Public Health Service Task Force

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

July 8, 2008

Revisions to the November, 2, 2007 Public Health Service Task Force 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 Perinatal HIV Guidelines Working Group

It is emphasized that concepts relevant to HIV management evolve rapidly. The Task Force 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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Introduction

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 evolved with an increasing proportion of women receiving highly active combination antiretroviral therapy (HAART) throughout pregnancy. With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral prophylaxis, scheduled cesarean delivery, and avoidance of breastfeeding, perinatal HIV infection has dramatically diminished to less than 2% in the United States *[3]*.

These guidelines update the November 2, 2007, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States∗. The Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, a working group of the Office of AIDS Research Advisory Council, develops these guidelines, which 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. Various circumstances that commonly occur in clinical practice are presented, and the factors influencing treatment considerations are highlighted in this report. 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 most recent information is available from the AIDS*info* Web site (available at **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 for 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 *[1, 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 restructured to better reflect the management of an individual mother-child pair, and are organized into principles for management of the woman and her infant during the antepartum, intrapartum, and postpartum period. Key issues and new information discussed in this report include:

- **Lessons learned from clinical trials of antiretroviral drugs to prevent perinatal HIV transmission.** The Panel reaffirms the importance of providing antiretroviral drugs during pregnancy, labor, and to the infant for optimal prevention of transmission; that combination antiretroviral regimens are more effective than single-drug regimens in

∗ Information included in these guidelines may not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

reducing transmission; and that antiretroviral prophylaxis to prevent perinatal HIV transmission should be offered to all HIV-infected women, regardless of CD4 cell count.

- **Issues on preconception care of HIV-infected women of childbearing age.** The Panel notes that contraceptive counseling is an essential component of care for HIV-infected women of reproductive age. The Panel also notes that choice of an antiretroviral regimen for treatment of HIV-infected women of childbearing potential needs to include consideration of effectiveness for treatment of maternal disease as well as teratogenic potential of the drugs should pregnancy occur. Attainment of a stable, maximally suppressed viral load prior to conception is recommended for HIV-infected women who are on antiretroviral therapy and wish to become pregnant.

- **Antepartum Management.** The Panel reaffirms recommendations for use of three-drug combination antiretroviral regimens for prevention of perinatal HIV transmission. New sections have been added regarding management of pregnant women with prior antiretroviral exposure, management of pregnant women with hepatitis B and hepatitis C coinfection, stopping antiretroviral therapy in pregnancy, management of women who fail to achieve viral suppression, and monitoring of the woman and fetus during pregnancy. The Panel recommends resistance testing for all HIV-infected pregnant women prior to initiation of treatment or prophylaxis and for women on treatment who have persistently detectable HIV RNA levels.

- **Intrapartum Management.** The Panel continues to recommend scheduled cesarean delivery for HIV-infected pregnant women with HIV RNA levels >1,000 copies/mL near the time of delivery. New information has been added regarding antiretroviral drug continuation during labor and management of women who have not received antepartum antiretroviral drugs, as well as choice of intrapartum prophylaxis regimen for such women.

- **Postpartum Management.** The Panel provides further detail on decision making related to whether to continue or stop antiretroviral drugs postpartum, reiterates that HIV-infected women in the United States should not breastfeed (even if receiving antiretroviral therapy), and discusses contraceptive counseling.

- **Infant Management.** New sections have been added regarding the management and choice of antiretroviral prophylaxis in the infant in situations where the mother has received antepartum antiretroviral drugs, only received intrapartum antiretroviral prophylaxis, or did not receive any prophylaxis, and more detailed information is provided on management of the infant with toxicities related to antiretroviral prophylaxis.

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 this report 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, local recommendations regarding breastfeeding by HIV-infected women, and alternative interventions being evaluated in that area.

Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission

One of the major achievements in HIV research was the demonstration by PACTG 076 that administration of ZDV to the pregnant woman and her infant could reduce the risk of perinatal transmission by nearly 70% *[4]*. In PACTG 076, ZDV 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 US and other countries with higher level resources, implementation of the ZDV regimen coupled with increased antenatal HIV counseling and testing rapidly resulted in significant declines in transmission *[2, 3, 6, 7]*. 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% *[3, 8, 9]*. It is currently estimated that fewer than 250 infected infants are currently born each year in the United States. *[2]*. However, while 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 *[10, 11]*. Important obstacles to eradication of perinatal transmission in the United States include the continued increase of HIV infection among women of childbearing age; delayed or lack of prenatal care, particularly in women using illicit drugs; poor adherence to prescribed antiretroviral regimens; and lack of full implementation of routine, universal prenatal HIV counseling and testing *[11]*.

Within resource-limited settings, the complexity and cost of the 3-part PACTG 076 regimen significantly limits 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 ZDV-alone prophylaxis regimens, and moved to evaluating whether combination antiretroviral regimens, such as short-course ZDV combined with lamivudine (3TC), might have improved efficacy over ZDV alone. Studies also evaluated whether even simpler, less expensive, single drug regimens, such as single-dose intrapartum/neonatal nevirapine (NVP), 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 HIV TRANSMISSION

Panel's Recommendations:

- 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 HIV transmission, combined antepartum, intrapartum, and infant antiretroviral prophylaxis is recommended.

There are a number of mechanisms through which ZDV 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 *[12]*. 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 *[3, 13]*.

An additional mechanism of protection is pre-exposure infant prophylaxis provided by administration of antiretroviral drugs that cross the placenta from the mother during labor, resulting in adequate systemic drug levels in the infant at a time of intensive exposure to maternal genital tract virus during passage through the birth canal. Post-exposure infant prophylaxis is provided through administration of drug to the infant after birth; this would protect against 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 *[14-20]*.

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

Panel's Recommendations:

- Combination antepartum antiretroviral drug regimens are more effective than single-drug regimens in reducing perinatal transmission.
- 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 by 28 weeks gestation (see **Recommendations for Use of Antiretroviral Drugs during Pregnancy**).
- If women do not receive antepartum antiretroviral drugs, intrapartum combined with infant antiretroviral prophylaxis should be given to reduce the risk of perinatal transmission (see **Intrapartum Care**), although this is not as effective as when antepartum therapy is also given.
- If women do not receive antepartum or intrapartum antiretroviral drugs, postnatal infant antiretroviral prophylaxis is recommended with a minimum of 6 weeks of ZDV (see **Postpartum Care**).
- In the United States, the addition of single-dose intrapartum/newborn NVP 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 NVP resistance.

A number of simple regimens have been identified that are effective in reducing perinatal transmission in resource-limited countries (see **Table 1**). 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 ZDV alone; ZDV plus 3TC; single-dose NVP; and more recently, combining single-dose NVP with either short-course ZDV or ZDV/3TC *[14, 15, 17-24]*. In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission, and when it is feasible and affordable, a longer 3-part regimen given antenatally, intrapartum, and postpartum is superior in preventing perinatal transmission than a shorter 2-part antepartum/intrapartum or intrapartum/postpartum regimen *[15, 25, 26]*.

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 *[21-23]*. However, longer duration of antenatal therapy (starting at 28 weeks gestation) is more effective than shorter (starting at 36 weeks gestation), suggesting that a significant proportion of *in utero* transmission occurs between 28 and 36 weeks gestation *[24]*. More prolonged post-exposure prophylaxis of the infant does not appear to substitute for longer duration of maternal therapy *[24]*.

Because some women may lack antenatal care and first present to the health care system during labor, regimens that do not include maternal therapy during pregnancy have been evaluated; in some resource-limited settings, this may constitute the majority of pregnant women. Regimens that include only intrapartum and postpartum drug administration have also been shown to be effective in reducing perinatal transmission *[14, 15, 17]*. However, intrapartum pre-exposure prophylaxis alone with NRTI drugs (ZDV/3TC), without continued post-exposure prophylaxis of the infant, is not effective *[15]*. The SAINT trial demonstrated that the two proven effective intrapartum/postpartum regimens (ZDV/3TC or NVP) are similar in efficacy and safety *[17]*.

In some situations, maternal antepartum and intrapartum therapy may not be possible, and only infant prophylaxis can be provided. Based on epidemiologic data *[16]*, in resource-rich countries, the standard prophylaxis regimen in the absence of maternal therapy is 6 weeks of infant ZDV. To define the optimal infant prophylaxis regimen in these settings, an ongoing multinational study in infants born to women who have not received antenatal therapy is comparing the standard 6-week infant ZDV regimen to 6 weeks of ZDV combined with either one or two additional drugs.

In resource-limited settings, administration of even 6 weeks of infant ZDV may be difficult to achieve, and single-dose NVP is widely used. In a study in South Africa, administration of single-dose infant NVP given within 24 hours of delivery was compared with 6 weeks of infant ZDV therapy in infants born to mothers who did not receive antenatal or intrapartum therapy; overall perinatal transmission rates were not significantly different *[20]*. A trial in Malawi compared single-dose infant NVP to a combination of single-dose NVP with a week of ZDV therapy when no antenatal maternal therapy was received. The addition of 1 week of ZDV therapy to infant single-dose NVP reduced the risk of transmission by 36% compared to infant single-dose NVP alone *[18]*. However, when maternal intrapartum NVP was received, thereby providing pre-exposure prophylaxis in addition to post-exposure prophylaxis, single-dose infant NVP alone was as effective as the combined NVP/ZDV infant post-exposure prophylaxis regimen *[19]*. One problem with use of single-dose infant NVP alone or in combination with a week of ZDV to prevent transmission is the risk of NVP resistance emerging in infants who become infected despite receipt of prophylaxis *[27]*. 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 ZDV.

In an attempt to improve the efficacy of short-course regimens but retain a regimen that remains appropriate to the cost limitations existing in resource-limited countries, more recently researchers have evaluated whether the addition of a potent intrapartum intervention — the single-dose NVP regimen — to short-course regimens might increase efficacy. In the setting of short-course

antenatal ZDV alone or ZDV/3TC, the Perinatal HIV Prevention Trial (PHPT)-2 study in non-breastfeeding women in Thailand, the DITRAME studies in a partially breastfeeding population in the Ivory Coast, and the Mashi study in Botswana (in the formula-fed, but not the breastfed, strata) demonstrated that the addition of single-dose NVP did significantly increase efficacy *[25, 28, 29]*. The relative importance of the maternal and infant components of single-dose NVP in the context of short-course ZDV regimens remains unclear; the Thailand PHPT-2 study suggests that the infant NVP dose at 48 – 72 hours of life may not add significant efficacy to the maternal NVP dose alone; however, the Botswana Mashi study suggests that maternal NVP may not be necessary when infant single-dose NVP is provided at birth *[28, 29]*.

Whether single-dose NVP provides any additional efficacy when combined with the standard recommended antiretroviral prophylaxis regimens used in the United States (e.g., HAART 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 non-breastfeeding women in resource-rich countries, the addition of single-dose NVP did not offer significant benefit in the setting of potent combination antiretroviral therapy throughout pregnancy and very low viral load at the time of delivery *[9]*. Thus, single-dose NVP is not recommended for women in the United States who are receiving the standard recommended antenatal antiretroviral prophylaxis regimens.

PERINATAL HIV TRANSMISSION AND MATERNAL HIV RNA COPY NUMBER

Panel's Recommendations:

- Antiretroviral prophylaxis to prevent perinatal HIV transmission should be provided to all HIV-infected women, regardless of HIV RNA copy number.

Initial data regarding the correlation of viral load with risk for perinatal transmission were conflicting; some studies suggested an absolute correlation between HIV RNA copy number and risk of transmission *[30]*. However, although higher HIV RNA levels have been observed among women who transmitted HIV to their infants, overlap in HIV RNA copy number has been observed in women who transmitted and those who did not transmit the virus. Transmission has been observed across the entire range of HIV RNA levels (including in women with an HIV RNA copy number below the limit of detection of the assay), and the predictive value of HIV RNA copy number for transmission in an individual woman is modest *[31-33]*. In PACTG 076, antenatal maternal HIV RNA copy number was associated with HIV transmission in women receiving placebo. In women receiving ZDV, the relationship was markedly attenuated and no longer statistically significant *[13]*. An HIV RNA threshold below which there was no risk for transmission was not identified; ZDV was effective in reducing transmission regardless of maternal HIV RNA copy number *[13, 34]*.

More recent data from larger numbers of ZDV-treated, HIV-infected pregnant women indicate that HIV RNA levels correlate with risk of transmission even among women treated with antiretroviral agents *[35-38]*. Although the risk for perinatal transmission in women with HIV RNA below the level of assay quantitation 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 *[35, 38, 39]*.

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 *[40-43]*. 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 compartment (such as can occur with antiretroviral treatment) may or may not be associated with comparable changes in other body 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 ZDV trial in Thailand, plasma and cervicovaginal HIV RNA levels were reduced by ZDV treatment, and each independently correlated with perinatal transmission *[44]*. 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 HAART that effectively reduces HIV RNA to <1,000 copies/mL or undetectable levels have very low rates of perinatal transmission *[3, 8, 9, 45]*. However, since 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 *[3, 12, 13, 46]*. Therefore, antiretroviral prophylaxis should be given even to women who have a very low or undetectable viral load on no therapy.

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

Panel's Recommendations:

- Select effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Contraceptive counseling is an essential component of care for HIV-infected women of reproductive age.
- Preconception counseling on safe sexual practices and eliminating alcohol, illicit drug use, and smoking are important both for maternal health as well as for fetal/infant health should the woman become pregnant.
- Choice of an antiretroviral regimen for treatment of HIV-infected women of childbearing potential needs to include consideration of effectiveness for treatment of maternal disease and the drug's potential for teratogenicity should pregnancy occur.
- Attainment of a stable maximally suppressed viral load prior to conception is recommended for HIV-infected women who are on antiretroviral therapy and wish to become pregnant.

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 *[47].* 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 *[48],* 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 have been outlined by the CDC Preconception Care Work Group's "**Recommendations to Improve Preconception Health and Health Care**" *[49].* 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 *[50].* Since many women infected with HIV are aware of their HIV status prior to pregnancy, there may be opportunities to address issues that impact pregnancy prior to conception during routine medical care for their HIV disease. In addition to those outlined by the CDC Preconception Care Work Group *[51],* the following components of preconception counseling and care are specifically recommended for HIV-infected women:

a. Select 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-Infected Adults and Adolescents*, Tables 21a and 21b**) *[5].*

b. Counsel on safe sexual practices that prevent HIV transmission to sexual partners and protect women

from acquiring sexually transmitted diseases (STDs) and 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 HIV transmission, strategies to reduce those risks, and potential effects of HIV or treatment on pregnancy course and outcomes *[51]*.

e. When prescribing antiretroviral treatment to women of childbearing potential, considerations should include the regimen's effectiveness for treatment of HIV disease and the drugs' potential for teratogenicity should pregnancy occur. Women who are planning to get pregnant should strongly consider use of antiretroviral regimens that do not contain efavirenz (EFV) or other drugs with teratogenic potential. In addition, the effectiveness of a regimen in preventing mother-to-child HIV transmission should be considered.

f. Attain a stable, maximally suppressed maternal viral load prior to conception in women who are on antiretroviral therapy and want to get pregnant.

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

h. Evaluate for appropriate prophylaxis for opportunistic infections and administration of medical immunizations (e.g., influenza, pneumococcal, or hepatitis B vaccines) as indicated.

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

j. Counsel regarding available reproductive options, such as intrauterine or intravaginal insemination, that prevent HIV exposure to an uninfected partner *[52];* expert consultation is recommended.

k. Breastfeeding by HIV-infected women is not recommended in the United States due to risk of HIV transmission.

MANAGEMENT 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 who 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 with incomplete HIV testing (e.g., undocumented HIV test results or only one rather than two HIV tests), then she should be screened with a rapid HIV test on the labor and delivery unit *[49]*. If 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 she experiences such symptoms.

If results from either conventional or rapid HIV testing are positive, then the woman should receive interventions to reduce perinatal HIV transmission, 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) then it is appropriate to initiate interventions to reduce perinatal transmission even in the absence of confirmatory testing (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.

Antepartum Care

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 antiretroviral treatment or alteration of her current antiretroviral regimen.
- The known benefits and potential risks of antiretroviral use during pregnancy should be discussed with all women.
- Antiretroviral therapy or antiretroviral prophylaxis for prevention of perinatal HIV transmission during the antepartum period should be recommended to all pregnant, HIV-infected women regardless of plasma HIV RNA copy number or CD4 cell count.
- ZDV should be included in the antenatal antiretroviral regimen unless there is severe toxicity or documented resistance.
- If HIV RNA is detectable, antiretroviral drug resistance studies should be performed before starting/modifying therapy (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**).
- The importance of adherence to the antiretroviral treatment or prophylaxis regimen should be emphasized.
- 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.

