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

December 17, 2004

Revisions to the June 23, 2004 Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing 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 ***AIDSinfo* Web site** (**http://AIDSinfo.nih.gov**).

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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

SUMMARY

These recommendations update the June 23, 2004 guidelines developed by the Public Health Service for the use of zidovudine (ZDV) to reduce the risk for perinatal human immunodeficiency virus type 1 (HIV-1) transmission*. This report provides health care providers with information for discussion with HIV-1 infected pregnant women to enable such women to make an informed decision regarding the use of antiretroviral drugs during pregnancy and use of elective cesarean delivery to reduce perinatal HIV-1 transmission. Various circumstances that commonly occur in clinical practice are presented, and the factors influencing treatment considerations are highlighted in this report. The Perinatal HIV-1 Guidelines Working Group recognizes that strategies to prevent perinatal transmission and concepts related to management of HIV disease in pregnant women are rapidly evolving and will continually review new data and provide regular updates to the guidelines. The most recent information is available from the *AIDSinfo* Web site (available at **http://aidsinfo.nih.gov/**)

In February 1994, the results of Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 documented that ZDV chemoprophylaxis could reduce perinatal HIV-1 transmission by nearly 70%. Epidemiologic data have since confirmed the efficacy of ZDV for reduction of perinatal transmission and have extended this efficacy to children of women with advanced disease, low $CD4^+$ T-lymphocyte counts, and prior ZDV therapy.

Additionally, substantial advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of persons with HIV-1 disease. These advances have resulted in changes in standard antiretroviral therapy for HIV-1 infected adults. More aggressive combination drug regimens that maximally suppress viral replication are now recommended. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy. Use of antiretroviral drugs in pregnancy requires unique considerations, including the possible need to alter dosage as a result of physiologic changes associated with pregnancy, the potential for adverse short- or long-term effects on the fetus and newborn, and the effectiveness of the drugs in reducing the risk for perinatal transmission. Data to address many of these considerations are not yet available. Therefore, offering antiretroviral therapy to HIV-1 infected women during pregnancy, whether primarily for HIV-1 infection, for reduction of perinatal transmission, or for both purposes, should be accompanied by a discussion of the known and unknown short- and long-term benefits and risks of such therapy to infected women and their infants. Standard antiretroviral therapy should be discussed with and offered to HIV-1 infected pregnant women. Additionally, to prevent perinatal transmission, ZDV chemoprophylaxis should be incorporated into the antiretroviral regimen.

* 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.

INTRODUCTION

In February 1994, the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 demonstrated that a three-part regimen of zidovudine (ZDV) could reduce the risk for mother-to-child human immunodeficiency virus type 1 (HIV-1) transmission by nearly 70% *[1]*. The regimen includes oral ZDV initiated at 14–34 weeks' gestation and continued throughout pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the infant for six weeks after delivery (**Table 1**). In August 1994, a U.S. Public Health Service (USPHS) task force issued recommendations for the use of ZDV for reduction of perinatal HIV-1 transmission *[2]*, and in July 1995, USPHS issued recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with consent for all pregnant women in the United States *[3]*. Since the publication of the results of PACTG 076, epidemiologic studies in the United States and France have demonstrated dramatic decreases in perinatal transmission with incorporation of the PACTG 076 ZDV regimen into general clinical practice *[4-9]*.

Since 1994, advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. The rapidity and magnitude of viral turnover during all stages of HIV-1 infection are greater than previously recognized; plasma virions are estimated to have a mean half-life of only 6 hours *[10]*. Thus, current therapeutic interventions focus on administration of aggressive combination antiretroviral regimens to maximally suppress viral replication, preserve immune function, and reduce the development of resistance *[11]*. Potent antiretroviral drugs that inhibit the protease enzyme of HIV-1 are now available. When a protease inhibitor is used in combination with nucleoside analog reverse transcriptase inhibitors, plasma HIV-1 RNA levels can be reduced for prolonged periods to levels that are undetectable by current assays. Improved clinical outcome and survival have been observed among adults receiving such regimens *[12, 13]*. Additionally, viral load can now be more directly quantified through assays that measure HIV-1 RNA copy number; these assays have provided powerful new tools to assess disease stage, risk for progression, and the effects of therapy. These advances have led to substantial changes in the standard of treatment and monitoring for HIV-1 infected adults in the United States *[14]*. (See the "**Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents**").

Advances also have been made in the understanding of the pathogenesis of perinatal HIV-1 transmission. Most perinatal transmission likely occurs close to the time of or during childbirth *[15]*. Additional data that demonstrate the short-term safety of the ZDV regimen are now available as a result of follow-up of infants and women enrolled in PACTG 076; however, data from studies of animals concerning the potential for transplacental carcinogenicity of ZDV affirm the need for long-term follow-up of children with antiretroviral exposure *in utero [16]*.

These advances have implications for maternal and fetal health. Health-care providers considering the use of antiretroviral agents for HIV-1 infected women during pregnancy must take into account two separate but related issues:

1. antiretroviral treatment of maternal HIV-1 infection, and
2. antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV-1 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. Although ZDV chemoprophylaxis alone has substantially reduced the risk for perinatal transmission, antiretroviral monotherapy is now considered suboptimal for treatment of HIV-1 infection, and combination drug regimens are considered the standard of care for therapy *[14]*.

This report:

- reviews the special considerations regarding use of antiretroviral drugs for pregnant women,
- updates the results of PACTG 076 and related clinical trials and epidemiologic studies,
- discusses the use of HIV-1 RNA and antiretroviral drug resistance assays during pregnancy,
- provides updated recommendations on antiretroviral chemoprophylaxis for reducing perinatal transmission, and
- provides recommendations related to use of elective cesarean delivery as an intervention to reduce perinatal transmission.

These recommendations have been developed for use in the United States. Although perinatal HIV-1 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-1 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-1-infected women, and alternative interventions being evaluated in that area.

BACKGROUND

Considerations Regarding the Use of Antiretroviral Drugs by HIV-1 Infected Pregnant Women and Their Infants

Treatment recommendations for pregnant women infected with HIV-1 have been based on the belief 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 *[17]*. Combination antiretroviral therapy, usually consisting of two nucleoside analog reverse transcriptase inhibitors and a protease inhibitor, is the recommended standard treatment for HIV-1 infected adults who are not pregnant *[14]*. (See the "**Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents**".) Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of 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 effects of antiretroviral drugs on the pregnant woman, and
c. the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, which may not be known for certain antiretroviral drugs.

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 unknown benefits and risks to her and her fetus.

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. Additional considerations regarding drug use in pregnancy are

a. the effects of the drug on the fetus and newborn, including the potential for teratogenicity, mutagenicity, or carcinogenicity, and
b. the pharmacokinetics and toxicity of transplacentally transferred drugs.

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 *[18]*. In addition to antiretroviral agents, certain drugs commonly used to treat HIV-1 related illnesses demonstrate positive findings on one or more of these screening tests. For example, acyclovir is positive in some in vitro carcinogenicity and clastogenicity assays and is associated with fetal abnormalities in rats; however, data collected on the basis of human experience from the Acyclovir in Pregnancy Registry have indicated no increased risk for birth defects in infants with *in utero* exposure to acyclovir *[19]*. Limited data exist regarding placental passage and long-term animal carcinogenicity for the FDA-approved antiretroviral drugs (**Table 2**).

Although clinical data on antiretroviral drugs in pregnant women are more limited than in non-pregnant 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-1-Infected Adults and Adolescents** when developing treatment regimens for pregnant women.

See **SAFETY AND TOXICITY OF INDIVIDUAL ANTIRETROVIRAL DRUGS IN PREGNANCY TO OBTAIN IMPORTANT AND DETAILED INFORMATION**

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 such as preterm delivery. A retrospective Swiss report evaluated the pregnancy outcome of 37 HIV-1 infected pregnant women treated with combination therapy; all received two reverse transcriptase inhibitors and 16 received one or two protease inhibitors *[20]*. Almost 80% of women experienced one or more typical adverse effects of the drugs, such as anemia, nausea/vomiting, aminotransferase elevation, or hyperglycemia. 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-1 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-1 Cohort Study investigated the effects of combination retroviral therapy in a population of 3,920 mother child pairs. Adjusting for $CD4^+$ T-lymphocyte count ($CD4^+$ count) and intravenous drug use, they found a 2.6-fold (95% confidence interval [CI] = 1.4–4.8) 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 *[21]*. However, combination therapy was received by only 323 (8%) women studied. Exposure to monotherapy was not associated with prematurity.

In contrast, in an observational study of pregnant women with HIV-1 infection in the United States (PACTG 367) in which 1,150 (78%) of 1,472 women received combination therapy, no association was found between receipt of combination therapy and preterm birth (R. Tuomala, July 2000 PACTG meeting). The highest rate of preterm delivery was among women who had not received any antiretroviral therapy, which is consistent with several other reports demonstrating elevated preterm birth rates among untreated women with HIV-1 infection *[22-24]*. In a French open-label study of 445 HIV-1 infected women receiving ZDV who had lamivudine (3TC) added to their therapy at 32 weeks' gestation, the rate of preterm delivery was 6%, similar to the 9% rate in a historical control group of women receiving only ZDV *[25]*. Additionally, in a large meta-analysis of seven clinical studies that included 2,123 HIV-1-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 *[26]*.

