov/pubmed/12545093

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 disoproxil fumarate 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 (IGF)-1 (a primary regulator of linear growth) and higher IGF binding protein (IGFBP)-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 the infant monkey postnatally resulted in significant growth restriction and severe bone toxicity in 25% of 8 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 to 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 to 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. The prevalence of birth defects with first-trimester tenofovir exposure was 2.4% (18/756, 95% CI: 1.4%–3.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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, the cord-to-maternal blood ratio ranged from 0.60 to 0.99, indicating high placental transfer*[4-6]*. In 2 studies including 21 pregnant women receiving tenofovir-based therapy, the cord-to-maternal blood ratio ranged from 0.95 to 0.99 *[4,5]*. There are no data on whether tenofovir is excreted in breast milk in humans.

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

  A recent case series found tenofovir to be well tolerated among 76 pregnant women, with 2 stopping therapy, 1 for rash and 1 for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV-uninfected *[7]*. A retrospective review of 16 pregnancy outcomes among 15 heavily antiretroviral experienced women demonstrated that tenofovir was well-tolerated by the women and associated with normal growth and development in the infants *[8]*.

References

1. Tarantal AF, Castillo A, Ekert JE, et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (*Macaca mulatta*). *J Acquir Immune Defic Syndr*, 2002. 29(3):207-20. http://www.ncbi.nlm.nih.gov/pubmed/11873070
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Tarantal AF, Marthas ML, Shaw JP, et al. Administration of 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) to gravid and infant rhesus macaques (*Macaca mulatta*): safety and efficacy studies. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1999. 20(4):323-33. http://www.ncbi.nlm.nih.gov/pubmed/10096575
4. Burchett S, Best B, Mirochnick M, et al. Tenofovir pharmacokinetics during pregnancy, at delivery, and postpartum. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 738b. http://www.retroconference.org/2007/Abstracts/30641.htm
5. Bonora S, de Requena DG, Chiesa E, et al. Transplacental passage of tenofovir and other ARVs at delivery. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 738a. http://www.retroconference.org/2007/PDFs/738a.pdf

6. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of tenofovir in HIV-infected pregnant women and their neonates: TemAA ANRS 12109. 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA Abstract 47LB. http://www.retroconference.org/2008/Abstracts/33470.htm
7. Habert A, Linde R, Reittner A, et al. Safety and efficacy of tenofovir in pregnant women. 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 627a. http://www.retroconference.org/2008/PDFs/627a.pdf
8. Nurutdinova D, Onen NF, Hayes E, et al. Adverse effects of tenofovir use in HIV-infected pregnant women and their infants. *Ann Pharmacother*, 2008. 42(11):1581-5. http://www.ncbi.nlm.nih.gov/pubmed/18957630

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 is mutagenic in 2 *in vitro* assays, clastogenic in 1 *in vitro* and 2 *in vivo* assays, but not cytogenic in a single-dose *in vivo* rat study. Long-term carcinogenicity studies have been performed with zidovudine in mice and rats *[1]*. In mice, 7 late-appearing (after 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, 2 late-appearing (after 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 of 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. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

  Two transplacental carcinogenicity studies were conducted in mice *[2,3]*. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally *[3]*. The doses of zidovudine 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. A second study administered zidovudine 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 through 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

  Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area, had no effect on fertility judged by conception rates.

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

- Teratogenicity/developmental toxicity

  Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after

one-half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 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 resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. 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 hypospadius *[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. The prevalence of birth defects with first-trimester zidovudine exposure was 3.1% (97/3,167, 95% CI: 2.5%–3.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 1 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 their nursing infants, who only received zidovudine 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 antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. No difference in disease progression between women in PACTG 076 who received zidovudine and those who received placebo has been seen in follow-up through 4 years postpartum *[11]*. Infants with *in utero* zidovudine exposure followed for nearly 6 years have shown no significant differences from those who received placebo in immunologic, neurologic, and growth parameters*[6,12]*; follow-up of these infants is continuing.