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. Cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk for perinatal HIV transmission *[53-57];* in addition to improving maternal health, discontinuing cigarette smoking and drug use, treatment of genital tract infections, and use of condoms with sexual intercourse during pregnancy may also 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 *[58]*.

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 regarding antiretroviral treatment or alteration of her current antiretroviral regimen. This initial assessment should include the following:

a. evaluation of the degree of existing immunodeficiency determined by past and current CD4 count;

b. evaluation of the risk for disease progression and perinatal HIV transmission as determined by current plasma HIV RNA copy number;

c. assessment of the need for prophylaxis against opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PCP) or *Mycobacterium avium* complex (MAC) *[59]*;

d. baseline evaluation with complete blood cell count, and renal and liver function testing;

e. history of prior and current antiretroviral therapy;

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

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

h. assessment of supportive care needs.

Decisions regarding initiation of or alterations to antiretroviral therapy and the choice of antiretroviral regimens during pregnancy are complex. Factors influencing benefit and risk that are unique to pregnancy in addition to those common to all HIV-infected adults must be weighed. General guidelines for the use of antiretroviral drug treatment for the benefit of maternal health are the same as for women who are not pregnant. In addition, there are recommendations for the use of antiretroviral drugs for prophylaxis to prevent perinatal HIV transmission even in women for whom therapy would not otherwise be indicated.

In general, if plasma HIV RNA is detectable, antiretroviral drug resistance studies should be performed before starting antiretroviral therapy or prophylaxis. However, if HIV is diagnosed late in pregnancy, therapy should be initiated while awaiting results of resistance testing (see **Antiretroviral Drug Resistance and Resistance Testing in 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 consequences for the woman on the use of antiretroviral drugs only during pregnancy for prophylaxis of transmission. Similarly, there are only limited data on the long-term consequences of *in utero* antiretroviral exposure for the infant.

Decisions regarding the use and choice of an antiretroviral regimen should be individualized based on the following factors:

a. gestational age of the pregnancy;

b. antiretroviral treatment recommendations for the health of the HIV-infected woman;

c. the efficacy of antiretroviral regimens for prevention of perinatal HIV transmission;

d. known, suspected, and in some cases unknown effects of particular drugs or regimens on the fetus and newborn, on the outcome of pregnancy, and for the woman; and

e. HIV antiretroviral drug resistance studies.

Discussion of treatment options 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 such therapy during pregnancy should be considered and discussed. Results from preclinical and animal studies and available clinical information about use of the various antiretroviral agents during pregnancy should be discussed with the woman (**Table 2** and **3**). Risks of these drugs during pregnancy should be placed in perspective by also discussing benefits of antiretroviral therapy for the health of the infected woman and for reducing the risk for HIV transmission to her infant.

Perinatal HIV transmission can occur even at low or undetectable HIV RNA copy numbers *[3, 12]*. Thus, 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 *[3, 12, 13, 46]*. Therefore, antiretroviral prophylaxis should be recommended even to women who have a very low or undetectable viral load on no therapy.

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

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

b. benefit of lowering HIV viral load to reduce the risk of perinatal transmission;

c. benefit of antiretroviral prophylaxis independent of the effect on viral load as well as the additive benefit of combination antiretroviral regimens for preventing perinatal HIV transmission *[3];*

d. the possibility of development of drug resistance, including the need for strict adherence to the prescribed drug schedule to avoid its development, as well as the increased likelihood of development of resistance in the setting of high viral loads with use of nonsuppressive therapy;

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

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 antiretroviral treatment regimens. 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.

RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL DRUGS DURING 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 will never have 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 indications for therapy.

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. However, certain drugs are of more concern than others (**Table 2** and see **Teratogenicity** and ****Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy****). For example, EFV should be avoided during the first trimester of pregnancy.

Three-drug combination regimens including nelfinavir have had extensive use in pregnancy. However, in September 2007, the U.S. manufacturer, Pfizer, sent a letter to providers regarding the presence of ethyl methane sulfonate (EMS), a process-related impurity, in Viracept (nelfinavir mesylate) available in the United States. 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 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 maternal-to-child transmission.

Table 3 provides recommendations about use of specific antiretroviral drugs in pregnancy as well as data on pharmacokinetics and toxicity in pregnancy. **Table 4** 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:

- Continue the antiretroviral treatment regimen if it is currently effective in suppressing viral replication; however, avoid use of EFV in the first trimester of pregnancy.
- HIV antiretroviral drug resistance testing is recommended if the woman has detectable viremia* on therapy (see **Failure of Viral Suppression**).
- Pregnant women receiving NVP-containing regimens who are virologically suppressed and tolerating the regimen should continue therapy, regardless of CD4 count.

*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.

While ZDV should be a component of the antenatal antiretroviral treatment regimen, there may be circumstances, such as the occurrence of severe ZDV-related toxicity or documented ZDV resistance, when this is not possible. Additionally, women receiving an antiretroviral regimen that does not contain ZDV but who have HIV RNA levels that are undetectable have a very low risk of perinatal transmission *[60],* and there may be concerns that substitution of ZDV for another component of the regimen or the addition of ZDV to the current regimen could compromise adherence to treatment. In such cases, continuing a non-ZDV-containing regimen that is fully suppressive is reasonable.

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, which could result in a decline in immune status and disease progression as well as adverse consequences for both the fetus and the woman, including increased risk of HIV transmission. Therefore, HIV-infected women receiving antiretroviral therapy at the time of conception whose pregnancy is identified after the first trimester should always continue therapy.

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, EFV should be avoided during the first trimester of pregnancy. If a woman is receiving EFV and her pregnancy is recognized during the first trimester, substitution of an alternative antiretroviral drug is recommended when possible (see **Monitoring of the Woman and Fetus during Pregnancy**).

Pregnant women who are receiving NVP-containing regimens with viral suppression and are tolerating the regimen well should continue therapy, regardless of CD4 count. While hepatic toxicity is a concern in women with a CD4 count >250 cells/mm^3 at the time they first initiate an NVP-containing regimen, an increased risk of hepatic toxicity has not been seen in women who are receiving NVP-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 use of specific drugs in pregnancy (**Table 3**).

- For women who require immediate initiation of therapy for their own health, treatment should be initiated as soon as possible, including in 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; use of ZDV prophylaxis alone is controversial, but may be considered for those women initiating prophylaxis with plasma HIV RNA levels <1,000 copies/mL on no therapy.

  - For women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, delaying initiation of prophylaxis until after the first trimester can be considered.

- Use of ZDV as a component of the antiretroviral regimen is recommended when feasible.
- NVP can be used as a component of initial therapy for pregnant women with CD4 cell counts <250 cells/mm^3, but 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 due to an increased risk of hepatic toxicity.

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 standard guidelines in nonpregnant adults *[5]*.

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 two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor(s), 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, as the potential benefit of treatment for the mother outweighs potential fetal risks. The regimen should be chosen from those recommended for nonpregnant adults taking into account what is known about use of the drugs during pregnancy and risk of teratogenicity (**Table 3** and see **Teratogenicity**) *[5]*.

Women with CD4 counts >250 cells/mm^3 have an increased risk of developing symptomatic, often rash-associated, NVP-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal *[61, 62]*. Therefore, NVP 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 risk. If NVP 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 NVP. NVP 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 therapy for prevention of perinatal transmission even when initiation of antiretroviral therapy is not recommended or considered optional on the basis of current guidelines for treatment of nonpregnant persons *[5]*. Although such women are at low risk for 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 patient; 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. While 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 *[3, 36, 37]*. The mechanism by which antiretroviral drugs reduce perinatal HIV transmission is multifactorial. While 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 and when maternal antenatal therapy is unable to be given *[12, 14-17]*. 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 during the birth process, and post-exposure prophylaxis through continued administration to the infant. Although placental passage of ZDV is excellent, that of other antiretroviral drugs may be variable (**Table 2**). Therefore, when combination antiretroviral therapy is initiated during pregnancy, ZDV should be included as a component of antenatal therapy whenever possible. If antenatal ZDV use is not possible, at least one agent with known transplacental passage should be part of the antiretroviral regimen (see **Table 2**).

Combination antiretroviral regimens containing at least three drugs (i.e., HAART) 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 ZDV 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 ZDV alone, 3.8% who received combination therapy without protease inhibitors (primarily dual NRTIs), and 1.2% who received combination therapy with protease inhibitors *[3]*.

If HAART is given solely to reduce perinatal transmission, would not have been needed if the woman were not pregnant, and will be stopped postpartum, use of a three-drug regimen that is not considered to be one of the standard first-line regimens used for adults who require therapy may be considered. However, the regimen should be among those considered an alternative effective treatment for adults. In particular, the triple NRTI combination ZDV/3TC/ABC regimen may be considered because of known pharmacokinetics profiles and published data suggesting acceptable toxicities during pregnancy. However, this regimen has inferior long-term virologic efficacy, and for women with high CD4 count but high viral load (i.e., CD4 count >350/mm³ and HIV RNA >100,000 copies/mL), use of first-line, more potent regimens should be considered. Dual NRTI therapy without the addition of a third drug (i.e., a protease inhibitor, NNRTI, or a third NRTI) is not recommended because of the potential for inadequate viral suppression and rapid development of resistance *[5, 63]*.

The time-limited use of ZDV monotherapy during pregnancy for chemoprophylaxis against perinatal transmission is controversial. However, some women may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of transmitting HIV to their infants. Additionally, for women with low viral load, time-limited use of ZDV 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 patient and the short duration of exposure to the antiretroviral drug. For example, the development of ZDV resistance was unusual among the healthy population of women who participated in PACTG 076 *[64]*. Thus, while controversial, the use of ZDV 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 therapy is 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 usual criteria for nonpregnant individuals. Discussion regarding the decision to continue or stop treatment postpartum should occur before beginning therapy 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 (e.g., 7 days) after stopping the NNRTI should be considered to prevent the development of NNRTI resistance.

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.
- Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy.
- Initiate HAART, with regimen chosen based on resistance testing and prior therapy history, and avoid drugs with teratogenic potential (EFV) or with known adverse potential for the pregnant mother (combination stavudine [d4T]/didanosine [ddI]).
- Women who do not show an appropriate virologic response to their antiretroviral regimen (see **Monitoring of the Woman and Fetus During Pregnancy**) require repeat antiretroviral drug resistance testing, as well as consultation with a clinician experienced in HIV treatment, to guide changes in antiretroviral therapy.

Following antiretroviral prophylaxis used solely for prevention of perinatal HIV transmission, there are no data to guide the choice of antiretroviral regimens to be used in a subsequent pregnancy.

There is concern that some women with such time-limited use of antiretroviral drugs may develop genotypic resistance to one or more components of the initial antiretroviral regimen, thus limiting the efficacy of such drugs for use during subsequent pregnancies. However, reduced efficacy of standard regimens, particularly those containing the dual NRTI backbone of ZDV and 3TC, 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 is complex, as the assay may not detect low-level drug resistant viral variants because wild-type sensitive virus may predominate when selective drug pressure is removed by stopping the drugs. 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 before the current pregnancy and may not be receiving antiretroviral drugs at the time they present for obstetrical care, 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, whether the drugs are currently needed for treatment or prophylaxis, and results of 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.

SPECIAL SITUATIONS

Hepatitis B Virus Coinfection

Panel's Recommendations:

- Screening for hepatitis B surface antigen is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy.
- Interferon-alpha and pegylated interferon-alpha are not recommended during pregnancy.
- For pregnant women with chronic hepatitis B virus (HBV) (i.e., hepatitis B surface antigen positive for >6 months)/HIV coinfection who require antiretroviral treatment for HIV disease or who require anti-HBV therapy, a three-drug regimen including a dual NRTI backbone of tenofovir plus 3TC or emtricitabine (FTC) is recommended.
    - For women who require treatment of HBV but not HIV, postpartum options include stopping antiretroviral drugs and initiating pegylated interferon-alpha for HBV treatment, or continuing the three-drug antiretroviral regimen. Consultation with an expert is advised.
- For pregnant women with HBV/HIV coinfection who do not require treatment for either HIV or HBV and therefore discontinue prophylaxis postpartum, consultation with an expert in HIV and HBV is recommended.
    - Many experts would give an antepartum three-drug regimen including the dual NRTI backbone of tenofovir plus 3TC or FTC and discontinue the regimen postpartum, with careful monitoring postpartum for HBV disease flare, which could be treated with HBV-specific therapy such as pegylated interferon-alpha.
    - Alternatively, some experts would give an antepartum three-drug regimen including a dual NRTI backbone that does not contain tenofovir, 3TC, or FTC (e.g., ZDV + ddI), with discontinuation postpartum.
- Pregnant women with HBV/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 and then at least monthly.
- Infants born to women with hepatitis B infection should receive hepatitis B immune globulin (HBIG) and initiate the three-dose hepatitis B vaccination series within 12 hours of birth.

All HIV-infected pregnant women should be screened for hepatitis B surface antigen. The management of HBV/HIV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is advised.

There is a paucity of 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 HBV 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 FTC or tenofovir plus 3TC as the dual NRTI backbone of an antiretroviral regimen, regardless of the need for concomitant HBV treatment *[5]*. Tenofovir, 3TC, and FTC all show activity against HBV. Because of the risk of development of HBV-resistant mutants, use of two agents active against HBV is recommended as the dual NRTI backbone when antiretroviral treatment is required**.**

3TC is a recommended and FTC is an alternative NRTI for use in pregnancy. There are currently insufficient data to recommend use of tenofovir in pregnancy, and therefore it is generally recommended to be used as a component of maternal combination regimen only after careful consideration of alternatives (see **Table 3**). However, for pregnant women with HBV/HIV coinfection who require treatment of HIV disease, the benefit of tenofovir outweighs potential risks, and tenofovir plus 3TC or FTC is recommended as the dual NRTI backbone of a three-drug therapeutic regimen. While ZDV 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 3TC or FTC is also recommended for HBV/HIV-infected pregnant women who do not require treatment of HIV but 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 3TC or FTC 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 *[65]*. 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.

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 HIV transmission and will discontinue therapy postpartum, there is controversy regarding the appropriate approach to therapy. Many experts recommend use of a three-drug regimen that includes the anti-HBV drug tenofovir plus 3TC or FTC 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 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 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, 3TC, or FTC could be considered, such as ZDV and ddI) to avoid the possibility of an HBV flare when treatment is discontinued postpartum.

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 NVP. 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 HBIG and initiate the three-dose 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.

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.
- Pegylated interferon-alpha is not recommended and ribavirin is contraindicated during pregnancy.
- Combination antiretroviral therapy with three drugs should be considered for all HCV/HIV coinfected pregnant women, regardless of CD4 count or HIV viral load; the antiretroviral drugs can be discontinued postpartum in women who do not require HIV therapy for their own health.
- 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.
- Decisions concerning mode of delivery in HCV/HIV coinfected pregnant women should be based on considerations related to HIV infection alone (see **Intrapartum Care**).
- Infants born to women with HCV/HIV coinfection should be evaluated for HCV infection by HCV RNA testing between 2 and 6 months of age and/or HCV antibody testing after 15 months of age.

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% *[66]*. 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 *[67]*. Ribavirin is labeled as FDA 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 *[68]*.

Coinfection with HIV has been shown to significantly increase the risk of perinatal HCV transmission, likely related to increase in HCV viremia and/or other HIV-related impact on HCV disease activity *[69]*. A European study of perinatal HCV transmission 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) *[70]*; in this study HCV median viral load was lower among HAART-treated women as compared to women on monotherapy or no treatment (656,101 copies/mL vs 850,000 copies/mL, respectively), although this difference was not statistically significant. Maternal HCV/HIV coinfection may also increase risk for perinatal HIV transmission *[71]*. 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 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 NVP. 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 section versus vaginal delivery for preventing mother-to-infant HCV transmission *[72]*. 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 antiretroviral treatment in the second report *[73]*. 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 as HCV viremia can be intermittent) and/or testing for anti-HCV antibody after age 15 months *[74]*.

Stopping Antiretroviral Therapy during Pregnancy

Panel's Recommendations:

- If antiretroviral therapy is stopped electively and the patient is receiving an NNRTI drug, consideration should be given to stopping the NNRTI first, and continuing the other antiretroviral drugs for a period of time (e.g., 7 days); however, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known.
- If antiretroviral therapy 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.
- If NVP is stopped and more than 2 weeks have passed prior to restarting therapy, NVP should be restarted with the 2-week dose escalation period.