Until more information is known, HIV-1 infected pregnant women who are receiving combination therapy for their HIV-1 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 nevirapine. These toxicities have been reported in patients on chronic therapy, and have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. Signs and symptoms of systemic toxicity may be non-specific, and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal hepatic transaminases *[27]*. The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women *[28-30]*. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2 fold more common in women than men *[31, 32]*. The degree of risk for hepatic toxicity varies with $CD4^+$ cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with $CD4^+$ counts greater than 250 cells/mm^3 were 9.8 times more likely than women with lower $CD4^+$ counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity *[31, 32]*. Higher $CD4^+$ cell counts have also been associated with increased risk of severe

nevirapine-associated skin rash *[29]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5-11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, ranging between 0.04-0.40% *[33, 34]*. Severe or life threatening rash occurs in approximately 2% of patients receiving nevirapine *[34]*.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs *[35, 36]*. Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication and conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase, ALT, and aspartate aminotransferase, AST), particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through 4 months, and every 1 to 3 months thereafter (see **Hepatotoxicity** section of the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy, and then monthly *[27]*. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST), or have asymptomatic but severe transaminase elevations, should stop nevirapine and not receive nevirapine therapy in the future. Nevirapine should be used with caution in pregnant antiretroviral-naïve women who are being started on combination antiretroviral therapy for the purpose of preventing perinatal HIV transmission, but who have $CD4^+$ counts that would not otherwise indicate that they require therapy for their own health (see **Women of Reproductive Age and Pregnant Women** section of the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*).

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-1 infected patients *[37-40]*. In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of protease inhibitors will increase the risk for pregnancy-associated hyperglycemia. Clinicians caring for HIV-1 infected pregnant women who are receiving protease inhibitor therapy should be aware of the risk of this complication and closely monitor glucose levels. Symptoms of hyper-glycemia should be discussed with pregnant women who are receiving protease inhibitors.

Mitochondrial Toxicity and Nucleoside Analog Drugs

Nucleoside analog 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 *[41]*. The relative potency of the nucleosides in inhibiting mitochondrial gamma DNA polymerase in vitro is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), ZDV, 3TC, abacavir (ABC), and tenofovir *[42]*. Toxicity related to mitochondrial dysfunction has been reported to occur in infected patients receiving long-term treatment with nucleoside analogs and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested *[41]*. These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to nucleoside analog 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 *[43]*. 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 combination of hemolysis, elevated liver enzymes and low platelets (the HELLP syndrome). Several investigators have correlated these pregnancy-related disorders with a recessively inherited mitochondrial abnormality in the fetus/infant that results in an inability to oxidize fatty acids *[44-46]*. Since the mother would be a heterozygotic carrier of the abnormal gene, the risk for liver toxicity might be increased during pregnancy because the mother would be unable to properly oxidize both maternal and accumulating fetal fatty acids *[47]*. Additionally, animal studies have demonstrated that in late gestation,

pregnant mice have significant reductions (25%–50%) in mitochondrial fatty acid oxidation and that exogenously administered estradiol and progesterone can reproduce these effects *[48, 49];* whether this can be translated to humans is unknown. However, these 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 and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

Lactic acidosis with microvacuolar hepatic steatosis is a toxicity related to nucleoside analog drugs that is thought to be related to mitochondrial toxicity; it has been reported to occur in infected persons treated with nucleoside analog drugs for long periods (>6 months). Initially, most cases were associated with ZDV, but later other nucleoside analog drugs, particularly d4T, have been associated with the syndrome. In a report from the FDA Spontaneous Adverse Event Program of 106 patients with this syndrome (60 receiving combination and 46 receiving single nucleoside analog therapy), typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness *[43]*. 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 nucleoside analog therapy or increased recognition of the syndrome. In a cohort of infected patients receiving nucleoside analog therapy followed at Johns Hopkins University during 1989–1994, the incidence of the hepatic steatosis syndrome was 0.13% per year *[50]*. However, in a report from a cohort of 964 HIV-1 infected persons followed in France for 2 years during 1997–1999, the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a regimen including d4T *[51]*.

The frequency of this syndrome in pregnant HIV-1 infected women receiving nucleoside analog treatment 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 *[52]*. 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 nevirapine) *[53, 54]*. 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 *[55]*.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for nonpregnant persons receiving nucleoside analog treatment. 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-1 infected pregnant women receiving nucleoside analog drugs to be alert for early signs of this syndrome. Pregnant women receiving nucleoside analog drugs should have hepatic enzymes and electrolytes assessed more frequently 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-1 infected pregnant women, clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

In Utero Exposure

A study conducted in France reported that in a cohort of 1,754 uninfected infants born to HIV-1 infected women who received antiretroviral drugs during pregnancy, eight infants with *in utero* or neonatal exposure to either ZDV-3TC (four infants) or ZDV alone (four infants) developed indications of mitochondrial dysfunction after the first few months of life *[56]*. Two of these infants (both of whom had been exposed to ZDV-3TC) contracted severe neurologic disease and died, three had mild to moderate symptoms, and three had no symptoms but had transient laboratory abnormalities.

A further evaluation of mitochondrial toxicity was conducted in 4,392 uninfected or HIV-indeterminate children (2,644 with perinatal antiretroviral exposure) followed within the French Pediatric Cohort or identified within a France National Register developed for reporting of possible mitochondrial dysfunction in HIV-exposed children. Evidence of mitochondrial dysfunction was identified in 12 children (including the

previous 8 reported cases), all of whom had perinatal antiretroviral exposure, an 18-month incidence of 0.26% *[57]*. Risk was higher among infants exposed to combination antiretroviral drugs (primarily ZDV/3TC) than ZDV alone. All children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or a significant episode of hyperlactatemia, and all had an identified deficit in one of the mitochondrial respiratory chain complexes and/or abnormal muscle biopsy histology. An additional 14 children with "possible" mitochondrial dysfunction had unexplained clinical and/or laboratory findings for which mitochondrial dysfunction could be included in the differential diagnosis, although none had respiratory chain enzyme deficits or histologic abnormalities. In a separate publication, the same group reported an increased risk of simple febrile seizures during the first 18 months of life among uninfected infants with antiretroviral exposure *[58]*.

A small study quantified mitochondrial DNA in cord blood and peripheral blood leukocytes at age 1 and 2 years in HIV-exposed infants with (N=10) and without (N=10) perinatal ZDV exposure and infants born to HIV-uninfected women (N=30) *[59]*. Mitochondrial DNA quantity was lower in infants born to HIV-infected women overall compared to those born to uninfected women, and was lowest among those HIV-exposed infants with ZDV exposure compared to those without exposure. 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 *[60]*. Thus, the clinical significance of these laboratory findings is unclear, and further studies are needed to validate these findings.

In infants followed through age 18 months in PACTG 076, the occurrence of neurologic events was rare; seizures occurred in one child exposed to ZDV and two exposed to placebo, and one child in each group had reported spasticity. Mortality at 18 months was 1.4% among infants given ZDV compared with 3.5% among those given placebo *[61]*. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring among children born to HIV-1 infected women and followed during 1986–1999 in five 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-1 infected women with and without antiretroviral drug exposure *[62]*. 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.

In an African perinatal trial (PETRA) that compared three regimens of ZDV-3TC (during pregnancy starting at 36 weeks' gestation, during labor, and through 1 week postpartum; during labor and postpartum; and during labor only) with placebo for prevention of transmission, data have been reviewed relating to neurologic adverse events among 1,798 children who participated. No increased risk of neurologic events was observed among children treated with ZDV-3TC compared with placebo, regardless of the intensity of treatment *[63]*. The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort, 1,008 of who had perinatal antiretroviral exposure. The median length of follow-up was 2.2 years (maximum, 16 years). 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.

Finally, in a study of 382 uninfected infants born to HIV-1 infected women, echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life; 9% of infants had been exposed to ZDV prenatally *[64]*. No significant differences in ventricular function were observed between infants exposed and not exposed to ZDV.

Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure. 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 *[65-67]*. 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 Pregnancy Registry

Health-care providers who are treating HIV-1 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.

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**

Update on PACTG 076 Results and Other Studies Relevant to ZDV Chemoprophylaxis for Perinatal HIV-1 Transmission

In 1996, final results were reported for all 419 infants enrolled in PACTG 076. The results concur with those initially reported in 1994; the Kaplan-Meier estimated HIV-1 transmission rate for infants who received placebo was 22.6%, compared with 7.6% for those who received ZDV, a 66% reduction in risk for transmission *[68]*.

The mechanism by which ZDV reduced transmission in PACTG 076 participants has not been fully defined. The effect of ZDV on maternal HIV-1 RNA does not fully account for the observed efficacy of ZDV in reducing transmission. Preexposure prophylaxis of the fetus or infant may offer substantial protection. If so, transplacental passage of antiretroviral drugs would be crucial for prevention of transmission. Additionally, in placental perfusion studies, ZDV has been metabolized into the active triphosphate within the placenta *[69, 70]*, which could provide additional protection against *in utero* transmission. This phenomenon may be unique to ZDV because metabolism to the active triphosphate form within the placenta has not been observed in the other nucleoside analogs that have been evaluated (i.e., ddI and ddC) *[71, 72]*.

In PACTG 076, similar rates of congenital abnormalities occurred among infants with and without *in utero* ZDV exposure. Data from the Antiretroviral Pregnancy Registry also have demonstrated no increased risk for congenital abnormalities among infants born to women who receive ZDV antenatally compared with the general population *[73]*. Among uninfected infants from PACTG 076 followed from birth to a median age of 4.2 years (range 3.2–5.6 years), no differences were noted in growth, neurodevelopment, or immunologic status between infants born to mothers who received ZDV compared with those born to mothers who received placebo *[74]*. No malignancies have been observed in short-term (i.e., up to age 6 years) follow-up of >727 infants from PACTG 076 or from a prospective cohort study involving infants with *in utero* ZDV exposure *[75]*. However, follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Long-term monitoring continues to be recommended for all infants who have received *in utero* ZDV exposure or *in utero* exposure to any of the antiretroviral drugs.