References

1. Ayers KM, Clive D, Tucker WE, Jr., et al. Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats. *Fundam Appl Toxicol*, 1996. 32(2):148-58. http://www.ncbi.nlm.nih.gov/pubmed/8921318

2. Olivero OA, Anderson LM, Diwan BA, et al. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. *J Natl Cancer Inst,* 1997. 89(21):1602-8. http://www.ncbi.nlm.nih.gov/pubmed/9362158
3. Ayers KM, Torrey CE and Reynolds DJ. A transplacental carcinogenicity bioassay in CD-1 mice with zidovudine. *Fundam Appl Toxicol,* 1997. 38(2):195-8. http://www.ncbi.nlm.nih.gov/pubmed/9299194
4. Toltzis P, Marx CM, Kleinman N, et al. Zidovudine-associated embryonic toxicity in mice. *J Infect Dis,* 1991. 163(6):1212-8. http://www.ncbi.nlm.nih.gov/pubmed/2037787
5. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med,* 1994. 331(18):1173-80. http://www.ncbi.nlm.nih.gov/pubmed/7935654
6. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 Study. *AIDS,* 1998. 12(14):1805-13. http://www.ncbi.nlm.nih.gov/pubmed/9792381
7. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr,* 2007. 44(3):299-305. http://www.ncbi.nlm.nih.gov/pubmed/17159659
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
9. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother,* 2009. 53(3):1170-6. http://www.ncbi.nlm.nih.gov/pubmed/19114673
10. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol,* 1993. 168(5):1510-6. http://www.ncbi.nlm.nih.gov/pubmed/8098905
11. Bardeguez AD, Shapiro D, Mofenson LM, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *JAIDS,* 2003. 32(2):170-81. http://www.ncbi.nlm.nih.gov/pubmed/12571527
12. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of *in utero* exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. *JAMA,* 1999. 281(2):151-7. http://www.ncbi.nlm.nih.gov/pubmed/9917118

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

For information regarding potential interaction of the non-nucleoside reverse transcriptase inhibitor drug class 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 in mice and rats have been completed. 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 an increase in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas above background were found in

female mice. In male and female rats administered systemic drug exposures lower than that in humans receiving therapeutic doses, no increase in tumor incidence above background was observed.

- Reproduction/fertility animal studies
  No effect of efavirenz on reproduction or fertility in rodents has been seen.

- Teratogenicity/developmental toxicity
  An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily). Central nervous system (CNS) malformations were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational Days 20 to 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 prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through July 2009, birth defects were observed in 14 (2.8%) of 501 (95% CI: 1.5%–4.7%) live births with first-trimester exposure. Defects reported prospectively after first-trimester efavirenz exposure included a case of sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome and a case of bilateral facial clefts, anophthalmia, and amniotic band *[2]*. Other defects reported included polydactyly (3 cases), hydronephrosis, bilateral hip dislocation and umbilical hernia, bilateral hip dislocation, urinary obstruction with duplicated right collecting system, long bone malformation, shortening of right leg, cutis aplasia, hip dysplasia with pulmonary stenosis, and unspecified heart anomaly. In retrospective case reports, there are 6 reports of central nervous system defects, including 3 cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester [Bristol-Myers Squibb April 14 2010, De Santis M, Arch Intern Med, 2002; Fundaro C, AIDS, 2002]. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

- 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 *[6]*. 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 about efavirenz in neonates are currently available.

- Human studies in pregnancy
  Limited data on use of efavirenz in pregnancy are available. In 1 study of 71 pregnancies occurring among women in a primary therapy study, the rate of early losses and stillbirths did not differ among women on efavirenz or other drugs *[7]*. Among 22 livebirths to women exposed to efavirenz in the first trimester, 1 (4.5%) infant had an abnormality, right limb shortening.

  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. Different types of contraception have known failure rates in women not receiving antiretroviral drugs; these failure rates may increase with drug interactions between estrogen-progesterone hormonal contraceptives and some antiretroviral drugs, including efavirenz. Alternate

antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception. Barrier contraception should always be used in combination with other methods of contraception (e.g., hormonal contraceptives, intrauterine device). A study evaluating the interaction between efavirenz and depomedroxyprogesetrone (DMPA) in 17 women found no change in the pharmacokinetic profile of either efaviraenz or DMPA with concomitant use *[8]*. DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

References

1. Nightingale SL. From the Food and Drug Administration. *JAMA*, 1998. 280(17):1472. http://www.ncbi.nlm.nih.gov/pubmed/9809716
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Bristol-Myers Squibb Company. Efavirenz drug label. Revised August 2008.
4. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med*, 2002. 162(3):355. http://www.ncbi.nlm.nih.gov/pubmed/11822930
5. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*, 2002. 16(2):299-300. http://www.ncbi.nlm.nih.gov/pubmed/11807320
6. Schneider S, Peltier A, Gras A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr*, 2008. 48(4):450-4. http://www.ncbi.nlm.nih.gov/pubmed/18614925
7. Bussmann H, Wester CW, Wester CN, et al. Pregnancy rates and birth outcomes among women on efavirenz-containing highly active antiretroviral therapy in Botswana. *J Acquir Immune Defic Syndr*, 2007. 45(3):269-73. http://www.ncbi.nlm.nih.gov/pubmed/17450102
8. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*, 2007. 81(2):222-7. http://www.ncbi.nlm.nih.gov/pubmed/17192768

Etravirine (Intelence, ETV) 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. In addition, no pharmacokinetic studies have been conducted in pregnant patients.