Discontinuation of antiretroviral therapy during pregnancy may be indicated in some situations including serious treatment-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 therapy 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 NVP and EFV have very long half-lives and can be detected for 21 days or longer after discontinuation *[75-79]*. As the other drugs with shorter half-lives are cleared, only the NNRTI drug may persist, resulting in functional monotherapy 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 *[77, 79]*. To prevent this functional monotherapy, some experts recommend stopping the NNRTI first, and continuing the other antiretroviral drugs for a period of time (e.g., 7 days) *[76]*. 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 *[79]*. Further research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens (see **Clinical Research Needs**).

An additional consideration is reintroduction of NVP 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 NVP. Dose escalation is necessary because NVP 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 NVP has been discontinued for more than 2 weeks, it is recommended that

another 2-week dose escalation be used when 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.
  - Consult an expert in the care of HIV-infected adults.
- Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery.

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 *[5]*. Baseline HIV RNA levels have been shown to affect the time course of response in pregnant as well as nonpregnant individuals *[80]*. 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 *[5]*. 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 section 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**).

MONITORING OF THE WOMAN AND FETUS DURING PREGNANCY

Panel's Recommendations:

- CD4 cell count should be monitored at the initial visit and at least every 3 months during pregnancy.
- Plasma HIV RNA levels should be monitored at the initial visit, 2 to 6 weeks after initiating (or changing) antiretroviral therapy, monthly until RNA levels are undetectable, and then at least every 2 months during pregnancy; HIV RNA levels should also be assessed at approximately 34 to 36 weeks gestation for decisions on mode of delivery (see **Transmission and Mode of Delivery**).
- Antiretroviral drug resistance testing should be performed on women who have persistently detectable plasma HIV RNA levels despite receiving antiretroviral drugs for treatment or prophylaxis.
- 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.
- 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**).
- Most experts would recommend assessment of fetal anatomy with second trimester ultrasound evaluation in women who have received combination antiretroviral therapy (particularly if the regimen included EFV) during the first trimester given the limited data on the effect of combination therapy on the fetus.

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 6 weeks after initiating or changing antiretroviral therapy, monthly until undetectable, and then at least every 2 months. The recommended monitoring of viral load in pregnancy is more frequent than in nonpregnant individuals because of the need to lower viral load as rapidly as possible to reduce transmission risk, and therefore there is a need to identify those women whose decline in viral load is slower than expected. 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 *[81, 82]*. However, since 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 women who have suboptimal viral suppression after initiation of antiretroviral drugs or who have persistently detectable plasma HIV RNA levels after having become undetectable on treatment (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**). Adult antiretroviral guidelines note that patients should have a decrease in plasma HIV RNA level by at least one $\log_{10}$ copies/mL by one month after initiation of potent therapy *[5]*.

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 ZDV-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, NVP-associated hepatotoxicity within the first 18 weeks after initiation of therapy. Pregnant women initiating therapy with NVP 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 to guide potential timing of scheduled cesarean delivery, if needed, since scheduled cesarean deliveries for prevention of perinatal HIV transmission should be performed at 38 weeks gestation (see **Transmission and Mode of Delivery**). First trimester ultrasound has been shown in research studies and is recommended by the ACOG as most accurate for dating of pregnancy *[83, 84]*. 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 EFV. Additionally, some experts would also recommend ultrasound assessment of fetal growth and well-being during the third trimester in addition to standard clinical monitoring, 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.

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**).
- Some protease inhibitors require altered dosing during pregnancy (**see Table 3**).
- EFV 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. EFV should not be used in the first trimester of pregnancy, and women on EFV should be counseled to avoid pregnancy.
- Women with CD4 counts >250 cells/mm^3 initiating NVP regimens have an increased risk of developing symptomatic, often rash-associated, NVP-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal. NVP should only be used in this setting if the benefits clearly outweigh the risks.
- Because of the potential for lactic acidosis with prolonged use of the combination of d4T and ddI by HIV-infected pregnant women, clinicians should not prescribe this antiretroviral combination during pregnancy unless no other antiretroviral options are available and potential benefits outweigh the risks.
- Because NRTI drugs may be associated with development of lactic acidosis, pregnant women receiving NRTI drugs should have hepatic enzymes and electrolytes assessed monthly during the last trimester of pregnancy and any new symptoms should be evaluated thoroughly.
- 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 of gestation. 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 such as maternal obesity, advanced maternal age, and family history of type II diabetes mellitus.

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 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 *[85]*. 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 3** 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-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. 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 dosing of antiretrovirals in pregnancy are summarized in **Table 3**. In general, the pharmacokinetics of NRTI and NNRTI drugs are similar in pregnant and nonpregnant women, while protease inhibitor 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 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 *[86]*. Limited data exist regarding placental passage, long-term animal carcinogenicity, and animal teratogenicity for the FDA-approved antiretroviral drugs (**Table 2**).

Human data on teratogenicity of FDA-approved antiretrovirals are summarized in **Table 3**. Concerns have been raised about the risk of several of the antiretroviral agents. In cynomolgus monkeys treated with EFV from gestational days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human therapeutic exposure, significant CNS malformations were observed in 3 of 20 infant monkeys *[87]*. The malformations included anencephaly and unilateral anophthalmia in one; microphthalmia in another; and cleft palate in the third. In prospectively reported pregnancies with exposure to EFV-based regimens in the Antiretroviral Pregnancy Registry through January 2007, birth defects were observed in 7 of 281 (2.5%) live births with first trimester exposure, not significantly higher than the prevalence of birth defects in the general population (2.7%), and none of the defects in the prospective report were neural tube defects *[88]*. However, in retrospective case reports, there are three cases of neural tube defects in infants born to mothers receiving EFV during the first trimester *[89],* as well as an additional infant with another CNS defect (Dandy-Walker malformation). Although a causal relationship of these

events to the use of EFV has not been established, in light of similar findings in primates, EFV 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 EFV, and treatment with EFV 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 EFV and should be counseled about the potential risk to the fetus and need to avoid pregnancy. Alternate antiretroviral regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception.

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 recommended for either routine therapeutic use or use in pregnancy.

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 2.6% in 266 women with first trimester tenofovir exposure, similar to that in the general population *[88]*. 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.

Among cases of first trimester ddI exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 5.8% (15/259), compared to a rate of 1.0% (2/195) among those with exposures later in pregnancy *[88]*. All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. However, these data do suggest a higher risk of birth defects with exposure to ddI in the first trimester as compared to the frequency of birth defects observed in the general population and with the use of other antiretroviral agents, and this is continuing to be followed by the Registry.

See **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
Internet access **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

Data are conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes, in particular preterm delivery. A retrospective Swiss report evaluated the pregnancy outcome of 37 HIV-infected pregnant women treated with combination therapy; all received 2 NRTIs and 16 received

1 or 2 protease inhibitors *[90]*. A possible association of combination antiretroviral therapy with preterm births was noted; 10 of 30 babies were born prematurely. The preterm birth rate did not differ between women receiving combination therapy with or without protease inhibitors. The contribution of maternal HIV disease stage and other covariates that might be associated with a risk for prematurity was not assessed.

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 2.6-fold increased odds of preterm delivery for infants exposed to combination therapy with or without protease inhibitors, compared with 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 *[91]*. However, combination therapy was received by only 323 (8%) women studied. Exposure to monotherapy was not associated with prematurity. An updated report from the European Collaborative Study including 4,372 women found, in an adjusted analysis, a 1.9-fold increased risk of delivery at less than 37 weeks with HAART started during pregnancy and 2.1-fold for HAART started pre-pregnancy *[92]*. In this report, 767 women received HAART 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 HAART during pregnancy and 4.4-fold for those entering pregnancy on HAART.

In contrast, the majority of data from the United States and Latin America do not suggest an increased risk of preterm birth associated with HAART during pregnancy. In a meta-analysis of seven 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, use of multiple antiretroviral drugs as compared with no treatment or treatment with one drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth *[93]*. An analysis from the Women and Infants Transmission Study, including 2,543 HIV-infected women (some of whom were included in the meta-analysis) did not show significant associations between use of antiretroviral by class or by category, including HAART, and adverse pregnancy outcome *[94]*. A prospective cohort study including 681 women from Brazil, Argentina, Mexico, and the Bahamas did not find significant associations between use of HAART and preterm birth or low birth weight *[95]*. 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 HAART compared with other combination therapy after adjustment for possible confounding variables *[96]*. However, women receiving protease inhibitor-containing HAART were uniformly 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 clinical studies that included both European and American studies found that antiretroviral use during pregnancy did not increase the risk of premature delivery when compared to no therapy *[97]*.

Until more information is known, HIV-infected pregnant women who are receiving combination therapy for their HIV infection should continue their provider-recommended regimen. 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 NVP. 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 *[98]*. The development of severe NVP-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 *[99-101]*. Other studies have found that hepatic adverse events

with systemic symptoms (predominantly rash) were 3.2-fold more common in women than men *[102, 103]*. The degree of risk for hepatic toxicity varies with CD4 count. In a summary analysis of data from 17 clinical trials of NVP 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, NVP-related hepatotoxicity *[102, 103]*. Higher CD4 counts have also been associated with increased risk of severe NVP-associated skin rash *[100]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5% – 11.0%) of patients who received NVP; however, the risk of NVP-associated liver failure or hepatic mortality has been lower, ranging between 0.04% – 0.40% *[61, 62]*. Severe or life threatening rash occurs in approximately 2% of patients receiving NVP *[62]*.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving NVP as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving NVP or other antiretroviral drugs *[104, 105]*. Women initiating NVP 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, NVP-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal *[61]*. NVP should therefore be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Regardless of maternal CD4 count, if NVP is used, health care providers should be aware of this potential complication 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 16a in the ***Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents***). In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy, and then monthly *[98]*. Transaminase levels should be checked in all women who develop a rash while receiving NVP. 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 NVP and not receive NVP therapy in the future. Hepatic toxicity has not been seen in women receiving single dose NVP during labor for prevention of perinatal transmission of HIV. Women who enter pregnancy on NVP-containing regimens and are tolerating them well may continue therapy, regardless of CD4 count.

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 *[106-109]*. 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 HAART found an increased risk of glucose intolerance, but not gestational diabetes, among women on HAART compared to ZDV alone *[110],* while 2 other retrospective studies did not find an increased risk of glucose intolerance with protease inhibitors *[111, 112]*. Secondary analyses of 2 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 *[94, 113]*. A recent 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 nonprotease-inhibitor-containing regimens *[114]*. The rate of impaired glucose tolerance was high (38%) in both groups, probably related to high body weights and ethnic composition (e.g., black or Hispanic race/ethnicity). 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.

Mitochondrial Toxicity and NRTI Drugs

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 *[115]*. The relative potency of the NRTI drugs in inhibiting mitochondrial gamma DNA polymerase *in vitro* is highest for zalcitabine (ddC), followed by ddI, d4T, ZDV, 3TC, abacavir (ABC), and tenofovir *[116]*. 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 *[115]*. 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 *[117, 118]*. 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 *[119-122]* and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

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 *[123]*. 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 d4T-3TC at the time of conception and throughout pregnancy and who experienced symptoms and fetal death at 38 weeks gestation *[124]*. 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 d4T and ddI in combination with other antiretroviral agents (either a protease inhibitor or NVP) *[125, 126]*. 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. Non-fatal cases of lactic acidosis in pregnant women receiving combination d4T-ddI have also been reported *[127]*.

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. Pregnant women receiving NRTI drugs should have hepatic enzymes and electrolytes assessed monthly during the last trimester of pregnancy, and any new symptoms should be evaluated thoroughly.

Additionally, because of the reports of several cases of maternal mortality secondary to lactic acidosis with prolonged use of the combination of d4T and ddI by HIV-infected pregnant women, clinicians should not prescribe this antiretroviral combination during pregnancy unless no other antiretroviral options are available and potential benefits outweigh the risks.

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 ZDV/3TC (4 infants), or ZDV alone (4 infants) who developed indications of mitochondrial dysfunction after the first few months of life *[128]*. Two of these infants (both exposed to ZDV/3TC) 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 France National Register, the 18-month incidence of clinical symptoms of mitochondrial dysfunction was 0.26%, and 0.07% for mortality *[129]*. All children had perinatal antiretroviral exposure; risk was higher among infants exposed to combination antiretroviral drugs (primarily ZDV/3TC) than ZDV 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 has also 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 *[130, 131]*.

In one 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 ZDV exposure compared to 10 without ZDV exposure *[132]*. 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 *[133]*. 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 d4T/3TC > ZDV/ddI > ZDV/3TC > 3TC. 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 *[134]*. Thus, the clinical significance of these laboratory findings is unclear, and further studies are needed to validate these findings. Clinical studies in the United States and Europe have generally not duplicated the French reports *[135-141]*. 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 *[136]*. However, most of the infants with antiretroviral exposure had been exposed to ZDV alone and only a relatively small proportion (approximately 6%) had been exposed to ZDV/3TC. 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 *[138]*. 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. However, similarly persistent, but clinically asymptomatic, hematologic abnormalities in uninfected infants with *in utero* exposure have been reported in the United States and Europe *[142-144]*. 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 *[140]*. Definitive diagnosis was not available as none of the children had biopsies for mitochondrial function. Three of the 20 children had no exposure to antiretroviral drugs. However, 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 ZDV/3TC limited to the third trimester.

Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure, and further studies are needed. If this association is demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and should be compared against the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more *[3, 138, 145]*. 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 Public Health Service recommendation for long-term follow-up for any child with in utero exposure to antiretroviral drugs.

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 antiretrovirals, before starting treatment or prophylaxis.
  - All pregnant women receiving antenatal antiretroviral therapy who have virologic failure with persistently detectable HIV RNA levels or who have suboptimal viral suppression after initiation of antiretroviral therapy.
- 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 results are available.

Resistance testing is recommended for all antiretroviral-naïve pregnant women before initiating treatment or prophylaxis if prior resistance testing has not been done. Ideally, this testing would be done at a preconceptional 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, that these viral variants may be detectable by standard assays used in clinical practice, that the prevalence of resistance in antiretroviral-naïve patients is increasing, and that baseline resistance may be associated with adverse virologic outcomes *[146-153]*. For these reasons, baseline HIV resistance testing is now recommended for all patients with established infection, including pregnant women, prior to initiating treatment *[154, 155]*.

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 who are already receiving antiretroviral therapy at the time they are seen, resistance testing is indicated if there is suboptimal initial viral suppression following initiation of antiretroviral therapy or if there is persistently detectable HIV RNA levels indicative of virologic failure on the current regimen.

While in most settings the results of resistance testing would be used to guide selection of the initial regimen, in some clinical situations the clinician may choose to initiate empiric antiretroviral therapy or prophylaxis before the results of resistance testing are available in order to maximize prevention of perinatal transmission; the antiretroviral drug regimen may be modified as needed once resistance test results become available. 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. For women who had resistance testing performed in the latter half of the second trimester, experts are divided as to whether the benefit of immediate initiation of antiretroviral drugs and more rapid reduction of viral load outweighed 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 *[156].* The administration of combination antiretroviral therapy 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 NVP combined with two nucleoside analogue drugs, discontinuation of all regimen components simultaneously postpartum may result in functional monotherapy and increase the risk of development of NVP resistance. 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 from the United States and Europe of newly infected, therapy-naïve persons, rates of primary resistance mutations appear to be increasing over time and have been reported as high as 23% *[150, 157, 158]*. 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 *[157]*.

More recently, studies have examined antiretroviral drug resistance in drug-naïve persons with newly diagnosed HIV infection of unknown duration, 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 *[149, 150]*. 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 *[159]*.

Pregnancy

There are limited data about the prevalence of antiretroviral drug resistance in pregnant women, but 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 *[160]*. 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 *[161]*. Among 220 pregnant antiretroviral-experienced women in the Perinatal AIDS Collaborative Transmission Study, all of whom had prior ZDV exposure in pregnancy from 1991 to 1997, 17.3% had ZDV-associated mutations *[162]*. In a substudy of the PACTG 316 protocol, an international, multicenter clinical trial comparing single-dose NVP 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 NVP resistance at 6 weeks postpartum, despite no history of prior exposure to non-nucleoside drugs or receipt of NVP at delivery *[163]*. Additionally, more than 60% of women receiving combination therapy (either dual nucleosides or combinations containing a protease inhibitor) had the M184V mutation conferring resistance to 3TC, 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% *[3, 164]*.

Incidence of Antiretroviral Resistance with Perinatal Prophylactic Regimens

Panel's Recommendations:

- The addition of single-dose maternal/infant NVP to an ongoing HAART regimen does not provide additional efficacy in reducing perinatal transmission and may result in NVP drug resistance in the mother, and is therefore not recommended.