The efficacy of ZDV chemoprophylaxis for reducing HIV-1 transmission among populations of infected women with characteristics unlike those of the PACTG 076 population has been evaluated in another perinatal protocol (PACTG 185) and in prospective cohort studies. PACTG 185 enrolled pregnant women with advanced HIV-1 disease and low $CD4^+$ counts who were receiving antiretroviral therapy; 24% had received ZDV before the current pregnancy *[76]*. All women and infants received the three-part ZDV regimen combined with either infusions of hyperimmune HIV-1 immunoglobulin (HIVIG) containing high levels of antibodies to HIV-1 or standard intravenous immunoglobulin (IVIG) without HIV-1 antibodies. Because advanced maternal HIV-1 disease has been associated with increased risk for perinatal transmission, the transmission rate in the control group was hypothesized to be 11%–15% despite the administration of ZDV. At the first interim analysis, the transmission rate for the combined group was only 4.8% and did not substantially differ by whether the women received HIVIG or IVIG or by duration of ZDV use *[76]*. The results of this trial confirm the efficacy of ZDV observed in PACTG 076 and extend this efficacy to women with advanced disease, low $CD4^+$ count, and prior ZDV therapy. Rates of perinatal transmission have been documented to be as low as 3%–4% among women with HIV-1 infection who receive all three components of the ZDV regimen, including women with advanced HIV-1 disease *[6, 76]*.

At least two studies suggest that antenatal use of combination antiretroviral regimens might further reduce transmission. In an open-label, nonrandomized study of 445 women with HIV-1 infection in France, 3TC was added at 32 weeks' gestation to standard ZDV prophylaxis; 3TC was also given to the infant for 6 weeks in addition to ZDV *[25]*. The transmission rate in the ZDV-3TC group was 1.6% (95% CI = 0.7%–3.3%); in comparison, the transmission rate in a historical control group of women receiving only ZDV was 6.8% (95% CI = 5.1%–8.7%). In a longitudinal epidemiologic study conducted in the United States since 1990, transmission was observed in 20% of women with HIV-1 infection who received no antiretroviral treatment during pregnancy, 10.4% who received ZDV alone, 3.8% who received combination therapy without protease inhibitors, and 1.2% who received combination therapy with protease inhibitors *[66]*.

International Antiretroviral Prophylaxis Clinical Trials

In a trial evaluating short-course antenatal/intrapartum ZDV prophylaxis and perinatal transmission among non-breastfeeding women in Thailand, administration of ZDV 300 mg twice daily for 4 weeks antenatally and 300 mg every 3 hours orally during labor was shown to reduce perinatal transmission by approximately 50% compared with placebo *[77]*. The transmission rate was 19% in the placebo group versus 9% in the ZDV group. A second, four-arm factorial design trial in Thailand compared administration of ZDV antenatally starting at 28 or 36 weeks' gestation, orally intrapartum, and to the neonate for 3 days or 6 weeks. At an interim analysis, the transmission rate in the arm receiving ZDV antenatally starting at 36 weeks and postnatally for 3 days to the infant was 10%, which was significantly higher than for the long arm (antenatal starting at 28 weeks and infant administration for 6 weeks) *[78]*. The transmission rate in the short arm of this study was similar to the 9% observed with short antenatal/intrapartum ZDV in the first Thai study. The rate of *in utero* transmission was higher among women in the short antenatal arms compared with those receiving longer antenatal therapy, suggesting that longer treatment of the infant cannot substitute for longer treatment of the mother.

A third trial in Africa (PETRA trial) among breastfeeding HIV-1 infected women has shown that a combination regimen of ZDV and 3TC administered starting at 36 weeks' gestation, orally intrapartum, and for 1 week postpartum to the woman and infant reduced transmission at age 6 weeks by approximately 63% compared with placebo *[63]*. The transmission rate at age 6 weeks was 15% in the placebo group versus 6% with the three-part ZDV-3TC regimen. This efficacy is similar to the efficacy observed in the Thailand study of antepartum/intrapartum short-course ZDV in non-breastfeeding women *[77]*.

Investigators have identified two possible intrapartum/ postpartum regimens (either ZDV-3TC or nevirapine) that could provide an effective intrapartum/postpartum intervention for women for whom the diagnosis of HIV-1 is not made until near to or during labor. The PETRA African ZDV-3TC trial among breastfeeding HIV-1 infected women also demonstrated that an intrapartum/postpartum regimen, started during labor and continued for 1 week postpartum in the woman and infant, reduced transmission at age 6 weeks from 15% in the placebo group to 9% in the group receiving the two-part ZDV-3TC regimen, a reduction of 42% *[63]*. In this trial, oral ZDV-3TC administered solely during the intrapartum period was not effective in lowering transmission. Another study in Uganda (HIVNET 012), again in a breastfeeding population, demonstrated that a single 200-mg oral dose of nevirapine given to the mother at onset of labor combined with a single 2-mg/kg oral dose given to her infant at age 48–72 hours reduced transmission by nearly 50% compared with a very short regimen of ZDV given orally during labor and to the infant for 1 week *[79]*. Transmission at age 6 weeks was 12% in the nevirapine group compared with 21% in the ZDV group. A subsequent trial in South Africa demonstrated similar transmission rates with a modified HIVNET 012 nevirapine regimen (nevirapine given to the woman as a single dose during labor with a second dose at 48 hours postpartum, and a single dose to the infant at age 48 hours) compared with the PETRA regimen of oral ZDV–3TC during labor and for 1 week after delivery to the mother and infant *[80]*. Transmission rates at age 8 weeks were 12.3% in the nevirapine arm and 9.3% in the ZDV-3TC arm (p=0.11).

Two clinical trials have suggested that the addition of the HIVNET 012 single-dose nevirapine regimen to short-course ZDV may provide increased efficacy in reducing perinatal transmission. A study of nonbreastfeeding women in Thailand compared a short-course ZDV regimen (starting at 28 weeks' gestation, given orally intrapartum, and for 1 week to the infant) with two combination regimens: short-course ZDV plus single-dose intrapartum/neonatal nevirapine, and short-course ZDV plus intrapartum maternal nevirapine only. In the short-course ZDV-only arm, enrollment was discontinued by the Data and Safety Monitoring Board at the first interim analysis because transmission was significantly higher among those receiving ZDV alone compared with those receiving the intrapartum/neonatal

nevirapine combination regimen *[81]*. The study is continuing to enroll to allow comparison of the two combination arms. A second open-label study in Cote d'Ivoire reported a 7.1% transmission rate at age 4 weeks with administration of short-course ZDV (starting at 36 weeks, given orally intrapartum, and for 1 week to the infant) combined with single-dose intrapartum/neonatal nevirapine. This was lower than for a nonconcurrent historical control group receiving ZDV alone *[82]*.

In contrast to these studies, which evaluated combining single-dose nevirapine with short-course ZDV, a study in the United States, Europe, Brazil, and the Bahamas (PACTG 316) evaluated whether the addition of the HIVNET 012 single-dose nevirapine regimen to standard antiretroviral therapy (at minimum the 3-part full ZDV regimen) would provide additional benefits in lowering transmission. In this study, 1,506 pregnant women with HIV-1 infection who were receiving antiretroviral therapy (77% were receiving combination antiretroviral regimens) were randomized to receive a single dose of nevirapine or nevirapine placebo at onset of labor, and their infants received a single dose (according to the maternal randomization) at age 48 hours. Transmission was not significantly different between groups, occurring in 1.6% of women in the placebo group and 1.4% among women in the nevirapine group *[83]*.

Certain data indicate that postexposure antiretroviral prophylaxis of infants whose mothers did not receive antepartum or intrapartum antiretroviral drugs might provide some protection against transmission. Although data from some epidemiologic studies do not support efficacy of postnatal ZDV alone, other data demonstrate efficacy if ZDV is started rapidly following birth *[6, 84, 85]*. In a study from North Carolina, the rate of infection among HIV-1 exposed infants who received only postpartum ZDV chemoprophylaxis was similar to that observed among infants who received no ZDV chemoprophylaxis *[6]*. However, another epidemiologic study from New York State determined that administration of ZDV to the neonate for 6 weeks was associated with a significant reduction in transmission if the drug was initiated within 24 hours of birth (the majority of infants started within 12 hours) *[84, 85]*. Results from a clinical trial in Malawi of infant postexposure prophylaxis in breastfeeding infants, when no maternal antepartum or intrapartum antiretroviral drug was received, compared the efficacy of single dose infant nevirapine to single dose infant nevirapine plus one week of ZDV. Overall transmission at 6-8 weeks of age was 20.9% in the single dose nevirapine arm versus 15.3% in the combination arm, an efficacy of 26.8%; when evaluation was confined to only those infants who were uninfected at birth, infection rates at 6-8 weeks were 12.1% with single dose nevirapine versus 7.7% with the combination, a 36.4% efficacy *[86]*. In the U.S., the standard recommendation for infant prophylaxis in the absence of maternal therapy is 6 weeks of ZDV. While the Malawi data suggest that combining 1 week of ZDV with single dose nevirapine is more effective than single dose nevirapine alone, it does not address whether such a regimen is more effective than 6 weeks of ZDV. Therefore, no changes are recommended to the current USPHS recommendations to give 6 weeks of infant ZDV as the standard prophylaxis. Several ongoing clinical trials are attempting to determine the optimal postexposure antiretroviral prophylaxis regimen for infants.