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 exposure 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. The prevalence of birth defects with first-trimester nevirapine exposure was 2.1% (18/842, 95% CI: 1.3%–3.4 %) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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]*. In a larger study, 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine in Kenya; median nevirapine breast milk concentration was 4,564 ng/mL *[4]*. Their infants, who only received nevirapine via breast milk, had a median nevirapine concentration of 734 ng/mL.

- Human studies in pregnancy

  Short-Term Peripartum Prophylaxis:

  A Phase I study (PACTG 250) evaluated the safety and pharmacokinetics 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 the infant at age 48 to 72 hours *[2]*. No adverse effects were seen in the women or the infants.

Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar although somewhat more variable than in nonpregnant adults, possibly due to 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 pharmacokinetics of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants *[5]*. Initial dose pharmacokinetic 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 4 of 8 infants, suggesting that nevirapine elimination was accelerated in infants whose mother received chronic nevirapine administration compared to newborns whose mothers received only a single intrapartum nevirapine 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) to 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 HIV transmission by nearly 50% during the first 14 to 16 weeks of life compared to zidovudine *[6]*. However, the women in this African trial were not receiving any other antiretroviral therapy.

In the United States, most infected women who know their HIV status during pregnancy receive combination antiretroviral therapy, usually including zidovudine, as well as intravenous zidovudine during delivery, with 6 weeks of zidovudine given to their infant. 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 antiretroviral therapy (at minimum the PACTG 076 zidovudine regimen; 77% of women in the trial received combination therapy) would provide additional benefits in reducing transmission. Transmission was not significantly different between those who had the addition of single-dose nevirapine (1.4%) and those who did not (1.6%) *[7]*.

Nevirapine resistance can be induced by a single mutation. As a result of its long half-life, nevirapine can be detected in plasma up to 3 weeks after administration of a single intrapartum dose *[8]*. This period of persistent subtherapeutic drugs levels exerts selective pressure that predisposes to the development of resistant strains of HIV *[9]*. Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of antiretroviral-naïve women in HIVNET 012 and 15% of a subset of women receiving additional antiretroviral drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor *[10-11]*. The clinical implications of the presence of nevirapine-resistant HIV are unclear. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13 to 18 months postpartum *[12]*. 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*[13-14]*. Several studies have suggested that there is no decrease in efficacy when nevirapine-based combination therapy is started at least 6 to 12 months after delivery*[15-18]*. Administration of postpartum antiretrovirals to the mother can reduce the frequency of detection of nevirapine-resistant strains*[9, 19-21]*.

Longer Term Antenatal Combination Therapy:

The pharmacokinetics of nevirapine have been evaluated in pregnant women receiving nevirapine as part of combination antiretroviral therapy during pregnancy. A study that determined nevirapine pharmacokinetics in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine pharmacokinetic parameters *[22]*. In contrast, in nevirapine pharmacokinetic data from a therapeutic drug monitoring program that included 12-hour sampling, nevirapine clearance was 20% greater, AUC was 28% lower, and C_{max} was 30% lower in 16 pregnant women compared to 13 nonpregnant women *[23]*.

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 HIV exposure *[24]*. 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 to 18 weeks of therapy, although the risk of toxicity continues past this period and monitoring should continue at frequent intervals.