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 *[162, 165-167]*. Development of ZDV drug resistance with the PACTG 076 ZDV regimen alone appears uncommon in women with higher CD4 count and low viral load *[64, 168],* but is more of a concern in women who have more advanced disease and lower CD4 count *[165]*.

Rapid development of resistance to 3TC, which requires only 1 point mutation for high-level resistance, was reported in 52 (39%) of 132 women with viral RNA samples amplified using standard genotypic assays at 6 weeks postpartum in a French cohort in which 3TC was added at 32 weeks gestation to the PACTG 076 ZDV regimen *[8]*. When women received 3TC for more than 2 months, resistance was identified in 50% (37/74), as compared to none of 12 women receiving it for less than 1 month. In the PETRA study, 12% of women who received 1 month antepartum, intrapartum, and 1 week postpartum combination ZDV/3TC developed 3TC resistance, while none of the women who received only intrapartum and 1 week postpartum ZDV/3TC developed resistance; none of the women in either arm developed ZDV resistance *[169]*.

NVP also has a low genetic barrier to resistance, with one point mutation conferring resistance to NVP 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 *[75]*. Factors associated with increased risk of resistance following single-dose NVP 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 NVP has varied in studies, ranging from 15% to 75% *[163, 170-179]*. 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 *[178-181]*. However, these studies demonstrate that while resistance occurs in the first few weeks post-exposure in the majority of women exposed to single-dose NVP, the prevalence of resistance declines rapidly over time and the proportion of resistant virus in those with detectable resistance 12 months after exposure is low; additionally, archiving of resistance in cellular provirus appears to 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 NVP 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 *[181]*.

Addition of single-dose NVP to other background regimens (77% of women received antenatal combination antiretroviral therapy) still resulted in NVP resistance in 14 of 95 (15%; 95% CI 8% – 23%)) women in the PACTG 316 study *[163]*. Because PACTG 316 demonstrated that the addition of single-dose NVP in situations where combination antiretroviral therapy is being received did not provide any additional efficacy in prevention of mother-to-child transmission, and because there is a risk of NVP 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 resistance 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 ZDV monotherapy for treatment of HIV disease in the early 1990s. In this study, detection of ZDV resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count *[165];* however, women in this cohort had characteristics that would indicate treatment with HAART under current U.S. Public Health Service (USPHS) recommendations for their own health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild-type and virus with low-level ZDV resistance, only wild-type virus was found in the infant *[182],* and other studies have suggested that drug resistance mutations may diminish the fitness of the virus *[183]*, 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 *[184, 185].* Neither resistance to NVP that develops as a result of exposure to single-dose NVP nor exposure to single-dose NVP in a prior pregnancy has been shown to affect perinatal transmission rates *[186, 187].*

Maternal Response to Subsequent Treatment Regimens

Although the development of drug resistance should be minimized by providing HAART to all women during pregnancy to maximally suppress viral replication, some women with low HIV RNA levels and higher CD4 counts may choose the PACTG 076 ZDV regimen to minimize exposure of the fetus to antiretroviral drugs. Women who enrolled in PACTG 076 had to have CD4 counts >200 cells/mm^3 at study entry. PACTG 288, a follow-up study of women enrolled in PACTG 076 who were monitored for a median of >4 years postpartum, found no substantial differences in CD4 count, HIV RNA level, time to progression to AIDS or death, or development of ZDV resistance among women who received ZDV compared with those who received placebo *[188].*

Because NVP resistance mutations can be detected in the postpartum period in a significant proportion of women receiving single-dose intrapartum/infant NVP prophylaxis, the response to non-nucleoside-based combination therapy when later required for maternal health reasons has been a concern. A study in Thailand reported lower rates of viral suppression to fewer than 50 copies/mL after 6 months of NVP-based combination therapy among women who had previously received single-dose NVP a median of 6 months prior to initiation of treatment, as compared to women without single-dose NVP exposure *[173].* However, 2 other studies from Botswana and South Africa reported that women who received single-dose NVP responded similarly to women without such exposure when NVP-based antiretroviral therapy was initiated more than 6 months after single-dose NVP exposure *[189, 190]*. Recent data using more sensitive resistance assays have demonstrated the fading of NVP resistant virus to very low frequency levels (0.7%) by 1 year post single-dose NVP exposure, with minimal persistent archiving of resistance in proviral DNA *[181];* these data are very consistent with the studies suggesting response to NVP-based therapy is not compromised if therapy is started at least 6 to 12 months post-exposure and the studies reporting that single-dose NVP is effective in second pregnancies *[186, 187, 189, 190].*

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, resistance should not occur. Issues relating to discontinuation of NVP-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 ZDV resistance and are on regimens that do not include ZDV for their own health should still receive intravenous ZDV during labor whenever possible, along with their established antiretroviral regimens and oral ZDV for their infants according to the PACTG 076 protocol. For women who are receiving a d4T-containing regimen, d4T should be discontinued during labor while intravenous ZDV is being administered (see **Intrapartum Care**).
- The optimal prophylactic regimen for newborns of women with ARV resistance is unknown (see **Infant Antiretroviral Prophylaxis**). Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery.

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 being used during pregnancy for prevention of mother-to-child HIV transmission. Although most transmission occurs during the intrapartum period, as much as 30% to 35% of transmission may occur *in utero [191-193]*; the majority of *in utero* infection is thought to occur later in pregnancy *[191],* and may be more likely in women with advanced HIV disease and/or high viral load *[192, 193]*. 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, empiric initiation of antiretroviral prophylaxis may be warranted to maximize prevention of perinatal transmission, with the regimen being modified if needed once resistance testing results become available.

For women who have documented ZDV resistance and whose antepartum regimen does not include ZDV, intravenous ZDV during labor should still be administered whenever possible (see **Intrapartum Care**). If the woman's antepartum regimen includes d4T, which may be antagonistic to ZDV, d4T 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. Oral ZDV for 6 weeks should also be administered to the infant. For an infant born to a woman with known ZDV-resistant virus, many clinicians would choose to provide additional antiretroviral agents to the infant in combination with ZDV (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 ZDV intrapartum and to the infant when a woman is known to harbor virus with ZDV 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 ZDV resistance, only wild-type virus is found in the infant *[182]*. Other studies have suggested that drug resistance mutations may diminish viral fitness and possibly decrease transmissibility *[183]*. Efficacy of the PACTG 076 ZDV regimen appears to be based not only on reduction of HIV levels, but also on pre- and post-exposure prophylaxis in the infant *[13, 16, 46]*. ZDV crosses the placenta readily and has one of the highest maternal:cord blood ratios among the nucleoside analogue agents. Additionally, ZDV is metabolized to the active triphosphate within the placenta *[194, 195]*, 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 (ddI and ddC) *[196,*

197]. In addition, ZDV has been shown to reduce genital HIV RNA levels, and genital viral levels have been shown to correlate with perinatal transmission *[44]*. 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 *[198-200]*. ZDV has better penetration into the CNS compared to other nucleoside analogues with the exception of d4T, whose CNS penetration is similar; this may help to eliminate a potential reservoir for transmitted HIV in the infant *[201, 202]*. Thus, intravenous intrapartum and oral ZDV for the infant should be included even in the presence of known ZDV resistance because of the unique characteristics of ZDV and its proven record in reducing perinatal transmission.

Prevention of Antiretroviral Drug Resistance

Panel's Recommendations:

- The use of HAART to maximally suppress viral replication during pregnancy is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission.
- All pregnant women should be counseled about the importance of adherence to prescribed antiretroviral medications to reduce the potential for development of resistance.
- NVP-based combination therapy should not be initiated in women with CD4 count >250 cells/mm^3 unless the benefit clearly outweighs the risk due to concern about increased risk of hepatic toxicity (see **Nevirapine and Hepatic/Rash Toxicity**). However, some pregnant women may receive an NVP-based combination antiretroviral therapy regimen for prophylaxis only, with plans to discontinue therapy after delivery. In this situation, consideration should be given to continuing the nucleoside analogue agents for 7 days after stopping NVP to minimize the risk of NVP resistance (See **Stopping Antiretroviral Therapy during Pregnancy** and **Postpartum Follow-Up of HIV-Infected Women**).

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 NVP or other NNRTI drugs are used as part of a prophylactic combination antiretroviral regimen that is stopped after delivery, there may be a risk of development of NNRTI resistance because of the drug's prolonged half-life, leading to a period of functional monotherapy if all drugs are discontinued at once. Studies in South Africa and Cote d'Ivoire have shown that the development of NVP resistance following exposure to single-dose intrapartum NVP (given alone or in combination with antenatal antiretroviral therapy) was significantly decreased (but not eliminated) if ZDV/3TC was given intrapartum and administered for 3 to 7 days postpartum after intrapartum NVP *[203, 204]*. Whether such a strategy will be useful when an antenatal NVP-based combination regimen is stopped after delivery is not known. 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 *[174]*. All 5 were on combination regimens that included NVP, 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 NVP). It is not known whether the incidence of resistance would have been significantly higher if drug discontinuation had not been staggered. NNRTI drugs have long half-lives, and drug levels can persist for up to 1 to 3 weeks after stopping the drug; EFV levels persist longer than NVP levels *[75,*

78]. Further research is needed on the optimal duration of time and regimen to "cover" this period of prolonged NNRTI exposure to prevent emergence of resistance following discontinuation of NNRTI-based therapy; many experts will stop the NNRTI drug and continue the other antiretroviral drugs for 7 days.

Intrapartum Care

INTRAPARTUM ANTIRETROVIRAL THERAPY/PROPHYLAXIS

Panel's Recommendations:

- Intrapartum intravenous ZDV is recommended for all HIV-infected pregnant women, regardless of their antepartum regimen, to reduce perinatal HIV transmission.
- For women who are receiving a d4T-containing antepartum regimen, d4T should be discontinued during labor while intravenous ZDV is being administered.
- 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 section.
- Women receiving fixed-dose combination regimens that include ZDV should have ZDV administered intravenously during labor while other antiretroviral components are continued orally.
- 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. The addition of intrapartum/newborn single-dose NVP is not recommended.
- Women of unknown HIV status who present in labor should have rapid HIV antibody testing performed, and intravenous ZDV initiated if the test is positive (without waiting for results of the confirmatory test), and infant ZDV initiated. A confirmatory test should be done postpartum; if positive, 6 weeks of infant ZDV is recommended, and if negative, the infant ZDV can be stopped.
- For HIV-infected women in labor who have not received antepartum antiretroviral drugs, intravenous ZDV during labor and 6 weeks of infant ZDV is recommended. Some experts would combine the intravenous intrapartum/6-week newborn ZDV regimen with single-dose intrapartum/newborn NVP.
- If single-dose NVP is given (alone or in combination with ZDV), consideration should be given to adding 3TC during labor and maternal ZDV/3TC for 7 days postpartum, which may reduce development of NVP resistance in the woman.

Table 5 shows dosing for intravenous intrapartum ZDV given in continuous infusion during labor and neonatal ZDV dosing; Table 6 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 ZDV during Labor

The goal for the management of HIV-infected pregnant women during labor and delivery is to both minimize the risk for perinatal HIV transmission and the potential for maternal and neonatal complications. The PACTG 076 results and subsequent epidemiologic studies have proven the efficacy of the three-part ZDV chemoprophylaxis regimen alone or in combination with other antiretroviral agents; the PACTG 076 ZDV regimen includes a continuous intravenous infusion of ZDV 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 ZDV during the intrapartum period should be discussed with and recommended to all HIV-infected pregnant women. For a scheduled cesarean delivery, intravenous ZDV should begin 3 hours before surgery, according to standard

dosing recommendations. Women receiving fixed-dose combination regimens that include ZDV (e.g., the ZDV/3TC combination Combivir) should have ZDV administered intravenously during labor while other antiretroviral components are continued orally (e.g., if a woman is receiving Combivir during pregnancy, ZDV should be given intravenously and 3TC given orally during labor).

If a woman has not received ZDV as a component of her antenatal antiretroviral regimen because of known or suspected ZDV resistance or toxicity, intrapartum ZDV according to the PACTG 076 protocol should still be recommended unless a history of hypersensitivity is documented, because of the unique characteristics of ZDV and its proven record in reducing perinatal transmission (see **Antiretroviral Resistance**). There is a pharmacologic antagonism between ZDV and d4T, and therefore these drugs should not be administered together during labor. Women who are receiving an antepartum d4T-containing regimen should discontinue d4T during labor while intravenous ZDV 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, regardless of route of delivery, 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, but consultation with the attending anesthesiologist should be obtained before administering 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 ZDV) 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

Scheduled cesarean delivery is recommended for women who have HIV RNA levels >1,000 copies/mL near the time of delivery (see **Transmission and Mode of Delivery**). It has not been shown that administration of single-dose NVP during labor to women who have received antepartum antiretroviral drugs but have suboptimal suppression of HIV RNA (i.e., >1,000 copies/mL) near the time of delivery provides added protection against perinatal transmission. In 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) and who generally had low viral load at the time of delivery, the addition of single-dose NVP did not reduce the risk of mother-to-child HIV transmission but was associated with the development of NVP resistance in 15% of women with detectable HIV RNA postpartum *[9, 163]*. Additionally, while the transmission rate was higher in women with lower baseline CD4 count and higher delivery HIV RNA levels, there was no significant difference in transmission rates between single-dose NVP or placebo in any subgroup or by mode of delivery (34% underwent elective cesarean delivery). Thus, because of the risk of development of resistance and the lack of data to suggest added efficacy, addition of single-dose NVP when a woman has received antepartum drugs is not recommended.

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). Statutes and regulations in this area vary from state to state (see **http://www.ucsf.edu/hivcntr/StateLaws/Index.html** for a review of state HIV testing laws). Current information should be

available at all facilities with a maternity service and/or neonate intensive care unit. Rapid HIV testing is also recommended for women who present in labor who had a negative test in early pregnancy, but are at increased risk of HIV infection (e.g., diagnosis of an STD, illicit drug use or exchange of sex for money or drugs, multiple sexual partners during pregnancy or a sexual partner at risk of HIV infection, or signs/symptoms of acute HIV infection) and were not retested in the third trimester *[58]*. Repeat HIV testing in the third trimester of pregnancy is recommended for women who are known to be at increased risk for HIV acquisition or who deliver in locations with elevated incidence or prevalence of HIV infection (where repeat third trimester testing should be routine). 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.

Women with a positive rapid antibody test should be presumed to be infected until standard HIV antibody confirmatory testing clarifies their status. Along with confirmatory HIV antibody testing, the woman should have appropriate assessments (e.g., CD4 count and HIV RNA copy number) in the immediate postpartum period 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 ZDV started immediately to prevent perinatal HIV transmission, 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 ZDV started immediately to prevent perinatal HIV transmission (see **Table 5** 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, ZDV and other NRTI drugs as well as NNRTI drugs cross the placenta well, while the protease inhibitor drugs do not (see **Table 2**).

Epidemiologic data indicate that intravenous maternal intrapartum ZDV followed by oral ZDV for 6 weeks for the infant significantly reduces transmission compared with no treatment *[16]*. In a New York State cohort study, transmission rates were 10% with intrapartum and neonatal ZDV compared with 27% without ZDV, a 62% reduction in risk *[16]*. The PETRA study demonstrated that intrapartum prophylaxis alone, without an infant post-exposure prophylaxis component, is not effective in reducing perinatal transmission *[15]*.

Whether the addition of other antiretroviral drugs to the intravenous intrapartum/newborn ZDV 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 ZDV/3TC during labor followed by 1 week of oral ZDV/3TC to the infant, and single-dose intrapartum/newborn NVP *[14, 15]*. However, none of these regimens has been compared to intravenous ZDV combined with 6 weeks of infant ZDV prophylaxis.

An ongoing study in the United States, Brazil, Argentina, and South Africa is assessing whether adding drugs to the intravenous intrapartum/newborn ZDV 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 NVP regimen to the intravenous/6-week infant ZDV regimen. While single-dose NVP 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 ZDV and NVP

intrapartum/neonatal regimens include the known short-term safety of each regimen alone; excellent transplacental passage of both drugs; greater antiviral activity of NVP compared with ZDV, as well as the activity of NVP against extracellular and intracellular virus *[205, 206]*; and the known synergy of ZDV and NVP in inhibiting HIV replication *in vitro [207]*.