Perinatal HIV-1 Transmission and Maternal HIV-1 RNA Copy Number

The correlation of HIV-1 RNA levels with risk for disease progression in nonpregnant infected adults suggests that HIV-1 RNA should be monitored during pregnancy at least as often as recommended for persons who are not pregnant (i.e., every 3 to 4 months or approximately once each trimester). In addition, HIV-1 RNA levels should be evaluated at 34–36 weeks of gestation to allow discussion of options for mode of delivery based on HIV-1 RNA results and clinical circumstances. Although no data indicate that pregnancy accelerates HIV-1 disease progression, longitudinal measurements of HIV-1 RNA levels during and after pregnancy have been evaluated in only a limited number of prospective cohort studies. In one cohort of 198 HIV-1 infected women, plasma HIV-1 RNA levels were higher at 6 months postpartum than during pregnancy in many women; this increase was observed in women regardless of ZDV use during and after pregnancy *[87]*.

Initial data regarding the correlation of viral load with risk for perinatal transmission were conflicting, with some studies suggesting an absolute correlation between HIV-1 RNA copy number and risk of transmission *[88]*. However, although higher HIV-1 RNA levels have been observed among women who transmitted HIV-1 to their infants, overlap in HIV-1 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-1 RNA levels (including in women with HIV-1 RNA copy number below the limit of detection of the assay), and the predictive value of RNA copy number for transmission in an individual woman has been

relatively poor *[87, 89, 90]*. In PACTG 076, antenatal maternal HIV-1 RNA copy number was associated with HIV-1 transmission in women receiving placebo. In women receiving ZDV, the relationship was markedly attenuated and no longer statistically significant *[68]*. An HIV-1 RNA threshold below which there was no risk for transmission was not identified; ZDV was effective in reducing transmission regardless of maternal HIV-1 RNA copy number *[68, 91]*.

More recent data from larger numbers of ZDV-treated infected pregnant women indicate that HIV-1 RNA levels correlate with risk of transmission even among women treated with antiretroviral agents *[77, 92-94]*. Although the risk for perinatal transmission in women with HIV-1 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-1 RNA. Additionally, although HIV-1 RNA may be an important risk factor for transmission, other factors also appear to play a role *[94-96]*.

Although there is a general correlation between viral load in plasma and in the genital tract, discordance has also been reported, particularly between HIV-1 proviral load in blood and genital secretions *[97-100]*. If exposure to HIV-1 in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV-1 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-1 transmission. In the short-course ZDV trial in Thailand, plasma and cervicovaginal HIV-1 RNA levels were reduced by ZDV treatment, and each independently correlated with perinatal transmission *[101]*. The full ZDV chemoprophylaxis regimen, alone or in combination with other antiretroviral agents, including intravenous ZDV during delivery and the administration of ZDV to the infant for the first 6 weeks of life, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level.

Results of epidemiologic and clinical trials suggest that women receiving highly active antiretroviral regimens that effectively reduce HIV-1 RNA to <1,000 copies/mL or undetectable levels have very low rates of perinatal transmission *[25, 66, 83, 102]*. However, since transmission can occur even at low or undetectable HIV-1 RNA copy numbers, RNA levels should not be a determining factor when deciding whether to use ZDV for chemoprophylaxis. Additionally, the efficacy of ZDV is not solely related to lowering viral load. In one study of 44 HIV-1 infected pregnant women, ZDV was effective in reducing transmission despite minimal effect on HIV-1 RNA levels *[103]*. These results are similar to those observed in PACTG 076 *[68]*. Antiretroviral prophylaxis reduces transmission even among women with HIV-1 RNA levels <1,000 copies/mL *[104]*. Therefore, at a minimum, ZDV prophylaxis should be given even to women who have a very low or undetectable plasma viral load.

PRECONCEPTIONAL COUNSELING AND CARE FOR HIV-1 INFECTED WOMEN OF CHILDBEARING AGE

Many women infected with HIV-1 (nearly 60% in some centers) enter pregnancy with a known diagnosis, and nearly half of these women enter the first trimester of pregnancy receiving treatment with single or multiagent antiretroviral therapy *[105]*. Additionally, as many as 40% of women who have begun antiretroviral therapy before their pregnancy might require adjustment of their therapeutic regimen during their pregnancy course.

The American College of Obstetrics and Gynecology advocates extending to all women of childbearing age the opportunity to receive preconception counseling as a component of routine primary medical care. It is recognized that >40% of pregnancies may be unintended and that the diagnosis of pregnancy most frequently occurs late in the first trimester when organogenesis is nearly completed. Preconception care can identify risk factors for adverse maternal or fetal outcome (e.g., age, diabetes, hypertension), provide education and counseling targeted to the patient's individual needs, and treat or stabilize medical conditions before conception to optimize maternal and fetal outcomes *[106]*.

For women with HIV-1 infection, preconception care must also focus on maternal infection status, viral load, immune status, and therapeutic regimen as well as education regarding perinatal transmission risks and prevention strategies, expectations for the child's future, and, where desired, effective contraception until the optimal maternal health status for pregnancy is achieved.

The following components of preconception counseling are recommended for HIV-1 infected women:

- Selection of effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy.

- Education and counseling about perinatal transmission risks, strategies to reduce those risks, and potential effects of HIV-1 or treatment on pregnancy course and outcomes.
- Initiation or modification of antiretroviral therapy:
  - Avoid agents with potential reproductive toxicity for the developing fetus (e.g. efavirenz, hydroxyurea). *See **Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**
  - Choose agents effective in reducing the risk of perinatal HIV-1 transmission
  - Attain a stable, maximally suppressed maternal viral load
  - Evaluate and control for therapy associated side effects which may adversely impact maternal-fetal health outcomes (e.g. hyperglycemia, anemia, hepatic toxicity)
- Evaluation and appropriate prophylaxis for opportunistic infections and administration of medical immunizations (e.g., influenza, pneumococcal, or hepatitis B vaccines) as indicated.
- Optimization of maternal nutritional status.
- Institution of the standard measures for preconception evaluation and management (e.g., assessment of reproductive and familial genetic history, screening for infectious diseases/sexually transmitted diseases, and initiation of folic acid supplementation).
- Screening for maternal psychological and substance abuse disorders.
- Planning for perinatal consultation if desired or indicated.

HIV-1 infected women of childbearing potential receive primary health-care services in various clinical settings, e.g., family planning, family medicine, internal medicine, obstetrics/gynecology. It is imperative that primary health-care providers consider the fundamental principles of preconception counseling an integral component of comprehensive primary health care for improving maternal/child health outcomes.

GENERAL PRINCIPLES REGARDING THE USE OF ANTIRETROVIRAL AGENTS IN PREGNANCY

Medical care of the HIV-1 infected pregnant woman requires coordination and communication between the HIV specialist caring for the woman when she is not pregnant and her obstetrician. Decisions regarding use of antiretroviral drugs during pregnancy should be made by the woman after discussion with her health-care provider about the known and unknown benefits and risks of therapy. Initial evaluation of an infected pregnant woman should include an assessment of HIV-1 disease status and recommendations regarding antiretroviral treatment or alteration of her current anti-retroviral regimen.

This assessment should include the following:

a. evaluation of the degree of existing immunodeficiency determined by $CD4^+$ count,
b. risk for disease progression as determined by the level of plasma RNA,
c. history of prior or current antiretroviral therapy,
d. gestational age, and
e. supportive care needs.

Decisions regarding initiation of therapy should be the same for women who are not currently receiving antiretroviral therapy and for women who are not pregnant, with the additional consideration of the potential impact of such therapy on the fetus and infant *[14]*. Similarly, for women currently receiving antiretroviral therapy, decisions regarding alterations in therapy should involve the same considerations as those used for women who are not pregnant. The three-part ZDV chemoprophylaxis regimen, alone or in combination with other antiretroviral agents, should be discussed with and offered to all infected pregnant women to reduce the risk for perinatal HIV-1 transmission.

Decisions regarding the use and choice of antiretroviral drugs during pregnancy are complex; several competing factors influencing risk and benefit must be weighed. Discussion regarding the use of antiretroviral drugs during pregnancy should include the following:

a. what is known and not known about the effects of such drugs on the fetus and newborn, including lack of long-term outcome data on the use of any of the available antiretroviral drugs during pregnancy;
b. what treatment is recommended for the health of the HIV-1 infected woman; and
c. the efficacy of ZDV for reduction of perinatal HIV-1 transmission.

Results from preclinical and animal studies and available clinical information about use of the various antiretroviral agents during pregnancy also should be discussed (**Table 2** and **3**). The hypothetical risks of these drugs during pregnancy should be placed in perspective with the proven benefit of antiretroviral therapy for the health of the infected woman and the benefit of ZDV chemoprophylaxis for reducing the risk for HIV-1 transmission to her infant.

Discussion of treatment options should be noncoercive, and the final decision regarding use of antiretroviral

drugs is the responsibility of the woman. Decisions regarding use and choice of antiretroviral drugs for persons who are not pregnant are becoming increasingly complicated as the standard of care moves toward simultaneous use of multiple antiretroviral drugs to suppress viral replication below detectable limits. These decisions are further complicated in pregnancy because the long-term consequences for the infant who has been exposed to antiretroviral drugs *in utero* are unknown. A woman's decision to refuse treatment with ZDV or other drugs should not result in punitive action or denial of care. Further, use of ZDV alone should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and therefore, after counseling, chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

A long-term treatment plan should be developed after discussion between the patient and the health-care provider and should emphasize the importance of adherence to any prescribed antiretroviral regimen. 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-1 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.