The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women *[25-27]*. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men *[28]*. 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 *[28]*. Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash *[26]*. 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% *[28-29]*. Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine *[29]*.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs *[30-31]*. In an analysis of two multi-center 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 *[32]*. Further data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination antiretroviral therapy versus non-nevirapine-based combination antiretroviral therapy *[33]*. These data suggest that nevirapine is no more toxic in pregnant women than in nonpregnant women. Women initiating nevirapine with CD4 counts >250 cells/mm^3, including pregnant women receiving antiretroviral 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 *[34]*. Nevirapine should therefore be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Women with CD4 counts less than 250/mm^3 can receive nevirapine-based regimens, and women who enter pregnancy on nevirapine regimens and are tolerating the regimens well may continue therapy, regardless of CD4 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 and conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), 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 to 3 months thereafter (**Adult Antiretroviral Guidelines**); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and then monthly *[35]*. 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 nevirapine therapy in the future.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Mirochnick M, Fenton T, Gagnier P, et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *J Infect Dis.* 1998;178(2):368-374.
3. Shapiro RL, Holland DT, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. *J Infect Dis.* 2005;192(5):720-727.
4. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother.* 2009;53(3):1170-1176.
5. Mirochnick M, Siminski S, Fenton T, et al. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis J.* 2001;20(8):803-805.
6. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet.* 1999;354(9181):795-802.
7. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. PACTG 316. *JAMA.* 2002;288(2):189-198.
8. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
9. Arrivé E, Newell ML, Ekouevi DK, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int J Epidemiol.* 2007;36(5):1009-1021.
10. Cunningham CK, Chaix ML, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis.* 2002;186(2):181-188.
11. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS.* 2001;15(15):1951-1957.
12. Jackson JB, Becker-Pergola G, Guay LA, et al. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. *AIDS.* 2000;14(11):F111-115.
13. McConnell M, Bakaki P, Eure C, et al. Effectiveness of repeat single-dose nevirapine for prevention of mother-to-child transmission of HIV-1 in repeat pregnancies in Uganda. *J Acquir Immune Defic Syndr.* 2007;46(3):291-296.
14. Martinson NA, Ekouevi DK, Dabis F, et al. Transmission rates in consecutive pregnancies exposed to single-dose nevirapine in Soweto, South Africa and Abidjan, Côte d'Ivoire. *J Acquir Immune Defic Syndr.* 2007;45(2):206-209.
15. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
16. Chi BH, Sinkala M, Stringer EM, et al. Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. *AIDS.* 2007;21(8):957-964.
17. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
18. Coffie PA, Ekouevi DK, Chaix ML, et al. Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV type 1, Ivory Coast, 2003-2006. *Clin Infect Dis.* 2008;46(4):611-621.
19. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487. Epub 2006 Jan 2011.
20. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med. 2009;6(10):e1000172.

21. Chi BH, Sinkala M, Mbewe F, et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet.* 2007;370(9600):1698-1705.
22. Capparelli EV, Aweeka F, Hitti J, et al. Chronic administration of nevirapine during pregnancy: impact of pregnancy on pharmacokinetics. *HIV Med.* 2008;9(4):214-220.
23. von Hentig N, Carlebach A, Gute P, et al. A comparison of the steady-state pharmacokinetics of nevirapine in men, nonpregnant women and women in late pregnancy. *BR J Clin Pharmacol.* 2006;62(5):552-559.
24. Patel SM, Johnson S, Belknap SM, et al. Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2004;35(2):120-125.
25. Mazhude C, Jones S, Murad S, et al. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS.* 2002;16(11):1566-1568.
26. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* 2001;32(1):124-129.
27. Knudtson E, Para M, Boswell H, et al. Drug rash with eosinophilia and systemic symptoms syndrome and renal toxicity with a nevirapine-containing regimen in a pregnant patient with human immunodeficiency virus. *Obstet Gynecol.* 2003;101(5 Pt 2):1094-1097.
28. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S21-33.
29. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. Revised January 2005.
30. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med.* 2006;7(4):255-260.
31. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr.* 2004;36(3):772-776.
32. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS.* 2009;23(18):2425-2430.
33. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS.* 2010;24(1):109-114.
34. Grimbert S, Fisch C, Deschamps D, et al. Effects of female sex hormones on mitochondria: possible role in acute fatty liver of pregnancy. *Am J Physiol.* 1995;268(1 Pt 1):G107-115.
35. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003;23(2):173-182.

PROTEASE INHIBITORS

For information regarding the protease inhibitor (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 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 7.2-fold higher than those in humans at the recommended therapeutic dose (400 mg once daily). There were no increases in the incidence of tumors in male mice at any dose. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 5.7-fold 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 (AUC up to 2 times those achieved in humans at the recommended therapeutic dose).

- Teratogenicity/developmental toxicity
  Atazanavir did not produce teratogenic effects in rabbits with maternal dosing producing systemic drug exposure equivalent to (rabbits) or 2-times that (rats) achieved in humans at the recommended therapeutic dose (400 mg once daily). In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure 2-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 were HIV infected. In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to atazanavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.6% (9/343, 95% CI: 1.2%–4.9%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[2]*.

  Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase 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 newborn period *[1,3-5]*.

- Placental and breast milk passage
  In studies of women receiving atazanavir/ritonavir-based combination therapy during pregnancy, cord blood atazanavir concentration averaged 13%–16% of maternal serum levels at delivery *[3,5]*. Atazanavir is excreted in the milk of lactating rats. In a small study of 3 women, the median ratio of breast milk atazanavir concentration to that in plasma was 13% *[6]*.

- Human studies in pregnancy
  The pharmacokinetics of atazanavir 300 mg when administered once daily during pregnancy with ritonavir 100 mg have been investigated in 4 studies. In a retrospective study, trough atazanavir concentrations were measured in 19 pregnant women at a median of 30 weeks gestation (14 in third trimester); all but 2 women had a trough atazanavir concentration greater than 100 ng/mL *[1]*. Full pharmacokinetic profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy have been evaluated in 3 studies. In a study of 17 pregnant women, atazanavir AUC was not different during pregnancy compared to 1–6 months postpartum (28.5 µg*hr/mL vs. 30.5 µg*hr/mL, respectively) *[3]*. In contrast, another study determined atazanavir pharmacokinetics in 12 pregnant women and found reductions in atazanavir concentrations of more than 50% during pregnancy, with a mean AUC of 26.6 µg*hr/mL during the third trimester compared to 57.0 µg*hr/mL at 4 weeks postpartum. All subjects had trough atazanavir concentrations greater than 150 ng/mL *[4]*. Similar results were found in another study of atazanavir pharmacokinetics in 18 women not receiving tenofovir, with median AUC of 41.9 µg*hr/mL during pregnancy versus 58.0µ g*hr/mL at 6–12 weeks postpartum *[5]*. Atazanavir AUC was further reduced in 15 women also receiving tenofovir, with median AUC of 30.5 µg*hr/mL during pregnancy compared to 44.1 µg*hr/mL postpartum. Mean atazanavir AUC in nonpregnant adults receiving 300 mg plus 100 mg ritonavir daily dosing is 57.0 µg*hr/mL and is reduced by about 25% in adults receiving concomitant tenofovir *[7,8]*. Investigations of atazanavir exposure with the use of an increased dose of 400 mg in combination with 100 mg ritonavir during pregnancy are under way.

References

1. Natha M, Hay P, Taylor G, et al. Atazanavir use in pregnancy: a report of 33 cases. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 750. http://www.retroconference.org/2007/Abstracts/28351.htm
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS*, 2007. 21(18):2409-15. http://www.ncbi.nlm.nih.gov/pubmed/18025877
4. Eley T, Vandeloise E, Child M, et al. Steady State Pharmacokinetics and Safety of Atazanavir after Treatment with ATV 300 mg Once Daily/Ritonavir 100 mg Once Daily + ZDV/3TC during the Third Trimester in HIV+ Women. 15th Conference on Retoviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. http://www.retroconference.org/2008/PDFs/624.pdf
5. Mirochnick M, Stek A, Capparelli E, et al. Atazanavir Pharmacokinetics with and without Tenofovir during Pregnancy. 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada. http://www.retroconference.org/2009/Abstracts/34312.htm
6. Spencer L, Neely M, Mordwinkin N, et al. Intensive Pharmacokinetics of Zidovudine, Lamivudine, and Atazanavir and HIV-1 Viral Load in Breast Milk and Plasma in HIV+ Women Receiving HAART. 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada. http://www.retroconference.org/2009/PDFs/942.pdf
7. Reyataz pacakage insert. Bristol-Myers Squibb Co., Princeton, NJ. September, 2008. Accessed on November 21, 2008 at http://www.fda.gov/cder/foi/label/2008/021567s017lbl.pdf.
8. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*, 2004. 48(6):2091-6. http://www.ncbi.nlm.nih.gov/pubmed/15155205

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 males and females of both 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 during lactation due to exposure of pups to drug substances via the milk. In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5 to 11 days) or multiple doses of darunavir (40 mg/kg to 1,000 mg/kg at age 12 days) caused mortality. The mortalities 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 CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or 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
  No studies of darunavir have been conducted in pregnant women or neonates. Darunavir is not recommended for children younger than 3 years.