However, single-dose NVP is associated with the development of NVP-resistant virus (see **Antiretroviral Resistance**) *[163, 170, 171, 173]*. Some studies suggest the addition of ZDV/3TC intrapartum and for 1 week postpartum to the mother to the single-dose intrapartum/newborn NVP regimen will reduce (but not eliminate) the development of NVP resistance (see **Antiretroviral Resistance**) *[203, 204]*. Because of this, if single-dose NVP is added to the intravenous intrapartum/newborn ZDV regimen, some experts would add oral 3TC to the mother during labor, followed by 7 days of maternal ZDV/3TC (see **Table 6** for dosing information). Development of resistance to 3TC given in an intrapartum/postpartum regimen is rare *[8]*. No ZDV or 3TC resistance was observed with intrapartum/1-week postpartum ZDV/3TC in the SAINT study in South Africa *[172]*. Several additional ongoing studies are evaluating alternative antiretroviral regimens and durations for prevention of resistance following single-dose NVP exposure.

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.
- 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.
- 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 unlikely that scheduled cesarean delivery would confer additional benefit in reduction of transmission. Decisions should be individualized based on discussion between the obstetrician and the mother.
- Although no controlled studies have evaluated the efficacy of antimicrobial prophylaxis specifically for HIV-infected women undergoing scheduled operative delivery, use of prophylactic antibiotics at the time of cesarean delivery is generally recommended
- 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.

The ACOG's *[208]* Committee on Obstetric Practice has issued a Committee Opinion concerning route of delivery, recommending consideration of scheduled cesarean delivery (cesarean delivery prior to labor and rupture of membranes) for HIV-infected pregnant women with HIV RNA levels >1,000 copies/mL near the time of delivery *[209]*. For women who have HIV RNA <1,000 copies/mL, the data regarding the benefit of scheduled cesarean delivery are insufficient to draw definitive conclusions; therefore, decisions regarding mode of delivery should be individualized. Women in these circumstances should be carefully counseled regarding the uncertain benefit and

known risks of scheduled cesarean delivery.

Pregnant women receiving HAART have transmission rates of 1.2% to 1.5%, unadjusted for mode of delivery. Given the low transmission rates among women on HAART, the benefit of scheduled cesarean delivery is difficult to evaluate. Data from PACTG 367, a chart review study including 2,756 women, found a transmission rate of 34 (1.3%) of 2,539 women on combination antiretroviral therapy. Women with HIV RNA levels <1,000 copies/mL on combination therapy had transmission rates of 0.8% with scheduled cesarean delivery and 0.5% with all other delivery modes (OR 1.4, 95% CI 0.2 – 6.4) *[60]*. In a recent report from the European Collaborative Study that included data from 4,525 women, the overall transmission rate among the subset of women on HAART was 11 (1.2%) of 918 *[164]*. Among the subset of 560 women with undetectable HIV RNA levels (≤200 – 500 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 versus any), the effect was no longer significant (adjusted OR 0.52, 95% CI 0.14 – 2.03, $p = 0.359$). These data do not confirm, but also do not rule out, a benefit from scheduled cesarean delivery among women with HIV RNA <1,000 copies/mL who are receiving antiretroviral therapy. Studies of women with detectable HIV RNA on HAART have had inadequate numbers to assess the potential additional benefit.

HIV-infected women who present in late pregnancy and are not receiving antiretroviral therapy may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be <1,000 copies/mL. Even if combination therapy were begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the starting RNA level *[80]*. Scheduled cesarean delivery is likely to provide additional benefit in reducing risk of perinatal transmission of HIV along with the three-part PACTG 076 ZDV regimen and/or HAART, given initiation so late in pregnancy.

If the decision is made to perform a scheduled cesarean delivery to prevent HIV transmission, ACOG recommends that it be done at 38 weeks gestation, determined by the best clinical and sonographic estimate and avoiding amniocentesis *[208, 210]*. For HIV-uninfected women, ACOG guidelines for scheduled cesarean delivery without confirmation of fetal lung maturity advise waiting until 39 completed weeks or the onset of labor to reduce the chance of iatrogenic prematurity and associated complications in the neonate *[211]*. Cesarean delivery at 38 versus 39 weeks entails a small absolute but substantially increased risk of development of infant respiratory distress requiring mechanical ventilation *[212, 213]*. This increased risk must be balanced against the potential risk for labor or membrane rupture before the woman would reach 39 weeks of gestation.

Because maternal infectious morbidity is potentially increased with cesarean delivery even among women without HIV infection, use of perioperative antimicrobial prophylaxis is generally recommended for all women undergoing cesarean delivery. Although no controlled studies have evaluated the efficacy of antimicrobial prophylaxis specifically for HIV-infected women undergoing scheduled cesarean delivery, clinicians should generally use perioperative antibiotics for their HIV-infected patients undergoing cesarean delivery *[208, 211]*. A narrow spectrum antibiotic such as cefazolin is preferred to minimize the selection of antibiotic resistant organisms.

No data are available to address the question of whether performing cesarean delivery soon after the onset of labor or membrane rupture to shorten labor and avoid vaginal delivery decreases the risk of perinatal HIV transmission when scheduled cesarean section would be recommended or if prolonged labor is anticipated. 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, although the duration of ruptured membranes in these women was often longer than 4 hours and HIV RNA measurements were not included *[214, 215]*. When an effect of duration of membrane rupture was demonstrated, the risk of transmission was twice as high among women with ruptured membranes for >4 hours before delivery, compared with those with shorter duration of membrane

rupture, although the risk increased continuously with increasing duration of rupture. It is not known if this increased risk applies to women with undetectable viral loads or to those who are on combination antiretroviral therapy.

If cervical dilatation is minimal and a long period of labor is anticipated, the clinician may begin the loading dose of intravenous ZDV and proceed as expeditiously as possible with cesarean delivery to minimize the duration of membrane rupture and avoid vaginal delivery in women who meet the criteria for cesarean delivery (i.e., HIV RNA >1,000 copies/mL). ZDV infusion should continue until cord clamping. Alternatively, the clinician might begin oxytocin augmentation to enhance contractions and potentially expedite delivery. If labor is progressing rapidly, the woman should be allowed to deliver vaginally. If the woman is allowed to labor, scalp electrodes and other invasive monitoring and operative vaginal delivery should be avoided if possible.

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 in neonatology/perinatology is recommended. Antiretroviral regimen should be continued and consideration given to initiating intravenous ZDV.

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

Maternal Risks of Morbidity by Mode of Delivery

Panel's Recommendations:

- Cesarean delivery is associated with a somewhat greater risk of complications among HIV-infected women than observed among uninfected women.
- Scheduled cesarean delivery poses a risk greater than that of vaginal delivery and less than that of urgent or emergent cesarean delivery.
- Complications are not of sufficient frequency or severity to outweigh the potential benefit of reduced transmission among women at heightened risk of transmission.
- Counseling should be provided regarding the increased risks and potential benefits associated with cesarean delivery based on HIV RNA levels.

Among women not infected with HIV, maternal morbidity and mortality are greater after cesarean than after vaginal delivery. Complications, especially postpartum infections, are approximately five to seven times more common after cesarean delivery, performed after labor or membrane rupture compared with vaginal delivery *[216, 217]*. Complications after scheduled cesarean delivery are more common than with vaginal delivery, but less than with urgent cesarean delivery *[218-222]*. Factors that increase the risk of postoperative complications include low socioeconomic status, genital infections, obesity or malnutrition, smoking, and prolonged labor or membrane rupture.

Several studies have compared the rate of postpartum complications by mode of delivery in HIV-infected women. In the European Mode of Delivery randomized trial in HIV-infected pregnant women, no major complications occurred in either the cesarean or vaginal delivery group, although postpartum fever occurred in more women with cesarean than vaginal delivery *[214]*. In a number of observational cohort studies, endometritis, wound infection, pneumonia, or postpartum fever were increased in HIV-infected women undergoing cesarean compared with vaginal delivery, but one study did not distinguish urgent from scheduled cesarean delivery, and in these older studies, scheduled cesarean delivery was not performed for prevention of transmission but for obstetric indications (e.g., previous

cesarean delivery or severe pre-eclampsia), which could increase observed rate of complications *[223, 224]*. In a more recent study including a cohort of HIV-infected women with a larger proportion of women undergoing scheduled cesarean delivery specifically for prevention of HIV transmission, febrile morbidity was increased among HIV-infected women with low CD4 cell counts who underwent scheduled cesarean compared to vaginal delivery *[224]*.

A number of studies have compared complication rates by mode of delivery between HIV-infected and -uninfected women. In a study from the European HIV in Obstetrics Group, the frequency of minor and major complications was higher in HIV-infected women who had cesarean compared to vaginal delivery and increased compared to matched HIV-uninfected women, but the relative difference in complications between vaginal and cesarean deliveries was similar in HIV-infected and -uninfected women *[225]*. In addition to the European HIV in Obstetrics Group study, nine other studies have compared postoperative complications between HIV-infected women and similar HIV-uninfected women *[226-234]*. Many of these studies were retrospective. Two studies found similar outcomes among HIV-infected women compared to controls, while seven detected an increase in minor complications in the HIV-infected women, such as postoperative fever, mild anemia, or pneumonia. In the five studies where it was evaluated, an increased risk of complications was seen among HIV-infected women with more advanced disease as measured by CD4 lymphocyte count or percent, consistent with the cohort studies *[223, 224]*.

In summary, data indicate that cesarean delivery is associated with a somewhat greater risk of complications among HIV-infected women than observed among uninfected women, with the difference most notable among women with more advanced disease. Scheduled cesarean delivery for prevention of HIV transmission poses a risk greater than that of vaginal delivery and less than that of urgent or emergent cesarean delivery. Complication rates in most studies 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 among women at heightened risk of transmission. 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.

OTHER INTRAPARTUM MANAGEMENT CONSIDERATIONS

Panel's Recommendations:

- Artificial rupture of membranes or invasive monitoring should be considered only when obstetrically indicated and the length of time for ruptured membranes or monitoring is anticipated to be short.
- Operative delivery with forceps or the vacuum extractor should be performed only in select circumstances.
- When uterine atony results in excessive postpartum bleeding in women receiving a protease inhibitor or EFV, 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, it should be used in as low a dosage and for as short a duration as possible.

Obstetric procedures increasing the risk of fetal exposure to maternal blood, such as amniocentesis and invasive monitoring, have been implicated in increasing vertical transmission rates by some, but not all, investigators *[36, 235-237]*. None of the studies that have assessed these risks has either controlled for viral load or have been conducted in women receiving potent combination antiretroviral therapy. 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. If labor is progressing and membranes are intact, artificial rupture of membranes and use of fetal scalp electrodes should be considered

only when obstetrically indicated and the length of time for ruptured membranes or monitoring is anticipated to be short. Operative delivery with forceps or the vacuum extractor may increase the risk of transmission and should be avoided if possible, but may be considered in selected circumstances to shorten the time to delivery or for firm obstetric indications *[235, 236]*.

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 and the NNRTI drugs EFV and delavirdine. The concomitant use of ergotamines and protease inhibitors has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving protease inhibitors or EFV or delavirdine 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.

Postpartum Management

POSTPARTUM FOLLOW-UP OF HIV-INFECTED WOMEN

Panel's Recommendations:

- The decision to continue or stop antiretroviral therapy after delivery depends on the nadir CD4 count, clinical symptoms/disease stage, presence of other indications for antiretroviral therapy, and patient and provider preference.
- The immediate postpartum period poses unique challenges for adherence; new or continued supportive services should be assured prior to hospital discharge.
- Women with a positive rapid HIV antibody test during labor require comprehensive follow-up, including confirmation of HIV infection, full health assessment including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of need for antiretroviral therapy.
- Breastfeeding is not recommended for HIV-infected women in the United States, where safe, affordable and feasible alternatives are available and culturally acceptable.
- Contraceptive counseling is a critical aspect of postpartum care. Although condoms are universally recommended for prevention of STD/HIV transmission, the unintended pregnancy rate with condom use alone is high.
- The postpartum period provides an opportunity to review and optimize women's health care, including cervical cancer screening, routine immunizations, mental health and substance abuse treatment as indicated, and assessment for signs of postpartum depression.

Comprehensive care and support services are particularly important for women with HIV infection and their families, who often face multiple social and medical challenges. Components of comprehensive care include the following medical and supportive care services:

a. primary, gynecologic/obstetric, pediatric, and HIV specialty care;
b. family planning services;
c. mental health services;
d. substance abuse treatment;
e. support services; and
f. coordination of care through case management for the woman, her children, 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, and transportation), peer counseling, and legal and advocacy services. Ideally, this care should begin before pregnancy and should be continued throughout pregnancy and postpartum.

Maternal medical services during the postpartum period must be coordinated between obstetric care providers and HIV specialists. Continuity of antiretroviral treatment when such treatment is required for the woman's HIV infection is especially critical and must be ensured. The decision whether or not 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, 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 about the fact 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 additional support may be

needed to maintain good adherence to their therapeutic antiretroviral regimen during this period *[238, 239, 322]*. 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 *[240-245]*. Efforts to maintain adequate adherence during the postpartum period might prolong the effectiveness of therapy. The **Adherence** section in the ***Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*** is available at the AIDS*info* Web site (**http://AIDSinfo.nih.gov**).

Women with nadir CD4 counts <350 cells/mm^3 and/or symptomatic HIV infection should be encouraged to continue antiretroviral therapy postpartum with no interruption. For women who began antiretroviral therapy with a nadir CD4 count ≥350 cells/mm^3 for prophylaxis of transmission, the decision on whether to continue therapy after delivery should be made in consultation with her HIV provider, taking into account current and nadir CD4+ lymphocyte counts and trajectory, HIV RNA levels, and patient preference. For women who received an NNRTI drug as part of the antepartum regimen and who plan to stop antiretroviral therapy after delivery, consideration should be given to stopping the NNRTI and continuing the other antiretroviral drugs for a short period of time (e.g., 7 days) to decrease the risk of NNRTI resistance (see **Stopping Antiretroviral Therapy during Pregnancy**).

A clinical trial in HIV-infected nonpregnant adults that evaluated planned interruption of treatment in individuals who required therapy (mean duration on treatment: 6 years) and had normalized their CD4 counts to >350 cells/mm^3 compared to continued therapy found higher rates of progression and death in the treatment interruption group *[246]*. 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 as a strategy to deal with the risk of incomplete adherence and virologic failure. Instead, every effort should be made to maximize adherence. Simplification of an antiretroviral regimen (for example, to once-daily medications) could also be considered. Interruption of antiretroviral therapy postpartum among women who require treatment for their own health, although preferable to intermittent adherence and virologic failure, should be a last resort.

Data on follow-up of women from PACTG 076 who received antepartum and intrapartum ZDV prophylaxis with discontinuation of drug after delivery (median follow-up 4 years) demonstrated no difference in clinical, immunologic, virologic, and resistance status compared to women who received placebo *[188]*. 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 *[247]*. 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 *[248]*. 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. Other children and the woman's partners should be referred for HIV testing.

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 *[249]*. There are no safe methods to treat breast milk that will effectively eradicate the risk of HIV transmission associated with breastfeeding. There are limited data 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 both regarding infant toxicity as well as selection of drug-resistant virus within breast milk *[250, 251]*. Additionally, drug levels in the neonate may be subtherapeutic and cannot be relied on to interrupt breast milk HIV transmission. Accordingly, 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 *[252]*.

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 EFV, women should be offered dual-method contraception *[253]*. Reversible options include intrauterine devices 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 NNRTI and protease inhibitor drugs (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, Tables 21a and 21b**) *[5]*; these interactions do not necessarily rule out the use of hormonal contraceptive methods, as there is no clear evidence of an effect on contraceptive or ARV 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 NVP, EFV, or nelfinavir, and levels of these drugs were not significantly altered by DMPA *[254]*. Potential interactions between antiretroviral agents and the transdermal contraceptive patch, vaginal ring, and other injectable 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. A woman's HIV status does not affect the suitability of sterilization as a permanent contraceptive method.

The postpartum period provides an opportunity to review and optimize women's health care; this should include assessing the need for prophylaxis against opportunistic infections, 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.

Neonatal Postnatal Care

INFANTS BORN TO MOTHERS WITH UNKNOWN HIV INFECTION STATUS

Panel's Recommendations:

- For infants whose mother's HIV status is unknown postpartum, rapid HIV antibody testing of the mother or infant is recommended as soon as possible, with initiation of infant antiretroviral prophylaxis immediately if the rapid test is positive.
- If the rapid HIV antibody test is positive, standard antibody confirmatory testing (e.g., Western blot) should be performed as soon as possible. If the confirmatory test is negative, antiretroviral prophylaxis can be discontinued.