General counseling should include what is known regarding risk factors for perinatal transmission. Cigarette smoking, illicit drug use, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk for perinatal HIV-1 transmission *[107-111],* and discontinuing these practices might reduce this risk. In addition, CDC recommends that infected women in the United States refrain from breastfeeding to avoid postnatal transmission of HIV-1 to their infants through breast milk *[3, 112];* these recommendations also should be followed by women receiving antiretroviral therapy. Passage of antiretroviral drugs into breast milk has been evaluated for only a few antiretroviral drugs. ZDV, 3TC, and nevirapine can be detected in the breast milk of women, and ddI, d4T, abacavir, delavirdine, indinavir, ritonavir, saquinavir and amprenavir can be detected in the breast milk of lactating rats. Limited data are available regarding either the efficacy of antiretroviral therapy for the prevention of postnatal transmission of HIV-1 through breast milk or the toxicity of long-term antiretroviral exposure of the infant through breast milk.

Women who must temporarily discontinue therapy because of pregnancy-related hyperemesis should not resume therapy until sufficient time has elapsed to ensure that the drugs will be tolerated. To reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be stopped and reintroduced simultaneously.

RECOMMENDATIONS FOR ANTIRETROVIRAL CHEMOPROPHYLAXIS TO REDUCE PERINATAL HIV TRANSMISSION

The following recommendations for use of antiretroviral chemoprophylaxis to reduce the risk for perinatal transmission are based on situations that may be commonly encountered in clinical practice (**Table 4**), with relevant considerations highlighted in the subsequent discussion sections. These recommendations are only guidelines, and flexibility should be exercised according to the patient's individual circumstances. In the 1994 recommendations *[2]*, six clinical situations were delineated on the basis of maternal $CD4^+$ count, weeks of gestation, and prior antiretroviral use. Because current data indicate that the PACTG 076 ZDV regimen also is effective for women with advanced disease, low $CD4^+$ count, and prior ZDV therapy, clinical situations based on $CD4^+$ count and prior ZDV use are not presented. Additionally, because data indicate that most transmission occurs near the time of or during delivery, ZDV chemoprophylaxis is recommended regardless of weeks of gestation; thus, clinical situations based on weeks of gestation also are not presented.

The antenatal dosing regimen in PACTG 076 (100 mg administered orally five times daily) (**Table 1**) was selected on the basis of the standard ZDV dosage for adults at the time of the study. However, recent data have indicated that administration of ZDV three times daily will maintain intracellular ZDV triphosphate at levels comparable with those observed with more frequent dosing *[113-115]*. Comparable clinical response also has been observed in some clinical trials among persons receiving ZDV twice daily *[116-118]*. Thus, the current standard ZDV dosing regimen for adults is 200 mg three times daily, or 300 mg twice daily. Because the mechanism by which ZDV reduces perinatal transmission is not known, these dosing regimens may not have equivalent efficacy to that observed in PACTG 076. However, a regimen of two or three times daily is expected to increase adherence to the regimen.

The recommended ZDV dosage for infants was derived from pharmacokinetic studies performed among full-term infants *[119]*. ZDV is primarily cleared through hepatic glucuronidation to an inactive metabolite. The glucuronidation metabolic enzyme system is immature in neonates, leading to prolonged ZDV half-life and clearance compared with older infants (ZDV half-life: 3.1 hours versus 1.9 hours; clearance: 10.9 versus 19.0 mL/minute/kg body weight, respectively). Because premature infants have even greater immaturity in hepatic metabolic function than full-term infants, further prolongation of clearance may be expected. In a study of 15 premature infants who were at 26–33 weeks' gestation and who received different ZDV dosing regimens, mean ZDV half-life was 7.2 hours and mean clearance was 2.5 mL/minute/kg body weight during the first 10 days of life *[120]*. At a mean age of 18 days, a decrease in half-life (4.4 hours) and increase in clearance (4.3 mL/minute/kg body weight) were found. Results of a pharmacokinetic study of ZDV dosing in infants <35 weeks gestation at birth (PACTG 331) indicated that the appropriate dose of ZDV for preterm infants 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 *[121]*.

Clinical Situations and Recommendations for Use of Antiretroviral Prophylaxis

Scenario #1: HIV-1 Infected Pregnant Women Who Have Not Received Prior Antiretroviral Therapy

Recommendation

Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed *[14]*. The three-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection, regardless of antenatal HIV-1 RNA copy number, to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic, or virologic status requires treatment or whose HIV-1 RNA is > 1,000 copies/mL regardless of their clinical or immunologic status**,** and can be considered for women with HIV-1 RNA < 1,000 copies/mL. Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks' gestation.

Discussion

When ZDV is administered in the three-part PACTG 076 regimen, perinatal transmission is reduced by approximately 70%. Although the mechanism by which ZDV reduces transmission is not known, protection is likely multifactorial. Pre-exposure prophylaxis of the infant is provided by passage of ZDV across the placenta so that inhibitory levels of the drug are present in the fetus during the birth process. 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. Because the mechanism by which ZDV reduces transmission is not known, the intrapartum and newborn ZDV components of the chemoprophylactic regimen should also be administered to reduce perinatal HIV-1 transmission. If a woman does not receive ZDV as a component of her antenatal antiretroviral regimen, intrapartum and newborn ZDV should still be recommended.

Because of the evolving and complex nature of the management of HIV-1 infection, a specialist with experience in the treatment of pregnant women with HIV-1 infection should be involved in their care. Women should be informed that potent combination antiretroviral regimens have substantial benefit for their own health and may provide enhanced protection against perinatal transmission. Several studies have indicated that for women with low or undetectable HIV-1 RNA levels (e.g., < 1,000 copies/mL), rates of perinatal transmission are extremely low, particularly when women have received antiretroviral therapy *[66, 92, 93]*. However, there is no threshold below which lack of transmission can be assured, and the long-term effects of *in utero* exposure to multiple antiretroviral drugs are unknown. Decisions regarding the use and choice of an antiretroviral regimen should be individualized based on discussion with the woman about the following factors:

a. her risk for disease progression and the risks and benefits of delaying initiation of therapy;
b. benefit of lowering viral load and reducing the risk of perinatal transmission;

c. independent benefit of combination antiretroviral regimens for reducing the risk of perinatal transmission *[92]*;
d. potential drug toxicities and interactions with other drugs;
e. the need for strict adherence to the prescribed drug schedule to avoid the development of drug resistance;
f. unknown long-term effects of *in utero* drug exposure on the infant; and
g. preclinical, animal, and clinical data relevant to use of the currently available antiretroviral agents during pregnancy.

Because the period of organogenesis (when the fetus is most susceptible to potential teratogenic effects of drugs) is during the first 10 weeks of gestation, and the risks of antiretroviral therapy during that period are unknown, women in the first trimester of pregnancy might wish to delay initiation of therapy until after 10–12 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 of delaying initiation of therapy for several weeks, and the fact that most perinatal HIV-1 transmission likely occurs late in pregnancy or during delivery. Treatment with efavirenz should be avoided during the first trimester because significant teratogenic effects in rhesus macaques were seen at drug exposures similar to those representing human exposure (**Table 2** and see ****Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy** **). Hydroxyurea is a potent teratogen in a variety of animal species, and should also be avoided during the first trimester.

When initiation of antiretroviral therapy is considered optional on the basis of current guidelines for treatment of nonpregnant persons *[14]*, infected pregnant women should be counseled regarding the benefits of standard combination therapy for fetal protection and should be offered such therapy, including the three-part ZDV chemoprophylaxis regimen. Although such women are at low risk for clinical disease progression if combination therapy is delayed, antiretroviral therapy that successfully reduces HIV-1 RNA to levels < 1,000 copies/mL substantially lowers the risk of perinatal HIV-1 transmission and may lessen the need for consideration of elective cesarean delivery as an intervention to reduce transmission risk.

When combination therapy is administered, the regimen should be chosen from those recommended for nonpregnant adults *[14]*. However, women, particularly those with $CD4^+$ counts > 250 cells/mm^3, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal *[33]*. Nevirapine should be used with caution in pregnant women who are being started on combination antiretroviral therapy for the purpose of preventing perinatal HIV transmission, but who have $CD4^+$ counts that would not otherwise indicate that they require therapy for their own health (see **Women of Reproductive Age and Pregnant Women** section of the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*). Pregnant women who receive nevirapine should have frequent and careful monitoring of transaminase levels, particularly during the first 18 weeks of treatment (see **Nevirapine and Hepatic/Rash Toxicity**). Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis.

Dual nucleoside analog therapy without the addition of either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor is not recommended for nonpregnant adults because of the potential for inadequate viral suppression and rapid development of resistance *[122]*. For pregnant women not meeting the criteria for antiretroviral therapy for their own health, and receiving antiretroviral drugs only for prevention of perinatal transmission, dual nucleoside therapy may be considered in selected circumstances (e.g., in those with HIV-1 RNA < 1,000 copies/mL).

If combination therapy is given principally to reduce perinatal transmission and would have been optional if the woman were not pregnant, consideration may be given to discontinuing therapy postnatally, with the option to reinitiate treatment according to standard criteria for nonpregnant women. Discussion regarding the decision to continue or stop combination therapy postpartum should occur before beginning therapy during pregnancy. Generally, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if the drugs have significantly different half-lives, such a strategy may result in functional monotherapy for a period of time and potential development of resistance. Pharmacokinetic data demonstrate that detectable drug levels may persist for 21 days or more after discontinuation of nevirapine *[123, 124]*. To avoid a period of functional monotherapy, some experts would continue the dual nucleoside analog components of the regimen for a period of time after nevirapine discontinuation. However, the optimal interval is not known, and further research is needed to assess

appropriate strategies for stopping nevirapine-containing combination regimens that are used during pregnancy for prevention of mother-to-child transmission (see **Clinical Research Needs**).