Fosamprenavir (Lexiva, f-APV) 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 hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only there was an increase in interstitial cell hyperplasia at higher doses and an increase in uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus the relevance of the uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 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 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No affect was seen on the development or maturation of sperm in rats at these doses.
- Teratogenicity/developmental toxicity
  Fosamprenavir was studied in rabbits at 0.8 and in rats at 2 times the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination) the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at 2 times human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls.
- Placental and breast milk passage
  It is unknown whether fosamprenavir crosses the placenta. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  There are very limited data on fosamprenavir in pregnant women. There is a pediatric liquid formulation approved for children older than 2 years of age, but there is no dosing information for neonates.

Indinavir (Crixivan, IDV) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  There is no evidence that indinavir is mutagenic or clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.
- Reproduction/fertility
  No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.
- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity or treatment-related effects on embryonic/fetal survival or fetal weights of indinavir in rats, rabbits, or dogs at exposures comparable to or slightly greater than therapeutic human exposure. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold greater than controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. 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 The prevalence of birth defects with first-trimester indinavir exposure was 2.2% (6/276, 95% CI: 0.8%–4.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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]*. Additionally, 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 pharmacokinetic study (PACTG 358) of indinavir (800 mg three times a day) in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants was conducted *[2]*. The mean indinavir plasma $AUC_{0\text{-}8hr}$ at weeks 30 to 32 of gestation (n =11) was 74% (95% CI: 50%–86%) lower than that observed 6 weeks postpartum. The pharmacokinetics 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, 2 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 to 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 indinavir used in conjunction with low-dose ritonavir in twice-daily dosing. The first evaluated 2 women whose regimen included indinavir 800 mg twice daily with ritonavir 200 mg twice daily. Both women achieved third-trimester AUC indinavir levels greater than those for historical nonpregnant controls *[4]*. A more recent study evaluated use of combination therapy including indinavir 400 mg twice daily with ritonavir 100 mg twice daily. Data are available for 28 women, 23 (82%) of whom had C_{trough} values above the targeted cutoff of 120 ng/mL. Of the 5 women with low C_{trough} 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.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*, 2007. 51(2):783-6. http://www.ncbi.nlm.nih.gov/pubmed/17158945
3. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805
4. Kosel BW, Beckerman KP, Hayashi S, et al. Pharmacokinetics of nelfinavir and indinavir in HIV-1-infected pregnant women. *AIDS*, 2003. 17(8):1195-9. http://www.ncbi.nlm.nih.gov/pubmed/12819521
5. Ghosn J, De Montgolfier I, Cornélie C, et al. Antiretroviral therapy with a twice-daily regimen containing 400 milligrams of indinavir and 100 milligrams of ritonavir in human immunodeficiency virus type 1-infected women during pregnancy. *Antimicrob Agents Chemother*, 2008. 52(4):1542-4. http://www.ncbi.nlm.nih.gov/pubmed/18250187

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. 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 both males and females in mice and males in rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on AUC_{0-24hr} measurement). Administration of 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
  There has been no evidence 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 exposures of 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. The prevalence of birth defects with first-trimester lopinavir + ritonavir exposure was 1.7% (95% CI: 0.8%–3.2%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Lopinavir crosses the human placenta; in a pharmacokinetic study, P1026s, 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 pharmacokinetic 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 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 pharmacokinetics 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 third-trimester pregnant women and that it should be considered in second-trimester pregnant women, especially those who are PI-experienced, and that lopinavir/ritonavir can be reduced to standard dosing shortly after delivery *[3]*.

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

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Khuong-Josses MA, Azerad D, Boussaïri A, et al. Comparison of lopinavir level between the two formulations

(soft-gel capsule and tablet) in HIV-infected pregnant women. *HIV Clin Trials*, 2007. 8(4):254-5. http://www.ncbi.nlm.nih.gov/pubmed/17720666

3. Best B, Stek A, Hu C, et al. for the PACTG/IMPAACT P1026S team. High-dose lopinavir and standard-dose emtricitabine pharmacokinetics during pregnancy and postpartum. 15th Conference on Retroviruses and Opportunistic Infections, February 3-8, 2008; Boston, MA. Abstract 629. http://www.retroconference.org/2008/PDFs/629.pdf

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, thyroid follicular cell adenomas and carcinomas were increased over baseline in male rats receiving 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) of nelfinavir.

- 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. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir.

- 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. The prevalence of birth defects with first-trimester nelfinavir exposure was 3.4% (37/1,075, 95% CI: 2.4%–4.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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]*. Additionally, 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 pharmacokinetic study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants *[2]*. Nelfinavir administered at a dose of 750 mg three times daily produced drug exposures in the first nine pregnant HIV-infected women enrolled in the study that were variable and generally lower than those reported in nonpregnant adults for both two 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 nelfinavir in pregnancy. However, in another 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 nelfinavir than women in their second trimester and lower concentration than in nonpregnant women *[4]*.