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 or the 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 unit. 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 *[248]*. A positive HIV antibody test in the infant indicates maternal but not necessarily infant HIV infection status (which requires virologic HIV testing for diagnosis if age <18 months). If the confirmatory test on the mother (or infant) is negative, antiretroviral prophylaxis can be discontinued.

INFANT ANTIRETROVIRAL PROPHYLAXIS

Panel's Recommendations:

- The 6-week neonatal component of the ZDV chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal HIV transmission.
- ZDV should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery.
- The 6-week ZDV prophylaxis regimen is recommended at gestational age-appropriate doses; ZDV should be dosed differently for premature infants <35 weeks than for infants ≥35 weeks (see text).
- The decision to combine additional drugs with the 6-week ZDV 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.
- Use of antiretroviral drugs other than ZDV cannot be recommended in premature infants due to lack of dosing and safety data.
- Some experts consider the use of ZDV in combination with other antiretroviral drugs in certain situations, although the optimal prophylactic regimen for infants born to women in these circumstances is unknown. These include:
  - infants born to mothers who received antepartum and intrapartum drugs but had suboptimal viral suppression at delivery, particularly if vaginal delivery;
  - infants born to mothers who have received only intrapartum drugs;
  - infants born to mothers who have received no antepartum or intrapartum drugs; and

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

- The use of intrapartum/neonatal ZDV is recommended regardless of maternal ZDV resistance history

- Decisions regarding use of additional drugs 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 should be determined in consultation with a pediatric HIV specialist.

All HIV-exposed infants should receive postpartum antiretroviral drugs to reduce perinatal HIV transmission. The 6-week neonatal ZDV chemoprophylaxis regimen is recommended for all HIV-exposed infants. **Table 5** shows dosing for intravenous intrapartum ZDV given in continuous infusion during labor and neonatal ZDV dosing; **Table 6** shows intrapartum and neonatal dosing for additional drugs to be considered in certain situations as delineated below.

The recommended dose of ZDV 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 at 6 to 8 hours of age (if given intravenously, the dose is 1.5 mg/kg body weight every 6 hours). However, some international studies have used an oral infant ZDV dose of 4 mg/kg body weight twice daily for prophylaxis *[15, 17-19, 29]*. There have been limited pharmacokinetic studies of twice daily ZDV in infants. In a study of South African neonates given 4 mg/kg body weight of ZDV twice daily combined with 3TC for the first week of life, serum ZDV exposure was reported to be similar to that achieved with the standard dose of 2 mg/kg body weight every 6 hours *[255]*. Limited data in HIV-infected children over age 1 year suggest that pharmacokinetic parameters of ZDV given every 12 hours are similar to ZDV given every 8 hours, as currently recommended for treatment in children *[256]*. While there are no definitive data to show pharmacokinetic equivalence of giving double the standard dose at a longer interval and 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.

Premature infants require different ZDV dosing from term infants. ZDV is primarily cleared through hepatic glucuronidation to an inactive metabolite; these metabolic enzymes are immature in neonates, leading to prolonged ZDV 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 *[257, 258]*. The recommended ZDV 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.

General Considerations for Choice of Infant Prophylaxis

In certain situations, some experts combine the 6-week infant ZDV prophylaxis regimen with additional antiretroviral drugs. Whether combining ZDV 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 for many drugs 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, use of combination antiretroviral prophylaxis for the infant involves complex balancing of potential benefits (in terms of preventing perinatal HIV transmission) and

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 ZDV 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 have received only intrapartum antiretroviral drugs;

c. infants born to mothers who have 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 ZDV 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 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. The data to show improved efficacy of combination regimens are not available and the choice of drugs in the neonate is limited (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis**).

Antiretroviral combinations with the greatest experience in neonates are ZDV in combination with single-dose NVP and the dual NRTI combination of ZDV and 3TC combined with the NNRTI NVP or the protease inhibitor nelfinavir. However, while nelfinavir has had extensive use in children, in September 2007, the U.S. manufacturer, Pfizer, sent a letter to providers regarding the presence of EMS, a process-related impurity, in Viracept (nelfinavir mesylate), the product available in the United States, and recommending against starting nelfinavir in pediatric patients initiating antiretroviral therapy. 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. Thus, nelfinavir can now be considered for use in neonatal prophylaxis when use of antiretroviral drugs in addition to ZDV is felt to be indicated. Neonatal dosing information is not available for other protease inhibitors, although dosing for lopinavir/ritonavir (Kaletra) is under study. Careful infant monitoring is needed if combination drugs are provided (see **Infant Monitoring**).

Decisions to use combination infant antiretroviral prophylaxis should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by a discussion with the mother of the potential risks and benefits of this approach.

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 protease inhibitor-based therapy was

0.7% of 269 infants if delivery HIV RNA was <400 copies/mL *[9]*. Such infants should receive the 6-week ZDV infant prophylaxis regimen. The benefit of combining ZDV 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 *[3, 36, 37]*. 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 if maternal delivery HIV RNA was >10,000 copies/mL and the infant underwent scheduled cesarean delivery *[9]*. However, not all such women 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 *[3]*.

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 ZDV for 6 weeks. As discussed earlier (see **Intrapartum Care**), in the PACTG 316 study, the addition of single-dose NVP 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 NVP 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 NVP in this study, and the risk of NVP resistance in the mother (and the infant should they become infected despite prophylaxis), addition of maternal/infant single-dose NVP is not recommended in this situation. Some experts would consider use of dual or triple antiretroviral drug infant prophylaxis in selected circumstances (e.g., infants born to mothers with very high viral load near delivery who were delivered vaginally).

Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs

All infants whose mothers have received only intrapartum antiretroviral drugs should be given ZDV for 6 weeks. The post-exposure prophylaxis provided by the 6-week course of infant ZDV 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 *[15]*. Additionally, a study in Thailand indicated that when the mother has <4 weeks of antenatal ZDV, longer infant ZDV prophylaxis (6 weeks compared to 3 days) is required for optimal efficacy *[24]*.

As discussed in the **Intrapartum Care** section, in this situation, some experts would add maternal/infant single-dose NVP to the standard intravenous intrapartum/6-week infant ZDV regimen. This situation differs from that studied in PACTG 316, as in this circumstance, the mother has received no antepartum antiretroviral drugs. NVP resistance can occur in infants exposed to single-dose NVP who become infected despite prophylaxis; the addition of 1 week of 3TC to the 6-week infant ZDV regimen may reduce the development of NVP resistance in such infants,

similar to what is recommended for women receiving single-dose NVP (see **Intrapartum Care** and **Resistance**) *[203, 204]*. However, while all HIV-infected mothers exposed to single-dose NVP are at risk of resistance, only a small proportion of infants exposed to single-dose NVP become infected and would benefit from the addition of 3TC. Combination ZDV/3TC may be associated with more severe hematologic toxicity than ZDV alone (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis** and see **Table 6** for dosing information), and more frequent hematologic monitoring of infants receiving this combination is recommended, particularly if given for more than 1 week.

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

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 ZDV 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 ZDV for the first 6 weeks of life compared with no prophylaxis *[16]*. Transmission rates were 9% (95% CI = 4.1% – 17.5%) with ZDV prophylaxis of newborns only (initiated within 48 hours after birth) versus 27% (95% CI = 21% – 33%) with no ZDV prophylaxis. For most infants in this study, prophylaxis was initiated within 24 hours *[259]*. Thus, when no maternal antepartum or intrapartum antiretroviral drugs have been received, the 6-week infant ZDV 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 *[260-262]*. 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 *[263]*.

Some clinicians view this situation as analogous to nosocomial post-exposure prophylaxis *[264]* and may wish to provide ZDV 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 ZDV for infant-only post-exposure prophylaxis in nonbreastfeeding populations, although there is an ongoing clinical trial in the United States, South America, and South Africa.

Data are not available to demonstrate that 6 weeks of infant ZDV combined with infant single-dose NVP at birth is superior to 6 weeks of ZDV alone. A clinical trial of infant post-exposure prophylaxis in breastfeeding infants in Malawi (see **International Antiretroviral Prophylaxis Clinical Trials** and **Table 1**) showed that the addition of 1 week of ZDV to single-dose infant NVP was 36% more effective in reducing perinatal transmission compared to single-dose infant NVP alone *[18]*. Although this situation is not analogous to adding NVP to 6 weeks of ZDV, particularly in formula-fed infants, some experts would provide single-dose NVP at birth to the infant in this situation with the addition of 1 week of 3TC to reduce the risk of NVP resistance should the infant become infected (see **Table 6** 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, preferably before delivery.

Data from the WITS suggest that in women who have mixed ZDV-resistant and ZDV-sensitive viral populations, the ZDV-sensitive rather than -resistant virus may be preferentially transmitted *[182, 265]* (see **Drug Resistance**). Thus, the 6-week infant ZDV prophylaxis (along with maternal intravenous intrapartum ZDV prophylaxis) continues to be recommended even when maternal ZDV-resistant virus is identified.

There have been some studies suggesting that antiretroviral drug resistant virus may have decreased replication capacity and transmissibility *[265]*. However, transmission of multi-drug resistant virus from mother to child has been reported *[266-268]*.

The use of ZDV 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.

Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis

Short-term toxicity of infant ZDV 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 ZDV, the NRTI with the most experience in use for neonatal prophylaxis is 3TC, although neonatal exposure to combination ZDV/3TC has generally been limited to 1 week *[15, 17, 269]*. Six weeks of infant ZDV/3TC exposure has been reported in a few studies; these studies suggest that hematologic toxicity may be increased over that seen with ZDV alone, although the infants also had *in utero* exposure to maternal combination therapy. In a French study where 6 weeks of ZDV/3TC was provided for infant prophylaxis in infants who were also exposed to antepartum ZDV/3TC, more severe anemia and neutropenia were observed than in a historical cohort exposed only to ZDV; anemia was observed in 15% and neutropenia in 18% of infants exposed to ZDV/3TC, with 2% of infants requiring blood transfusion and 4% requiring treatment discontinuation for toxicity *[8]*. Similarly, in a Brazilian study using maternal antepartum and 6-week infant ZDV/3TC prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of infants *[270]*. In a Phase I study of d4T in pregnant women, infants received 6 weeks of ZDV/3TC and a single dose of d4T at age 1 and 6 weeks; 43% of 14 infants experienced grade 3 hematologic toxicity after birth (36% neutropenia and 7% anemia) *[271]*. Finally, in 3 Phase I studies of protease inhibitors (saquinavir/ritonavir, indinavir, or nelfinavir) in pregnancy, a total of 52 infants received 6 weeks of ZDV/3TC (in 26 infants, ZDV/3TC was combined with nelfinavir); grade 2 or higher hematologic toxicity was observed in 46% to 62% of infants *[272-274]*. Experience with other NRTI drugs for neonatal prophylaxis is more limited *[275, 276]*. Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs *[8, 131, 142, 277, 278]*.

NVP 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 NVP

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 NVP. However, NVP drug resistance may occur with exposure to single-dose NVP should the infant become infected despite prophylaxis (see **Resistance**). If multiple-dose daily NVP is used as part of a combination infant prophylaxis regimen, some experts would stop NVP first and continue the other drugs for a period of time (e.g., 1 to 2 weeks); this is because the prolonged half-life of NVP in infants results in a period of functional NVP monotherapy if all drugs are stopped simultaneously, resulting in a risk of NVP 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 protease inhibitors, nelfinavir, lopinavir/ritonavir, ritonavir, and fosamprenavir have pediatric drug formulations, but 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***) *[274, 276]*.

Dosing for premature infants is only available for ZDV (see **Table 5**), 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, ZDV is the only antiretroviral drug available in intravenous formulation. Therefore, the 6-week ZDV prophylaxis regimen is recommended for preterm infants at gestational age-appropriate doses, and use of antiretroviral drugs other than ZDV 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 before administration of ZDV.
- 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 child, receipt of concomitant medications, and maternal antepartum therapy. Some experts re-check hematologic values in healthy infants receiving ZDV prophylaxis only if the child is symptomatic, while others re-check hemoglobin and neutrophil count after 4 to 6 weeks of ZDV treatment.
- 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.
- If hematologic abnormalities are identified while the child is receiving prophylaxis, decisions on whether to continue infant antiretroviral prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether the child has any 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 or transfusion). Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.
- 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). If serum lactate is significantly abnormal (>5 mmol/L) in a child with symptoms, antiretroviral prophylaxis should be discontinued and an expert in pediatric HIV infection should be consulted regarding potential alternate prophylaxis.

- Virologic tests are required to diagnose HIV infection in infants <18 months of age and should be performed at age 14 to 21 days; 1 to 2 months; and 4 to 6 months.
- To prevent PCP, all infants born to women with HIV infection should begin PCP prophylaxis at age 6 weeks, after completion of the ZDV 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**).

A CBC and differential should be performed on the newborn as a baseline evaluation before administration of ZDV. Anemia has been the primary complication of the 6-week ZDV regimen in the neonate. In PACTG 076, infants in the ZDV group had lower hemoglobin at birth than infants in the placebo group, with the maximal difference (1 gm/dL) occurring at age 3 weeks *[4]*. The lowest mean value for hemoglobin (10 gm/dL) occurred at 6 weeks of age in the ZDV 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 child, receipt of concomitant medications, and maternal antepartum therapy. Some experts re-check hematologic values in healthy infants receiving ZDV prophylaxis only if the child is symptomatic, while others re-check hemoglobin and neutrophil count after 4 weeks of ZDV treatment.

If hematologic abnormalities are found, decisions on whether to continue infant antiretroviral prophylaxis need to be individualized. Some of the considerations include the extent of the abnormality, whether the child has any 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). 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 ZDV prophylaxis.

Some studies suggest a higher incidence of anemia and/or neutropenia in infants who receive ZDV prophylaxis but are born to mothers who received combination therapy compared to those born to mothers who received only ZDV during pregnancy *[278-280]*. 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 ZDV/3TC combination prophylaxis than those receiving ZDV 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, since 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 ZDV and 3TC as infant prophylaxis for 6 weeks and who were exposed to antepartum ZDV/3TC;

more frequent monitoring of hematologic values in these infants versus in infants who receive only ZDV prophylaxis might be considered *[8]*.

Although hyperlactatemia has been reported in infants with *in utero* antiretroviral exposure, this appears transient and in most cases asymptomatic *[281, 282]*. Routine measurement of serum lactate in asymptomatic neonates to assess for potential mitochondrial toxicity is not recommended as the clinical relevance is unknown and predictive value for toxicity appears poor *[281, 282]*. 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 in a child with symptoms, an expert in pediatric HIV infection should be consulted regarding potential discontinuation of prophylaxis.

To prevent PCP, all infants born to women with HIV infection should begin trimethoprim-sulfamethoxazole prophylaxis at age 6 weeks, after completion of the ZDV prophylaxis regimen, unless there is adequate virologic test information to presumptively exclude HIV infection (see **USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children**).

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 and should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed at age 14 to 21 days; 1 to 2 months; and 4 to 6 months *[5]*. 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 in infants who have received the ZDV regimen *[4, 283]*. However, the effect of combination antiretroviral therapy in the mother or newborn on the sensitivity of infant virologic diagnostic testing is unknown. 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 non-breastfed 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 *[5]*.)

Following birth, HIV-exposed infants should have a detailed physical examination and a thorough maternal history 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 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**).

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.
- Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding 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 and, for adolescent females, gynecologic evaluation with Pap tests.

Data remain insufficient to address the effect that exposure to ZDV or other antiretroviral agents *in utero* might have on long-term risk for 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 ZDV regimen and those who received placebo, and no malignancies have been seen *[285-287]*. As discussed earlier in the section on **Mitochondrial Toxicity and NRTI Drugs**, 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 ZDV 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 *[128, 129, 288]*. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding 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.

Clinical Research Needs

The following clinical research needs are relevant to the United States and other developed countries. Study findings continue to evolve rapidly, and research needs and clinical practice will require continued reassessment over time. The current guidelines do not attempt to address the complex research needs or antiretroviral prophylaxis recommendations for resource-limited international settings.

EVALUATION OF DRUG SAFETY AND PHARMACOKINETICS

Many pregnant women with HIV infection in the United States are receiving combination antiretroviral therapy for their own health care along with standard ZDV prophylaxis to reduce perinatal HIV transmission. Additionally, data indicate that antenatal use of potent antiretroviral combinations capable of reducing plasma HIV RNA copy number to very low or undetectable levels near the time of delivery may lower the risk of perinatal transmission to < 2% *[3, 12]*. While the number of antiretroviral agents and combination regimens used for treatment of infected persons is increasing rapidly, the number of drugs evaluated in pregnant women remains limited.