Antiretroviral prophylaxis has been beneficial in preventing perinatal transmission even for infected pregnant women with HIV-1 RNA levels < 1,000 copies/mL. In a meta-analysis of factors associated with perinatal transmission among women whose infants were infected despite maternal HIV-1 RNA < 1,000 copies/mL at or near delivery, transmission was only 1.0% among women receiving antenatal antiretroviral therapy (primarily ZDV alone), compared with 9.8% among those receiving no antenatal therapy *[104]*. Therefore, use of antiretroviral prophylaxis is recommended for all pregnant women with HIV-1 infection, regardless of antenatal HIV-1 RNA level.

The time-limited use of ZDV alone during pregnancy for chemoprophylaxis against perinatal transmission is controversial. Standard combination antiretroviral regimens for treatment of HIV-1 infection should be discussed and should be offered to all pregnant women with HIV-1 infection regardless of viral load; they are recommended for all pregnant women with HIV-1 RNA levels > 1,000 copies/mL. There is some evidence that even with HIV-1 RNA levels < 1,000 copies/mL, combination antiretroviral regimens may further decrease perinatal transmission compared with ZDV alone *[125]*. However, some women may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of transmitting HIV-1 to their infants. Additionally, for women with HIV-1 RNA levels < 1,000 copies/mL, 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 limited viral replication in the patient and the time-limited 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 *[126]*. The use of ZDV chemoprophylaxis alone (or, in selected circumstances, dual nucleosides) during pregnancy might be an appropriate option for these women.

Scenario #2: HIV-1 Infected Women Receiving Antiretroviral Therapy During the Current Pregnancy

Recommendation

HIV-1 infected women receiving antiretroviral therapy whose pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal antiretroviral treatment regimen after the first trimester whenever possible, although this may not always be feasible. Women receiving antiretroviral therapy whose pregnancy is recognized during the first trimester should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance. Regardless of the antepartum antiretroviral regimen, ZDV administration is recommended during the intrapartum period and for the newborn.

Discussion

Women who have been receiving antiretroviral treatment for their HIV-1 infection should continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load, which could result in decline in immune status and disease progression as well as adverse consequences for both the fetus and the woman.

Although ZDV should be a component of the antenatal antiretroviral treatment whenever possible, there may be circumstances, such as the occurrence of significant ZDV-related toxicity, when this is not feasible. Additionally, women receiving an antiretroviral regimen that does not contain ZDV but who have HIV-1 RNA levels that are consistently very low or undetectable (e.g., <1,000 copies/mL) have a very low risk of perinatal transmission *[66]*, and there may be concerns that the addition of ZDV to the current regimen could compromise adherence to treatment.

The maternal antenatal antiretroviral treatment regimen should be continued on schedule as much as possible during labor to provide maximal virologic effect and to minimize the chance of development of drug resistance. If a woman has not received ZDV as a component of her antenatal therapeutic antiretroviral regimen, intravenous ZDV should still be administered during the intrapartum period whenever feasible. ZDV and d4T should not be administered together because of potential pharmacologic antagonism; options for

women receiving oral d4T as part of their antenatal therapy include either continuation of oral d4T during labor without intravenous ZDV or withholding oral d4T during the period of intravenous ZDV administration during labor. Additionally, the infant should receive the standard 6-week course of ZDV.

For women with suboptimal suppression of HIV-1 RNA (i.e., >1,000 copies/mL) near the time of delivery despite having received prenatal ZDV prophylaxis with or without combination antiretroviral therapy, it is not known if administration of additional antiretroviral drugs during labor and delivery provides added protection against perinatal transmission. In the HIVNET 012 study among Ugandan women who had not received antenatal antiretroviral therapy, a 2-dose nevirapine regimen (single dose to the woman at the onset of labor and single dose to the infant at age 48 hours) significantly reduced perinatal transmission compared with a very short intrapartum/1 week postpartum ZDV regimen *[79]*. For women in the United States, Europe, Brazil, and the Bahamas receiving antenatal antiretroviral therapy, addition of the 2–dose nevirapine regimen did not result in lower transmission rates *[83]*. Given the lack of further reduction of transmission with nevirapine added to one of the standard antepartum regimens used in developed countries and the potential development of nevirapine resistance (See **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**), addition of nevirapine during labor for women already receiving antiretroviral therapy is not recommended in the United States.

Women receiving antiretroviral therapy may realize they are pregnant early in gestation and want to consider temporarily stopping antiretroviral treatment until after the first trimester because of concern for potential teratogenicity. Data are insufficient to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation; certain drugs are of more concern than others. (**Table 2** and see ****Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy****). The decision to continue therapy during the first trimester should be carefully considered by the clinician and the pregnant woman. Discussions should include considerations such as gestational age of the fetus; the woman's clinical, immunologic, and virologic status; and the known and unknown potential effects of the antiretroviral drugs on the fetus. If antiretroviral therapy is discontinued during the first trimester, all agents should be stopped and restarted simultaneously in the second trimester to avoid the development of drug resistance. No data are available to address whether temporary discontinuation of therapy is harmful for the woman or fetus.

Health-care providers might consider administering ZDV in combination with other antiretroviral drugs to newborns of women with a history of prior antiretroviral therapy, particularly in situations in which the woman is infected with HIV-1 with documented high-level ZDV resistance, has had disease progression while receiving ZDV, or has had extensive prior ZDV monotherapy. The efficacy of this approach is unknown but would be analogous to the use of multiple agents for postexposure prophylaxis for adults after inadvertent exposure. However, the appropriate dosage and short- and long-term safety of many antiretroviral agents in the neonate has not been established. The half-lives of ZDV, 3TC, and nevirapine are prolonged during the neonatal period because of immature liver metabolism and renal function, requiring specific dosing adjustments when these agents are administered to neonates. Optimal dosages for protease inhibitors in the neonatal period are still under study. The infected woman should be counseled regarding the theoretical benefit of combination antiretroviral drugs for the neonate, potential risks, and available data on appropriate dosing. She should also be informed that using antiretroviral drugs in addition to ZDV for prophylaxis of newborns is of unknown efficacy in reducing risk of perinatal transmission.

Scenario #3: HIV-1 Infected Women in Labor Who Have Had No Prior Therapy

Recommendation

Several effective regimens are available for intrapartum therapy for women who have had no prior therapy (**Table 5**).

1. intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn;
2. oral ZDV and 3TC during labor, followed by one week of oral ZDV-3TC for the newborn;
3. a single dose of nevirapine at the onset of labor, followed by a single dose of nevirapine for the newborn at age 48 hours; and
4. the two-dose nevirapine regimen combined with intrapartum intravenous ZDV and six weeks of ZDV for the newborn.

In the immediate postpartum period, the woman should have appropriate assessments (e.g., $CD4^+$ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

Discussion

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-1 in maternal genital secretions and blood during birth.

Several intrapartum/neonatal antiretroviral prophylaxis regimens are applicable for women in labor who have had no prior antiretroviral therapy (**Table 5**). Available epidemiologic data from non-breastfeeding populations support the efficacy of intrapartum intravenous ZDV followed by six weeks of infant ZDV. Two regimens, one using a combination of ZDV and 3TC, and the other using two doses of nevirapine (one each for the mother and infant), were shown to reduce perinatal transmission in randomized clinical trials among breastfeeding women. The fourth regimen, combining ZDV with nevirapine, is based upon theoretical considerations.

Epidemiologic data indicate that intravenous maternal intrapartum ZDV followed by oral ZDV for 6 weeks for the infant may significantly reduce transmission compared with no treatment (**Table 5**) *[6, 84, 85]*. In a study in New York State, transmission rates were 10% with intrapartum and neonatal ZDV compared with 27% without ZDV, a 62% reduction in risk *[84, 85]*. However, oral intrapartum ZDV combined with very short-term ZDV administration to infants postnatally, for example, the 1-week postnatal infant ZDV course in HIVNET 012 *[79]*, was inferior to single-dose nevirapine. This underscores the necessity of recommending a full 6-week course of infant treatment when ZDV alone is used.

In the PETRA trial, conducted in a breastfeeding population in Uganda, South Africa, and Tanzania, ZDV and 3TC were administered orally intrapartum and to the woman and infant for 7 days postnatally (**Table 5**). At age 6 weeks, the rates of transmission were 9% in the ZDV-3TC arm versus 15% in the placebo arm, a 42% reduction in transmission *[63]*. However, no differences in transmission were observed when ZDV and 3TC were administered only during the intrapartum period (transmission of 14% in the ZDV-3TC arm versus 15% in the placebo arm), indicating that some postexposure prophylaxis is needed, at least in breastfeeding settings. In the United States, administration of ZDV-3TC to the mother postnatally in addition to the infant would not be required for prophylaxis against transmission because HIV-1 infected women in the U.S. are advised not to breastfeed their infants (although ZDV-3TC might be indicated as part of a combination postnatal treatment regimen for a woman who requires treatment).

In the HIVNET 012 trial, conducted in a breastfeeding population in Uganda, a regimen consisting of a single dose of oral nevirapine given to the woman at onset of labor and a single dose to the infant at age 48 hours was compared with oral ZDV given to the woman every 3 hours during labor and postnatally to the infant for 7 days (**Table 4**). At age 6 weeks, the rates of transmission were 12% in the nevirapine arm versus 21% in the ZDV arm, a 42% reduction in transmission *[79]*. No significant short-term toxicity was observed in either group.