  In a pharmacokinetic study of combination therapy including the new nelfinavir 625-mg tablet formulation (given as 1,250 mg twice daily) in 25 women at 30 to 36 weeks gestation (and 12 also at 6 to 12 weeks

postpartum), peak levels and AUC were lower in the third trimester than postpartum *[5]*. Only 16% (4/25) of women during the third trimester and 8% (1/12) women postpartum had trough values greater that 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.

In September 2007, the manufacturer of nelfinavir (Viracept) in the United States (Pfizer) sent a letter to providers regarding the presence of low levels of ethyl methane sulfonate (EMS), a process-related impurity, in nelfinavir. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data from humans exist and no increase in birth defects has been observed in the Antiretroviral Pregnancy Registry. Health care providers were advised not to initiate antiretroviral regimens containing Viracept (nelfinavir) in their pregnant female or new pediatric patients and to switch pregnant patients receiving Viracept (nelfinavir) to an alternative therapy unless no alternative was available. As of March 31, 2008, all Viracept (nelfinavir) manufactured and released by Pfizer now meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients. Viracept (nelfinavir) may now be prescribed for pregnant women as an alternate PI for women receiving antiretroviral therapy during pregnancy solely for prevention of mother-to-child transmission.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Bryson YJ, Mirochnick M, Stek A, et al. Pharmacokinetics and safety of nelfinavir when used in combination with zidovudine and lamivudine in HIV-infected pregnant women: Pediatric AIDS Clinical Trials Group (PACTG) Protocol 353. *HIV Clin Trials*, 2008. 9(2):115-25. http://www.ncbi.nlm.nih.gov/pubmed/18474496
3. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805
4. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and nonpregnant women. *Br J Clin Pharmacol*, 2006. 62(3):309-15. http://www.ncbi.nlm.nih.gov/pubmed/16934047
5. Read JS, Best BM, Stek AM, et al. Pharmacokinetics of new 625 mg nelfinavir formulation during pregnancy and postpartum. *HIV Med*, 2008. 9(10):875-82. http://www.ncbi.nlm.nih.gov/pubmed/18795962

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, at levels of 50, 100, or 200 mg/kg/day, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed; 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 due to hepatic toxicity in the rodents.
- Teratogenicity/developmental toxicity
  No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity was observed in rats, including early resorptions, decreased body weight, ossification delays, and developmental variations

such as wavy ribs and enlarged fontanelles; 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. The prevalence of birth defects with first-trimester ritonavir exposure was 2.2% (22/1,000, 95% CI: 1.4%–3.3%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 pharmacokinetic study (PACTG 354) of ritonavir in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants showed lower levels of ritonavir during pregnancy compared to postpartum *[3]*.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. *Am J Obstet Gynecol*, 1998. 179(3 Pt 1):758-61. http://www.ncbi.nlm.nih.gov/pubmed/9757985
3. Scott GB, Rodman JH, Scott WA, et al. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-10-infected pregnant women and their infants. 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 794-W. http://www.retroconference.org/2002/Abstract/13702.htm
4. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805

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]*. Additionally, 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 pharmacokinetics of saquinavir-hard gel capsules (HGC) combined with low-dose ritonavir (saquinavir-HGC 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-HGC 1,200 mg/ritonavir 100 mg given once daily, trough levels were 285 and 684 ng/mL and the $AUC_{0\text{-}24}$ 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-HGC 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 HGC administered once daily at 1,200mg/100mg ritonavir combined with various NRTIs during 46 pregnancies, demonstrated saquinavir levels greater than the target 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 1,600mg/100mg. The drug was well tolerated.

  The pharmacokinetics 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 antiretroviral drug regimen in 42 women during pregnancy reported abnormal transaminase levels in 13 women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity grade 1–2 in most, grade 3 in 1 woman) *[8]*.