Preclinical evaluations of antiretroviral drugs for potential pregnancy- and fetal-related toxicities need to be completed for all existing and new antiretroviral drugs. More data are needed regarding the safety and pharmacokinetics of antiretroviral drugs in pregnant women and their neonates, particularly when used in combination regimens. Further research is also needed on whether the effects of intensive combination treatment on viral load differ in various body compartments, such as plasma and genital tract secretions, and how this may relate to risk of perinatal transmission.

Continued careful assessment for potential short- and long-term consequences of antiretroviral drug use during pregnancy for both the woman and her child is important. Consequences of particular concern include mitochondrial dysfunction; hepatic, hematologic, and other potential end-organ toxicities; development of antiretroviral drug resistance; and adverse effects on pregnancy outcome. Because the late consequences of *in utero* antiretroviral exposure for the child are unknown, innovative methods need to be developed to detect possible rare late toxicities of transient perinatal antiretroviral drug exposure that may not be observed until later in childhood or in adolescence or adulthood.

OPTIMIZING NEONATAL REGIMENS FOR PERINATAL PROPHYLAXIS

Several studies have demonstrated the efficacy of postnatal therapy to the newborn when the mother did not receive antenatal or intrapartum treatment. A 6-week course of ZDV, as well as single-dose NVP and single-dose NVP in combination with 1 week of ZDV given to the infant soon after birth, can result in a reduced risk of infection. Further research is needed to identify the optimal regimen for preventing infection in infants born to women who did not receive antiretroviral treatment during pregnancy or delivery. More potent regimens with two- and three-drug combinations may further reduce transmission risk. The efficacy of more potent prophylactic neonatal antiretroviral regimens, as well as their short- and long-term toxicities, requires further study.

ASSESSMENT OF DRUG RESISTANCE

The risk of emerging drug resistance during pregnancy or the postpartum period requires further study. The administration of ZDV as a single drug for prophylaxis of transmission may increase the incidence of ZDV resistance mutations in women with viral replication that is not maximally suppressed. Administration of drugs such as NVP and 3TC (for which a single point mutation can confer genotypic resistance) to pregnant women with inadequate

viral suppression may result in the development of virus with genotypic drug resistance in a substantial proportion of women *[163, 170]*. The clinical consequences of emergence of genotypic resistance during pregnancy or in the postpartum period with respect to risk of transmission of resistant virus and future treatment options require further assessment.

STOPPING ANTIRETROVIRAL THERAPY

When stopping antiretroviral therapy, current recommendations suggest discontinuing all antiretroviral drugs simultaneously to avoid the development of drug resistance. However, if the drugs have significant differences in half-life, such a strategy may result in functional monotherapy for a period of time; if there is actively replicating virus, this could lead to development of resistance. This issue is a particular concern with the NNRTI class of drugs, both because of their long half-lives and low genetic barrier to resistance. This has clinical relevance in pregnancy, as women may interrupt ongoing therapy in early pregnancy because of nausea and vomiting or concerns about first trimester fetal exposure. Additionally, many pregnant women may not yet meet criteria for maternal treatment and are prescribed combination antiretroviral therapy solely for prophylaxis against perinatal transmission. In this situation, therapy is routinely stopped after delivery.

Recent data indicate that there may be significant plasma levels of NVP or efavirenz for prolonged periods of time (more than 2 weeks) after stopping chronic therapy, as well as after receipt of single-dose NVP *[289, 290]*. NVP resistance mutations have been identified postpartum in women who have received single-dose intrapartum NVP prophylaxis, as well as in women who have stopped NVP-containing combination regimens taken during pregnancy for prevention of mother-to-child transmission *[170, 174]*. In the latter study, NVP resistance was seen in 16% of women despite staggered stopping of the antiretroviral drugs (in which the nucleoside backbone was continued for 5 days after stopping NVP) *[174]*. Preliminary data from a South African study suggest that administration of single-dose NVP combined with ZDV/3TC given intrapartum and for 3 or 7 days postpartum may reduce, although not eliminate, the development of resistance compared with administration of single-dose NVP alone *[291]*. Further research is needed to assess appropriate strategies for stopping NVP and other NNRTI-containing combination regimens that are used during pregnancy for prevention of mother-to-child transmission, and to prevent development of resistance after receipt of single-dose NVP for prevention of intrapartum transmission. Additionally, research is needed to evaluate the effect of transient NVP resistance on later treatment options.

OPTIMIZING ADHERENCE

The complexity of combination antiretroviral regimens and prophylaxis against opportunistic infections often leads to poor adherence among HIV-infected persons. Innovative approaches are needed to improve adherence in women with HIV infection during and following pregnancy and to ensure that infants receive ZDV prophylaxis.

ROLE OF CESAREAN DELIVERY AMONG WOMEN WITH UNDETECTABLE VIRAL LOAD OR WITH SHORT DURATION OF RUPTURED MEMBRANES

Scheduled cesarean delivery has increased among women with HIV infection since the demonstration that delivery before labor and membrane rupture can reduce intrapartum HIV transmission *[214, 292, 293]*. Further study is needed regarding whether scheduled cesarean delivery provides clinically significant benefit to infected women with low or undetectable viral load and to those receiving combination antiretroviral therapy. Additionally, data from a meta-analysis by the International Perinatal HIV Group indicate that, among women receiving ZDV or not receiving antiretroviral drugs, the risk of perinatal transmission increases by 2% for every 1-hour increase in duration of

membrane rupture in infected women with <24 hours of membrane rupture *[294]*. Therefore, further study is also needed to evaluate the role of cesarean delivery in reducing perinatal transmission in women on limited therapy with very short duration of ruptured membranes and/or labor.

MANAGEMENT OF WOMEN WITH PREMATURE RUPTURE OF MEMBRANES

With evidence that increasing duration of membrane rupture is associated with an increasing transmission risk *[292],* more study is needed to determine the appropriate management of pregnant women with HIV infection who present with ruptured membranes at different points in gestation.

OFFERING RAPID TESTING AT DELIVERY TO LATE PRESENTING WOMEN

Women who have not received antenatal care and were not offered HIV counseling and testing are one of the groups still at high risk for transmitting HIV to their infants. The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study has demonstrated the acceptability and feasibility of offering counseling and rapid HIV testing to women of unknown HIV status who present while in labor *[1, 295]*. Rapid testing during labor can enable pregnant women with undocumented HIV status to learn their HIV infection status so they can receive antiretroviral prophylaxis and be referred for comprehensive medical care and follow-up, if necessary. A model protocol on implementing rapid HIV testing at labor/delivery is available from CDC at **http://www.cdc.gov/hiv/rapid_testing/**.

Antiretroviral prophylaxis should be initiated as soon as possible after a positive rapid HIV test result and prior to standard confirmatory testing, as the benefit of reducing the risk of mother-to-child HIV transmission outweighs the risk of exposure to an intrapartum course of antiretroviral medications. Further studies are needed to assess the relative acceptability and efficacy of intrapartum/postpartum versus postpartum infant interventions to reduce the risk of intrapartum transmission by women first identified as HIV-infected during delivery, and to identify the optimal antiretroviral prophylaxis regimen for this situation.

Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother to Child HIV Transmission

Study/Location/Mode Infant Feeding	Drugs	Antenatal and Intrapartum	Postpartum	Mother to Child Transmission Rate and Efficacy
PACTG 076, United States, France Formula feeding *[4]*	ZDV vs placebo	Long (from 14 weeks); intravenous IP	Long (6 weeks), infant only	• 8.3% in ZDV arm vs 25.5% in placebo arm at 18 months (68% efficacy)
CDC short-course ZDV trial, Thailand *[23]* Formula feeding	ZDV vs placebo	Short (from 36 weeks); oral IP	None	• 9.4% in ZDV arm vs 18.9% in placebo arm at 6 months (50% efficacy)
DITRAME (ANRS 049a) trial, Côte d'Ivoire, Burkina Faso *[22, 296]* Breastfeeding	ZDV vs placebo	Short (from 36 weeks); oral IP	Short (1 week), mother only	• 18.0% in ZDV arm, 27.5% in placebo arm at 6 months (38% efficacy); 21.5% vs 30.6% at 15 months (30% efficacy) • 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 *[21, 22]* Breastfeeding	ZDV vs placebo	Short (from 36 weeks); oral IP	None	• 16.5% in ZDV arm vs 26.1% in placebo arm at 3 months (37% efficacy) • 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 *[15]* Breastfeeding and formula feeding	Antenatal, 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	• 5.7% at 6 weeks for AP/IP/PP ZDV + 3TC, 8.9% for IP/PP ZDV + 3TC, 14.2% for IP-only ZDV + 3TC and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively) • 14.9% at 18 months for AP/IP/PP ZDV + 3TC, 18.1% for IP/PP ZDV + 3TC, 20.0% for IP-only ZDV + 3TC and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively)
HIVNET 012 trial, Uganda *[14]* Breastfeeding	SD NVP vs. ZDV	No AP ARV; oral IP: SD NVP vs oral ZDV	SD NVP within 72 hours of birth (infant only) vs ZDV (1 week), infant only	• 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 *[17]* Breastfeeding and formula feeding	SD NVP vs ZDV + 3TC	No AP ARV; oral IP: SD NVP vs ZDV + 3TC	SD NVP within 48 hours of birth (mother and infant) vs ZDV + 3TC (1 week), mother and infant	• 12.3% in SD NVP arm vs 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, p=0.11)

Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother to Child HIV Transmission

Perinatal HIV Prevention Trial (PHPT-1), Thailand *[24]* 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 6.5% in long-long arm vs 4.7% in long-short arm and 8.6% in the short-long arm at 6 months (no statistical difference); *in utero* transmission 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 *[9]* Formula feeding	SD NVP vs placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)	Non-study ARV regimen; oral IP: placebo vs SD NVP + intravenous ZDV	Placebo vs SD NVP within 72 hours of birth + non-study 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 SD NVP arm vs 1.6% in placebo arm (53% of MTCT was *in utero*)
Perinatal HIV Prevention Trial (PHPT-2), Thailand *[28]* Formula feeding	ZDV alone vs ZDV + maternal and infant SD NVP vs ZDV + maternal SD NVP	ZDV from 28 weeks; oral IP: ZDV alone or ZDV + SD NVP	ZDV for 1 week with or without SD NVP, 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 SD NVP, MTCT rate did not differ significantly between the infant receiving or not receiving SD NVP (2.0% vs 2.8%)
DITRAME Plus (ANRS 1201.0) trial, Abidjan, Côte d'Ivoire *[25]* Breastfeeding and formula feeding	Open label, ZDV + SD NVP	ZDV from 36 weeks; oral IP: ZDV plus SD NVP	SD NVP + ZDV for 1 week, infant only	• 6.5% (95% CI 3.9–9.1%) at 6 weeks; historical control group receiving short ZDV only had MTCT 12.8% (98% breastfed in historical control group)
DITRAME Plus (ANRS 1201.1) trial, Abidjan, Côte d'Ivoire *[25]* Breastfeeding and formula feeding	Open label, ZDV + 3TC + SD NVP	ZDV + 3TC from 32 weeks (stopped at 3 days PP); oral IP: ZDV + 3TC + SD NVP	SD NVP + ZDV for 1 week, infant only	• 4.7% (95% CI 2.4–7.0%) at 6 weeks; historical control group receiving short ZDV only had MTCT 12.8% (98% breastfed in historical control group)
NVAZ trial, Malawi *[18]* Breastfeeding	Neonatal SD NVP vs SD NVP + ZDV	No AP or IP ARV (latecomers)	SD NVP with or without ZDV for 1 week, infant only	• 15.3% in SD NVP + ZDV arm and 20.9% in SD NVP only arm at 6 to 8 weeks; MTCT rate at 6 to 8 weeks among infants who were HIV-uninfected at birth 7.7% and 12.1%, respectively (36% efficacy)

Table 1. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother to Child HIV Transmission

Postnatal NVP + ZDV trial, Malawi *[19]* Breastfeeding	Neonatal SD NVP vs SD NVP + ZDV	No AP ARV; oral IP: SD NVP	SD NVP with or without ZDV for 1 week, infant only	• 16.3% in NVP + ZDV arm and 14.1% in SD NVP-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 6.5% and 16.9%, respectively
Post-exposure Infant Prophylaxis, South Africa *[20]* Breastfeeding and formula feeding	Neonatal SD NVP vs ZDV for 6 weeks	No AP or IP ARV	SD NVP vs ZDV for 6 weeks	• Formula-fed infants only, 14.3% in SD NVP arm and 14.1% in ZDV arm at 6 weeks (not significant, p=0.30); breastfed infants only, 12.2% in SD NVP arm and 19.6% in ZDV arm (p=0.03).
MASHI, Botswana *[29, 297]* Breastfeeding and formula feeding	Initial: short-course ZDV with/without maternal and infant SD NVP and with/without breastfeeding Revised: short-course ZDV + infant SD NVP with/without maternal SD NVP and with/without breastfeeding; women with CD4 <200 receive HAART	1st randomization ZDV from 34 weeks ; oral IP: ZDV + either SD NVP vs. placebo	2nd randomization Breastfeeding + ZDV (infant) 6 months + SD NVP, infant only vs. Formula feeding + ZDV (infant) 4 weeks + SD NVP, infant only	• Initial design: In formula-feeding arm, MTCT at 1 month, 2.4% in maternal & infant SD NVP arm and 8.3% in placebo arm (p=0.05); in breastfeeding + infant ZDV arm, MTCT at 1 month 8.4% in SD NVP arm and 4.1% in placebo arm (difference not statistically significant) • Revised design: MTCT at 1 month 4.3% in maternal + infant SD NVP arm and 3.7% in maternal placebo + infant SD NVP arm (no significant difference; no interaction with mode of infant feeding) • MTCT at 7 months 9.1% in breastfeeding + ZDV arm and 5.6% in formula feeding arm; mortality at 7 months, 4.9% breastfeeding + ZDV vs 9.3% formula feeding; HIV-free survival at 18 months 15.6% breastfeeding + ZDV vs 14.2% formula feeding

3TC: lamivudine; AP: antepartum; ARV: antiretroviral; HAART: highly active antiretroviral therapy; IP: intrapartum; MTCT: mother to child transmission; NVP: nevirapine; PP: postpartum; SD: single-dose; ZDV: zidovudine

Table 2. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy

(see *Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy* for more detail on drugs)

Antiretroviral drug	FDA pregnancy category †	Placental passage (newborn: mother drug ratio)	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Emtricitabine (Emtriva, FTC)	B	Yes (mice and rabbits) [0.4–0.5]	Negative (no tumors, lifetime rodent study)	Negative
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive (mice and rats, at very high dose exposure, liver and bladder tumors)	Negative (but sternal bone calcium decreases in rodents)
Tenofovir DF (Viread)	B	Yes (human) [0.95–0.99]	Positive (hepatic adenomas in female mice at high doses)	Negative (osteomalacia when given to juvenile animals at high doses)
Zalcitabine (HIVID, ddC)*	C	Yes (rhesus monkey) [0.30–0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent hydrocephalus at high dose)
Zidovudine† (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent near lethal dose)
Non-nucleoside reverse transcriptase inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)	Positive (rodent ventricular septal defect)
Efavirenz (Sustiva)	D	Yes (cynomologus monkey, rat, rabbit) [~1.0]	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/ bronchiolar adenomas in female but not male mice)	Positive (cynomologus monkey anencephaly, anophthalmia, microophthalmia)
Nevirapine (Viramune)	B	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)*	C	Minimal/variable (human)	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Minimal/variable (human)	Positive (hepatocellular adenomas in female mice)	Negative
Darunavir (Prezista)	B	Unknown	Not completed	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive (benign and malignant liver tumors in male rodents)	Negative (deficient ossification with amprenavir but not fosamprenavir)
Indinavir (Crixivan)	C	Minimal (human)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Yes (human) [0.20 +/- 0.13]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
Nelfinavir (Viracept)	B	Minimal/variable (human)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (human)	Positive (liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (human)	Negative	Negative

Table 2. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy

(see ***Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy*** for more detail on drugs)

Tipranavir (Aptivus)	C	Unknown	In progress	Negative (decreased ossification and pup weights in rats at maternally toxic doses)
Entry inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative
Maraviroc (Selzentry)	B	Unknown	Negative	Negative
Integrase inhibitors				
Raltegravir (Isentress)	C	Yes (rats [1.5-2.5], rabbits [0.02])#	In progress	Negative (extranumerary ribs in rats at dose exposure 3-fold higher than human)

* No longer available in the United States.

Values obtained from fetal (not newborn) blood samples. See text in Raltegravir (Isentress™): Placental and breast milk passage section

† 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.

Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

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

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended 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 (ZDV alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL).
Recommended agents			
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[298]*.	No evidence of human teratogenicity *[88]*. 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; should be included in regimen unless significant toxicity or stavudine use.
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[269]*.	No evidence of human teratogenicity *[88]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Alternate agents			
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[299]*.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[125, 126]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine†	No pharmacokinetic studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[271]*.	No evidence of human teratogenicity *[88]*. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[125, 126]*.	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.
Abacavir*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. 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.#
Insufficient data to recommend use			
Tenofovir†	Limited studies in human pregnancy; data indicate AUC lower in third trimester than postpartum but trough levels similar. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy *[300]*. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown *[301, 302]*. Significant placental passage in humans (cord:maternal blood ratio ~1.0).	Because of lack of 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 alternatives.
Not recommended			
Zalcitabine *(no longer available in the United States)*	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity (see **Table 2**).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.

Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
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 *[303, 304]*.	No evidence of human teratogenicity *[88]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250/mm^3 when first initiating therapy *[102, 305]*; 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.
Not recommended			
Efavirenz†	No studies in human pregnancy.	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 3 case reports of neural tube defects in humans after first trimester exposure *[88, 306, 307]*; relative risk unclear.	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of child-bearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.
Delavirdine	No pharmacokinetic studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity (see Table 2).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.
Protease inhibitors		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 standard dose of lopinavir/ritonavir capsules (3 capsules twice daily) during third trimester indicated levels were significantly lower than during postpartum period and in nonpregnant adults *[308]*; an increased dose of 4 capsules of lopinavir/ritonavir twice daily starting in the third trimester resulted in adequate lopinavir exposure *[309]*; by 2 weeks postpartum, standard dosing was again appropriate. Pharmacokinetic studies of the new lopinavir/ritonavir tablet formulation are underway, but data are not yet available.	No evidence of human teratogenicity *[88]*.Well-tolerated, short-term safety demonstrated in Phase I/II studies.	The capsule formulation is no longer available. Pharmacokinetic studies of the new tablet formulation are underway, but there are currently insufficient data to make a definitive recommendation regarding dosing 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.

Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Alternate agents			
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 *[273, 310]*.	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 to consider if unable to use lopinavir/ritonavir, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir in pregnancy is unknown.
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250 mg, given twice daily although levels are variable in late pregnancy *[317-319]*. In a similar study of pregnant women in their second and third trimester dosed at 1,250mg given twice daily, women in the third trimester had lower concentration of nelfinavir than women in their second trimester *[319]*. 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 *[320]*.	No evidence of human teratogenicity. 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 HAART only for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant 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.
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum *[311]*.	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-hard gel capsule [HGC] (Invirase®)/ ritonavir	Pharmaockinetic studies of saquinavir-soft gel capsules (SGC) indicated that inadequate drug levels were observed in pregnant women given 1,200 mg of saquinavir-SGC as a sole PI three times daily *[272, 312]*, but adequate levels were achieved when 800 mg saquinavir-SGC boosted with ritonavir 100 mg was given twice daily *[313]*. However, saquinavir-SGC are no longer produced. Limited pharmacokinetic data on saquinavir-hard gel capsule (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 *[314]*.	Well-tolerated, short-term safety demonstrated for mother and infant for both saquinavir-SGC and -HGC in combination with low-dose ritonavir.	Saquinavir-SGC are no longer available. 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 non-pregnant adults.
Insufficient data to recommend use			
Amprenavir *(no longer available in the U.S.)*	Limited studies in human pregnancy.	Oral solution contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use of capsules during pregnancy.
Atazanavir	Limited studies in small number of pregnant women atazanavir (N=33) and atazanavir-ritonavir (N=9) suggest standard dosing achieves adequate drug levels *[315, 316]*.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage is very low and likely to be variable (10%).	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Insufficient data to recommend use (cont)			
Darunavir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Fosamprenavir	No pharmacokinetic studies in human pregnancy.	Limited experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Tipranavir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Entry Inhibitors			
Insufficient data to recommend use			
Enfuvirtide	No pharmacokinetic studies in human pregnancy.	Minimal data in human pregnancy *[321]*.	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.
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.

HGC = hard gel capsule; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft gel capsule.

* 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.

† 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 HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.

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

Clinical Situation	Recommendation
HIV-infected woman of childbearing potential but not pregnant, and who has indications for initiating antiretroviral therapy	• Initiate HAART as per adult treatment guidelines. • Avoid drugs with teratogenic potential (e.g., EFV) in women of childbearing age unless adequate contraception ensured. Exclude pregnancy before starting treatment with EFV.
HIV-infected woman who is receiving HAART and becomes pregnant	**Woman:** • Continue current HAART regimen if successfully suppressing viremia, except avoid use of EFV or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (combination d4T/ddI). • HIV antiretroviral drug resistance testing is recommended if the woman has detectable viremia on therapy. • In general, if woman requires treatment, antiretroviral drugs should not be stopped during the 1st trimester. • Continue HAART regimen during intrapartum period (ZDV given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Scheduled cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • ZDV for 6 weeks started within 6 to 12 hours after birth.[2]

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

HIV-infected pregnant woman who is antiretroviral naïve and has indications for antiretroviral therapy	**Woman:** • HIV antiretroviral drug resistance testing is recommended prior to the initiation of therapy, and if suboptimal viral suppression after initiation of HAART. • Initiate HAART regimen. - Avoid use of EFV or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (combination d4T/ddI). - Use of ZDV as a component of the antiretroviral regimen is recommended when feasible. - NVP can be used as a component of HAART for women with CD4 count ≤250 cells/mm^3, but should only be used as a component of therapy in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • For women who require immediate initiation of therapy for their own health, treatment should be initiated as soon as possible, including in the first trimester. • Continue HAART regimen during intrapartum period (ZDV given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Scheduled cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • ZDV for 6 weeks started within 6 to 12 hours after birth.[2]

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

HIV-infected pregnant woman who is antiretroviral naïve and does <u>not</u> require treatment for her own health	**Woman:** • HIV antiretroviral drug resistance testing is recommended prior to the initiation of therapy, and if suboptimal viral suppression after initiation of HAART. • HAART is recommended for prophylaxis of perinatal transmission in women who do not require treatment for their own health. - Consider delaying HAART initiation until after first trimester is completed. - Avoid use of EFV or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (combination d4T/ddI). - Use of ZDV as a component of the antiretroviral regimen is recommended when feasible. - NVP should only be used as a component of therapy in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Use of ZDV prophylaxis alone is controversial, but may be considered for those women with plasma HIV RNA levels <1,000 copies/mL on no therapy. • Continue HAART regimen during intrapartum period (ZDV given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continued therapy postpartum; discontinue HAART unless has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs 7 days after stopping NNRTI. (Limited data exist on this.) • Scheduled cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • ZDV for 6 weeks started within 6 to 12 hours after birth.[2]

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

HIV-infected pregnant woman who is antiretroviral experienced but not currently receiving antiretroviral drugs	**Woman:** • Obtain full antiretroviral treatment history and evaluate need for antiretroviral treatment for own health. • Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy, and if suboptimal viral suppression after initiation of HAART. • Initiate HAART, with regimen chosen based on resistance testing and prior therapy history. - Avoid use of EFV or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (combination d4T/ddI). - Use of ZDV as a component of the antiretroviral regimen is recommended when feasible. - NVP should only be used as a component of therapy in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Continue HAART regimen during intrapartum period (ZDV given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continued therapy postpartum; discontinue HAART unless has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs 7 days after stopping NNRTI. (Limited data exist on this.) • Scheduled cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • ZDV for 6 weeks started within 6 to 12 hours after birth.[2]

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

HIV-infected woman who has received no antiretroviral therapy prior to labor	ZDV **Woman:** ZDV given as continuous infusion[1] during labor. **Infant:** ZDV for 6 weeks started within 6 to 12 hours after birth.[2] ***OR*** Combination ZDV + Single-Dose NVP: **Woman:** ZDV given as continuous infusion[1] during labor, plus single-dose NVP[3] at onset of labor. Consideration should be given to adding 3TC during labor and maternal ZDV/3TC for 7 days postpartum, which may reduce development of NVP resistance. **Infant:** Single-dose NVP[3] plus ZDV for 6 weeks. ***OR*** **Woman:** ZDV given as continuous infusion[1] during labor. **Infant:** Some clinicians may choose to use ZDV in combination with additional drugs in the infant, but appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consultation with a pediatric HIV specialist is recommended. • 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	• ZDV given for 6 weeks to the infant, started as soon as possible after birth.[2] ***OR*** • Some clinicians may choose to use ZDV in combination with additional drugs, but appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consultation with a pediatric HIV specialist is recommended. • Evaluate need for initiation of maternal therapy postpartum.

3TC: Lamivudine; EFV: Efavirenz; HAART: Highly active antiretroviral therapy, a minimum of three antiretroviral agents; NVP: Nevirapine; ZDV: Zidovudine

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

[2] ZDV 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 NVP: 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 NVP, or given at birth if mother did not receive intrapartum single-dose NVP.

Table 5. Intrapartum Maternal and Neonatal Zidovudine Dosing for Prevention of Mother to Child HIV Transmission

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 (term [≥35 weeks] infant)	2 mg per kg body weight per dose given orally (or 1.5 mg per kg body weight per dose given intravenously) started as close to birth as possible (by 6-12 hours of delivery), then every 6 hours*	Birth to 6 weeks
ZDV (<35 weeks but >30 weeks)	2 mg per kg body weight per dose given orally (or 1.5 mg per kg body weight per dose given intravenously) every 12 hours, advanced to every 8 hours at 2 weeks of age	Birth to 6 weeks
ZDV (<30 weeks)	2 mg per kg body weight per dose given orally (or 1.5 mg/kg/dose given intravenously) every 12 hours, advanced to every 8 hours at 4 weeks of age	Birth to 6 weeks

ZDV = zidovudine

* ZDV 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. While there are no definitive data to show equivalent pharmacokinetic parameters or efficacy in preventing transmission, a regimen of ZDV 4 mg per kg body weight per dose given orally twice daily instead of 2 mg per kg body weight per dose given orally four times daily may be considered when there are concerns about adherence to drug administration to the infant.

Table 6. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs to be Considered Only in Selected Circumstances

(see pages 42, 51-55 for further discussion)

Maternal Intrapartum/Postpartum		
Drug	**Dosing**	**Duration**
NVP (as single dose intrapartum)*	200 mg given orally as single dose	Given once at onset of labor
ZDV + 3TC (given with single dose NVP as "tail" to reduce NVP resistance	ZDV: IV intrapartum as per table 5, then after delivery 300 mg orally twice daily 3TC: 150 mg orally twice daily starting at labor onset	Through 1 week postpartum
Neonatal		
Drug	**Dosing**	**Duration**
NVP (as single dose)**	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, infant dose should be administered as soon as possible following birth.
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

NVP = nevirapine, ZDV = zidovudine, 3TC = lamivudine

* 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 7 days postpartum to reduce development of NVP resistant virus is recommended.

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

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

Clinical Situation	Recommendation
HIV-infected women presenting in late pregnancy (after about 36 weeks gestation), known to be HIV-infected but not receiving antiretroviral therapy, and who have 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 4**. • The woman should be counseled that scheduled cesarean section is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her from cesarean section, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. • If cesarean section is chosen, the procedure should be scheduled at 38 weeks gestation based on the best available clinical information. • When scheduled cesarean section is performed, the woman should receive continuous intravenous ZDV infusion beginning 3 hours before surgery and her infant should receive 6 weeks of ZDV therapy after birth (see **Table 4**). • 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.
HIV-infected women who initiated prenatal care early in the third trimester, are receiving HAART, and have an initial virologic response, but have HIV RNA levels that remain substantially more than 1,000 copies/mL at 36 weeks gestation.	• The current combination antiretroviral regimen should be continued as 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 section may provide additional benefit in preventing intrapartum transmission of HIV. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and surgical risks. • If she chooses scheduled cesarean section, it should be performed at 38 weeks gestation according to the best available dating parameters, and intravenous ZDV should be begun at least 3 hours before surgery and her infant should receive 6 weeks of ZDV therapy after birth (see **Table 4**). • 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 be treated with 6 weeks of ZDV therapy after birth (see **Table 4**).
HIV-infected women on HAART 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 2% or less, even with vaginal delivery. There is currently no information to evaluate whether performing a scheduled cesarean section will lower her risk further. • Cesarean section 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 section in this case.

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

HIV-infected women who have elected scheduled cesarean section but present in early labor or shortly after rupture of membranes.	• Intravenous ZDV should be started immediately since the woman is in labor or has ruptured membranes. • If labor is progressing rapidly, the woman may deliver vaginally. • If cervical dilatation is minimal and a long period of labor is anticipated, some clinicians may choose to administer the loading dose of intravenous ZDV and proceed with cesarean section to minimize the duration of membrane rupture and avoid vaginal delivery. Others might begin pitocin augmentation to enhance contractions and potentially expedite delivery. • If the woman is allowed to labor, scalp electrodes and other invasive monitoring and operative delivery should be avoided if possible. • The infant should be treated with 6 weeks of ZDV therapy after birth (see **Table 4**).

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Appendix: Perinatal Antiretroviral Guidelines Working Group Conflict of Interest Disclosure – October 3, 2007

Name	Company	Relationship
Erika Aaron	Abbott Laboratories Boehringer Ingelheim	▪ Speaker with honoraria ▪ Grant recipient
Elaine Abrams	Abbott Laboratories	▪ Advisory Board member
Jean Anderson	Pfizer Inc. GlaxoSmithKline Abbott Laboratories Boehringer Ingelheim	▪ Advisory Board member ▪ Speakers bureau ▪ Research support ▪ Educational program support ▪ Stockholder ▪ Speaker with honoraria ▪ Educational program support ▪ Speaker with honoraria ▪ Educational program support ▪ Educational program support ▪ Advisory Board member
Magda Barini-Garcia	NONE	N/A
Dawn Averitt Bridge	NONE	N/A
Susan Cohn	Merck & Co., Inc. Quest Diagnostics The Well Project, Inc.	▪ Vaccine Advisory Panel ▪ Stockholder ▪ Stockholder ▪ Women's Health Initiative member
Amanda Cotter	NONE	N/A
Susan Cu-Uvin	HIVMA Bristol Myers Squibb Boehringer Ingelheim Evo Pharmaceutical Merck & Co., Inc. GlaxoSmithKline	▪ Board of Directors ▪ Advisory Board ▪ Advisory Board ▪ Speaker ▪ Advisory Board ▪ Speakers bureau ▪ Honoraria
Brian Feit	NONE	N/A

Name	Company	Relationship
Judith Feinberg	Boehringer Ingelheim	▪ Advisory Board member ▪ Speakers bureau
	Bristol Myers Squibb	▪ Advisory Board member ▪ Speakers bureau ▪ Grant recipient
	Abbott Laboratories	▪ Speakers bureau ▪ Consultant
	GlaxoSmithKline	▪ Speakers bureau
	Achillion	▪ Grant recipient
	Panacos	▪ Grant recipient
	Koronis	▪ Advisory Board ▪ Grant recipient
	Pfizer Inc.	▪ Speakers bureau ▪ Advisory Board ▪ Grant recipient
	Tibotec	▪ Speakers bureau ▪ Advisory Board ▪ Grant recipient
	Roche	▪ Grant recipient
	Theratechonology	▪ Grant recipient
	Neurogesx	▪ Grant recipient
	Gilead	▪ Speakers bureau ▪ Consultant
	Merck & Co., Inc.	▪ Speakers bureau ▪ Consultant
	The Well Project, Inc	▪ Think tank member
	American Academy of HIV Medicine	▪ Board of Directors member
Patricia Flynn	MedImmune, Inc.	▪ Clinical research support
	Merck & Co., Inc.	▪ Clinical research support
	Tibotec	▪ Clinical research support
Mary Glenn Fowler	NONE	N/A
Edward Handelsman	NONE	N/A
Jane Hitti	Boehringer Ingelheim	▪ Advisory Board
Denise Jamieson	NONE	N/A
Robert Maupin	Pfizer Inc.	▪ Research support
Howard Minkoff	NONE	N/A
Mark Mirochnick	GlaxoSmithKline	▪ Clinical research support
Lynne Mofenson	NONE	N/A
Fatima Prioleau	NONE	N/A
Alan Shapiro	NONE	N/A
Steve Spector	Pfizer Inc.	▪ Stockholder
Ruth Tuomala	Boehringer Ingelheim	▪ (Ad hoc) Consultant
	Pfizer Inc.	▪ Data Safety Monitoring Board
Heather Watts	NONE	N/A