In a trial in non-breastfeeding women in Thailand, combining single-dose nevirapine with a short-course ZDV regimen that includes ZDV administration during pregnancy was shown to have improved efficacy compared to ZDV alone *[127]*. However, in a study in breastfeeding women in Malawi, the addition of one week of infant ZDV to infant single-dose nevirapine did not provide any added benefit compared to single-dose maternal/infant nevirapine alone when the maternal intrapartum nevirapine dose was received. The combination did provide additional benefit when the maternal dose was *not* received *[86, 128]*. There are no studies that address whether the combination of single-dose nevirapine with a ZDV regimen that is given intrapartum and for 6 weeks to the infant provides added benefit over that observed with each regimen alone.

Theoretical advantages of combining the ZDV and nevirapine intrapartum/neonatal regimens include the known short-term safety of each regimen alone; excellent transplacental passage of both drugs; greater antiviral activity of nevirapine compared with ZDV, as well as the activity of nevirapine against extracellular and intracellular virus *[129, 130]*; and the known synergy of ZDV and nevirapine in inhibiting HIV-1 replication *in vitro [131]*. However, single-dose nevirapine has been associated with nevirapine-resistant virus in women and infants who become infected despite receiving nevirapine *[132, 133]*, even when the mother receives additional antiretroviral drugs during pregnancy and intrapartum *[134, 135]* (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**).

Genotypic nevirapine resistance was detected at 6 weeks postpartum in 15% of women who received

single-dose nevirapine and who had received ZDV alone or combination antiretroviral drugs during pregnancy and intrapartum *[134, 135]*. Thus, the potential benefits of combination prophylaxis with intrapartum/neonatal nevirapine and ZDV must be weighed against the increased cost, possible problems with nonadherence**,** the risk of emergence of nevirapine-resistant virus, and the lack of definitive data to show that combining the two intrapartum/postpartum regimens offers any additional benefit for prevention of transmission over the use of either drug alone.

Minimal data are available to address the relative efficacy of these four intrapartum/neonatal antiretroviral regimens for prevention of transmission. In a clinical trial (SAINT) in South Africa that compared a modified HIVNET 012 nevirapine regimen (in which the woman received a single dose of nevirapine at the onset of labor and a second dose at 48 hours postpartum, and the infant received a single dose at 48 hours) and the PETRA intrapartum/postpartum ZDV-3TC regimens, no significant differences were observed between the two regimens in terms of efficacy in reducing transmission or in maternal and infant toxicity *[80]*. In the absence of data to suggest the superiority of one or more of the possible regimens, choice should be based upon the specific circumstances of each woman.

Factors to be considered in the choice of which intrapartum/neonatal regimen to administer include: availability of the drug and appropriate formulation (e.g., intravenous ZDV); ability to adhere to the regimen, particularly to the infant postnatal component of the regimen; potential toxicity of the regimen; potential for development of drug resistance in the woman and infants infected despite prophylaxis (of particular concern for 3TC and nevirapine, where a single mutation is associated with resistance); and the implications of such resistance for future treatment options and the efficacy of prophylaxis for future pregnancies.

Development of resistance to 3TC given in an intrapartum/postpartum regimen is rare, although it does occur when 3TC is administered for longer periods during pregnancy as a component of a non-suppressive regimen. In a study in France of ZDV-3TC given during pregnancy and for 6 weeks to the infant, the M184V mutation associated with 3TC resistance was observed at 6 weeks postpartum in 52 of 132 women (39%) with HIV RNA levels > 200 copies/mL; resistance was only observed in women who had received antenatal ZDV-3TC for 4 weeks or longer *[25]*. However, no ZDV or 3TC resistance was observed with intrapartum/1 week postpartum ZDV-3TC in the SAINT study in South Africa *[136]*.

The single-dose nevirapine regimen offers the advantage of lower cost, the possibility of directly observed therapy, and increased adherence compared with the other regimens. However, single-dose nevirapine can be associated with the transient detection of nevirapine resistance in women and in infants who become infected despite receiving nevirapine. Nevirapine resistance mutations were detected at 6 weeks postpartum in 25% of the subset of women with detectable viremia who received single-dose intrapartum nevirapine in HIVNET 012 *[132, 133]*. These mutations were no longer detectable in plasma virus at 13-18 months postpartum, in a setting where none of the women received postnatal antiretroviral therapy. Nevirapine resistance mutations were also detected at 6-8 weeks of age in 11 of 24 (46%) infants who became infected despite receiving nevirapine. Ten of the 11 infected infants with nevirapine resistance had positive HIV tests at birth, and the specific genotypic resistance mutations differed between the mother and infant, suggesting that the nevirapine resistance developed *de novo* in infants who were infected *in utero* and had active viral replication at the time of nevirapine exposure, as opposed to nevirapine resistant virus being transmitted from the mother. As in the mothers, these mutations were no longer detectable in plasma virus by 12 months of age.

In the SAINT trial, in which women received 2 doses rather than a single dose of nevirapine, nevirapine resistance was detected in 67% of women and 53% of infected infants *[136]*. Thus, a regimen containing two maternal doses of nevirapine (intrapartum and 48 hours postpartum) appears to offer no additional benefit over single-dose nevirapine in reducing transmission, but significantly increases the risk of developing nevirapine resistance, and is not recommended.

The clinical consequence of transient detection of NVP-resistant virus following single-dose nevirapine prophylaxis is uncertain, but there are concerns this could negatively impact the response to subsequent antiretroviral treatment that includes nevirapine or other non-nucleoside reverse transcriptase inhibitors (NNRTIs) with cross-resistance. In a study in Thailand, response to nevirapine-based therapy was assessed in immunocompromised women with and without prior single-dose nevirapine exposure. In women with exposure, receipt of single-dose nevirapine prior to initiation of therapy was recent (median 6 months after receipt of prophylaxis, interquartile range 3-14

months). The rate of maximal viral suppression (HIV-1 RNA <50 copies/mL) after 6 months of nevirapine-based therapy was lower in women with recent prior single-dose nevirapine exposure, although immunologic response and weight gain were not different *[137]*. Further research is ongoing to more definitively address this issue, including whether duration of time between receipt of single-dose nevirapine and initiation of therapy impacts response to therapy.

Research is ongoing to develop interventions to prevent development of resistance following single-dose nevirapine. Nevirapine has a prolonged half-life following single-dose exposure, with drug levels at which resistance could occur detected for as long as 21 days post-dose *[124]*. Preliminary data from a study in South Africa suggest that administration of single-dose nevirapine combined with ZDV/3TC given intrapartum and for 4 or 7 days postpartum reduced the rate of development of resistance *[138]*. However, a final analysis of the data is needed before definitive conclusions can be drawn, and the optimal regimen and duration of regimen following single-dose nevirapine requires further study.

Scenario #4: Infants Born to Mothers Who Have Received No Antiretroviral Therapy During Pregnancy or Intrapartum

Recommendation

The 6-week neonatal component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after delivery, preferably within 6–12 hours of birth. Some clinicians may use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, 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. In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., $CD4^+$ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if he or she is HIV-1 infected, treatment can be initiated as soon as possible.

Discussion

Postexposure prophylaxis has prevented retroviral infection in some studies involving animals *[139-141]*. Definitive clinical trial data in humans are not available to address whether ZDV administered only during the neonatal period would reduce the risk of perinatal 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 *[84, 85]*. Transmission rates were 9% (95% CI = 4.1%–17.5%) with ZDV prophylaxis of newborns only (initiated within 48 hours after birth) versus 18% (95% CI = 7.7%–34.3%) with prophylaxis initiated after 48 hours, and 27% (95% CI = 21%–33%) with no ZDV prophylaxis *[84]*. Epidemiologic data from North Carolina did not demonstrate a benefit of ZDV for newborns only compared with no prophylaxis *[6]*. Transmission rates were 27% (95% CI = 8%–55%) with prophylaxis of newborns only and 31% (95% CI = 24%–39%) with no prophylaxis. The timing of initiation of infant prophylaxis was not defined in this study.

Data from a clinical trial of infant post exposure prophylaxis in breastfeeding infants in Malawi indicated that the combination of single dose infant nevirapine with 1 week of ZDV was 36% more effective in preventing transmission than was single dose infant nevirapine alone (see **International Antiretroviral Prophylaxis Clinical Trials**) *[86]*. However, in the U.S., single dose infant nevirapine is not the recommended prophylaxis regimen for preventing transmission, and there has been no comparison of the standard infant prophylaxis regimen of 6 weeks of ZDV with other regimens. Thus, single dose infant nevirapine plus 1 week of ZDV is not recommended for infant prophylaxis when the mother has not received any antiretroviral drugs in the U.S., where the standard 6 weeks of ZDV prophylaxis can be administered.

The interval during which benefit may be gained from postexposure prophylaxis is undefined. When prophylaxis was delayed beyond 48 hours after birth in the New York State study, no efficacy could be demonstrated. For most infants in this study, prophylaxis was initiated within 24 hours *[85]*. 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 24–36 hours after exposure has usually not been effective for preventing infection, although later administration has been associated with decreased viremia *[139-141]*. In cats, ZDV treatment

initiated within the first 4 days after challenge with feline leukemia virus afforded protection, whereas treatment initiated 1 week postexposure did not *[142]*. The relevance of these animal studies to prevention of perinatal HIV-1 transmission in humans is unknown. HIV-1 infection is established in most infected infants by age 1–2 weeks. In a study of 271 infected infants, HIV-1 DNA polymerase chain reaction (PCR) was positive in 38% of samples from infants tested within 48 hours of birth. No substantial change in diagnostic sensitivity was observed within the first week of life, but detection increased rapidly during the second week of life, reaching 93% by age 14 days *[143]*. Initiation of postexposure prophylaxis after age 2 days is not likely to be efficacious in preventing transmission, and by age 14 days, infection would already be established in most infants.