References

1. Zorrilla CD, Van Dyke R, Bardeguez A, et al. Clinical response and tolerability to and safety of saquinavir with low-dose ritonavir in human immunodeficiency virus type 1-infected mothers and their infants. *Antimicrob Agents Chemother*, 2007. 51(6):2208-10. http://www.ncbi.nlm.nih.gov/pubmed/17420209
2. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805
3. Hanlon M, O'Dea S, Woods S, et al. Evaluation of saquinavir/ritonavir based regimen for prevention of MTCT of HIV. 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 721. http://www.retroconference.org/2006/PDFs/721.pdf
4. Khan W, Hawkins DA, Moyle G, et al. Pharmacokinetics (PK), safety, tolerability and efficacy of saquinavir hard-gel capsules/ritonavir (SQV/r) plus 2 nucleosides in HIV-infected pregnant women. XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract ThPeB 7064.
5. Lopez-Cortes LF, Ruiz-Valderas R, Pascual R, et al. Once-daily saquinavir-hgc plus low-dose ritonavir (1200/100 mg) in HIV-infected pregnant women: pharmacokinetics and efficacy. *HIV Clin Trials*, 2003. 4(3):227-9. http://www.ncbi.nlm.nih.gov/pubmed/12815561

6. Lopez-Cortes LF, Ruiz-Valderas R, Rivero A, et al. Efficacy of low-dose boosted saquinavir once daily plus nucleoside reverse transcriptase inhibitors in pregnant HIV-1-infected women with a therapeutic drug monitoring strategy. *Ther Drug Monit*, 2007. 29(2):171-6. http://www.ncbi.nlm.nih.gov/pubmed/17417070
7. Burger D, Eggink A, van der ende I, et al. The pharmacokinetics of saquinavir in the new tablet formulation + ritonavir (1000/100 mg twice daily) in HIV-1-infected pregnant women. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 741. http://www.retroconference.org/2007/PDFs/741.pdf
8. Hanlon M, O'Dea S, Clarke S, et al. Maternal hepatotoxicity with boosted saquinavir as part of combination ART in pregnancy. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 753. http://www.retroconference.org/2007/PDFs/753.pdf

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. The incidences of benign hepatocellular adenomas and combined adenomas/carcinomas were increased in females of all groups except in females given the low dose of tipranavir. These tumors were also increased in male mice at the high dose of tipranavir and in the tipranavir/ritonavir combination group. Hepatocellular carcinoma incidence 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 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 in male rats were observed. 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. In rats exposed to 400 mg/kg/day (~0.8-fold human exposure) and greater, fetal toxicity (decreased ossification and body weights) was observed. Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold exposures in humans. In rats, no adverse effects were seen on development at levels of 40 mg/kg/day (~0.2-fold human exposure), but growth inhibition in pups and maternal toxicity were seen at 400 mg/kg/day (~0.8-fold human exposure).
- 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 conducted in pregnant women or neonates.

ENTRY INHIBITORS

Two drugs have been approved in this new class of antiretrovirals aimed at inhibiting viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein gp120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor (e.g., CCR5 or CXCR4) on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein 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 antiretroviral drugs to treat advanced HIV infection in adults and children aged 6 years 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 a m^2 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 a m^2 basis.
- Placental and breast milk passage
  Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity was present in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or radio-labeled 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. 20(2):297-9. http://www.ncbi.nlm.nih.gov/pubmed/16511429
2. Ceccaldi PF, Ferreira C, Gavard L, et al. Placental transfer of enfuvirtide in the ex vivo human placenta perfusion model. *Am J Obstet Gynecol*, 2008. 198(4):433. e1-2. http://www.ncbi.nlm.nih.gov/pubmed/18241815
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. 19(9):989-90. http://www.ncbi.nlm.nih.gov/pubmed/15905684

4. Meyohas MC, Lacombe K, Carbonne B, et al. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS*, 2004. 18(14):1966-8. http://www.ncbi.nlm.nih.gov/pubmed/15353987

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 animals or humans. 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 malignancy has been observed, maraviroc has a potential for an increased risk of malignancy due to the drug's mechanism of action and possible effects on immune surveillance.

INTEGRASE INHIBITORS

One drug has been approved in this new class of antiretrovirals aimed at inhibiting the viral enzyme integrase, the viral enzyme catalyzing 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 of 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 resistant to other classes of antiretroviral 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. 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. There were no effects in rat offspring attributable to raltegravir exposure through breast milk.
- Human studies in pregnancy
  No studies of raltegravir have been conducted in pregnant women or neonates. It is unknown if raltegravir is secreted in human milk.

ANTIRETROVIRAL PREGNANCY REGISTRY

The Antiretroviral Pregnancy Registry is an epidemiologic project to collect observational, nonexperimental data on antiretroviral 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 antiretroviral 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 by registry staff 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
www.APRegistry.com