When the mother has received neither the antenatal nor intrapartum parts of the three-part ZDV regimen, administration of antiretroviral drugs to the newborn provides chemoprophylaxis only after HIV-1 exposure has already occurred. Some clinicians view this situation as analogous to nosocomial postexposure prophylaxis *[144]* and may wish to provide ZDV in combination with one or more other antiretroviral agents. 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.

ANTIRETROVIRAL DRUG RESISTANCE AND RESISTANCE TESTING IN PREGNANCY

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV-1 infected persons. Resistant viral variants emerge under selective pressure, especially with incompletely suppressive regimens, because of the inherent mutation-prone process of reverse transcription with viral replication. 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. Some have raised concern that using non-highly active antiretroviral regimens, such as ZDV monotherapy, for prophylaxis against perinatal transmission could result in the development of resistance, which, in turn, could influence perinatal transmission and limit future maternal therapeutic options. Additionally, the general implications of antiretroviral resistance for maternal, fetal, and newborn health are of increasing interest as more HIV-1 infected women enter pregnancy with prior exposure to antiretroviral drugs.

The prevalence of antiretroviral drug resistance mutations in virus from newly infected, therapy-naïve persons has varied by geographic area and the type of assay used (genotypic versus phenotypic) *[145-149]*. In surveys from the United States and Europe, rates of primary resistance mutations in the reverse transcriptase gene were >10% in the majority of studies and ranged as high as 23%. Primary resistance mutations in the protease gene ranged from 1% to 16%, and secondary mutations and polymorphisms of the protease gene were very common. The presence of high-level phenotypic resistance (>10-fold increase in 50% inhibitory concentration [IC_{50}]) was uncommon but tended to occur among isolates with genotypic resistance. Lower level resistance (2.5- to 10-fold decrease in susceptibility) was more common and tended to occur in the absence of genotypic mutations known to confer resistance.

The prevalence of resistance mutations during pregnancy also varies depending on the characteristics of the population studied. No high-level resistance to ZDV was detected at baseline among a subset of women enrolled in PACTG 076, all of whom had $CD4^+$ counts >200 cells/mL and had received no or only limited prior ZDV therapy *[126]*. Conversely, among women receiving ZDV for maternal health indications before 1994 in the Women and Infants Transmission Study (WITS), any ZDV resistance mutation was detected in 35 (25%) of 142 isolates, and high-level ZDV resistance was detected in 14 (10%) isolates *[150]*. Codon 215 mutations, associated with high-level ZDV resistance, were detected in isolates from 9.6% of 62 consecutive women in the Swiss HIV-1 in Pregnancy Study *[151]*. Similarly, in New York, codon 215 mutations were detected in no isolates from 33 women who delivered before 1997 and three (9.7%) from 31 women who delivered from 1997 to 1999; mutations were detected only among women with previous ZDV exposure *[152]*. Among 220 pregnant women with prior ZDV exposure who were enrolled in the Perinatal AIDS Collaborative Transmission Study, virus with primary mutations conferring resistance to nucleoside analog drugs was observed in 17.7%, and primary or secondary resistance mutations in 22%; none of the women had virus containing primary nonnucleoside resistance mutations, 2.3% had secondary nonnucleoside resistance mutations, and 0.5% had virus with a primary mutation conferring resistance to protease inhibitors *[153]*. In all these studies, women evaluated for resistance mutations were

a subset of the larger studies, chosen because of detectable HIV-1 RNA levels with amplifiable virus and often because of clinical findings suggesting an increased risk of resistance. Thus, the rate of resistance mutations in the entire population is likely to be much lower than in the subsets.

The detection of ZDV or other resistance mutations was not associated with an increased risk of perinatal transmission in the PACTG 076, PACTG 185, Swiss cohort, or PACTS studies *[126, 151, 153, 154]*. In the WITS substudy, detection of ZDV resistance was not significantly associated with transmission on univariate analysis, but when adjusted for duration of ruptured membranes and total lymphocyte count, resistance mutations conferred an increased risk of transmission *[150]*. Women in this cohort were receiving ZDV during pregnancy for their own health (mean $CD4^+$ count at delivery 315 cells/mL), usually without intravenous ZDV during labor or ZDV for the infants. Factors associated with resistance at delivery included ZDV use before pregnancy, higher log HIV-1 RNA, and lower $CD4^+$ count. Women with characteristics similar to those in the WITS substudy should be advised to take highly active antiretroviral therapy for their own health and for prevention of perinatal transmission. Although perinatal transmission of resistant virus has been reported *[155, 156]*, it appears to be unusual, and it is not clear that the presence of mutations increases the risk of transmission. In the WITS substudy, when a transmitting mother had a mixed viral population of wild-type and low-level resistant virus, only the wild-type virus was found in the infant, suggesting that virus with low-level ZDV resistance may be less transmissible *[157]*.

Another concern is the potential for resistance developing in the mother during prophylaxis against perinatal transmission, which may then influence future therapy options. In some combination antiretroviral clinical trials, patients with previous ZDV therapy experienced less benefit from combination therapy than those who had never received prior antiretroviral therapy *[12, 158]*. However, in these studies the median duration of prior ZDV use was 12–20 months, and enrolled patients had more advanced disease and lower $CD4^+$ counts than did the population of women enrolled in PACTG 076 or those for whom initiation of therapy would be considered optional. In one study, patients with <12 months of ZDV responded as favorably to combination therapy as those without prior ZDV therapy *[158]*. In PACTG 076, the median duration of ZDV therapy was 11 weeks; the maximal duration of ZDV (begun at 14 weeks' gestation) would be 6.5 months for a full-term pregnancy. Additionally, the development of resistance should be minimized by providing highly active antiretroviral regimens for all women during pregnancy to suppress viral replication to undetectable levels. However, women with low maternal HIV-1 RNA levels may choose the PACTG 076 ZDV regimen to minimize exposure of the fetus to antiretroviral drugs, provided their plasma HIV-1 RNA remains very low or undetectable. Among a subset of women from PACTG 076 (transmitters in the ZDV group, a random selection of nontransmitters in the ZDV group, and women with a history of prior ZDV therapy), no high-level resistance mutations were detected at baseline or delivery, and a low-level resistance mutation developed between baseline and delivery in virus from one (2.6%) of 39 women *[126]*. Data from an analysis of PACTG 288, a follow-up study of the women enrolled in PACTG 076 who were monitored for a median of >4 years postpartum, indicate no substantial differences in $CD4^+$ count, HIV-1 RNA copy number, development of ZDV resistance, or time to progression to AIDS or death among women who received ZDV compared with those who received placebo *[159]*.

Rapid development of resistance to 3TC has been reported among persons receiving dual nucleoside therapy without other agents. In a small study, the M184V 3TC resistance mutation was detectable by delivery in four (80%) of five women treated with ZDV-3TC during pregnancy *[160]*. In a French cohort in which 3TC was added at 32 weeks' gestation to the PACTG 076 ZDV regimen, among 132 samples tested from 6 weeks postpartum, the M184V mutation was detected in 52 (39%); the prevalence of this mutation, before receipt of 3TC, was only 2% *[25]*. ZDV resistance mutations included T215Y/F in nine (7%), M41L in nine (7%), and K70R in 14 (11%). In multivariate analyses, factors associated with detection of the M184V mutation after delivery included lower $CD4^+$ count, higher HIV-1 RNA levels, and longer duration of 3TC therapy. Thus, dual nucleoside therapy is not recommended for treatment of nonpregnant persons with HIV-1 infection or pregnant women who fulfill criteria for initiation of antiretroviral therapy for their own health. These 3TC resistance mutations have also been noted in clinical trials of three drug combinations including 3TC *[161, 162]*. In selected circumstances, dual nucleoside therapy may be considered for pregnant women who are receiving antiretroviral agents for perinatal prophylaxis only. The potential benefits and risks of this approach have not been well studied, and concerns exist about the potential for inadequate viral suppression and rapid development of resistance with use of dual nucleoside treatment.

Selection of nevirapine-resistant virus has also been detected at 6 weeks postpartum in women receiving a single dose of nevirapine during labor. In HIVNET 012, in which antiretroviral-naïve Ugandan women received a single dose of nevirapine during labor to prevent perinatal HIV-1 transmission, genotypic mutations associated with nevirapine resistance were detected at 6 weeks postpartum in samples from 21 (19%) of 111 women with detectable viral replication who received nevirapine *[132]*. The rate of resistance was similar among mothers whose children were or were not infected. Development of resistance was associated with significantly higher baseline viral loads and lower $CD4^+$ counts. Samples taken 12–24 months after delivery from a subset of these women no longer had detectable nevirapine resistance, suggesting that this regimen might be effective for perinatal prophylaxis in subsequent pregnancies. Implications concerning the transient development of detectable nevirapine genotypic resistance mutations from single-dose nevirapine for future maternal therapeutic options are unclear.

Further data are needed to assess the frequency of development of resistance with single-dose intrapartum nevirapine used alone versus with other agents such as ZDV in women who have not received antenatal treatment. In PACTG 316, in which single-dose nevirapine administered during labor and to the newborn was added to the woman's existing antiretroviral regimen, newly detectable nevirapine-resistance mutations were detected at 6 weeks postpartum in 14 (15%) of 95 women who received single-dose intrapartum nevirapine and had detectable HIV-1 RNA at delivery *[134]*. The risk for development of a new nevirapine resistance mutation did not correlate with $CD4^+$ count at delivery, HIV-1 RNA copy number, or type of antenatal antiretroviral treatment (resistance occurred in women receiving highly active antiretroviral therapy as well as ZDV monotherapy). Given lack of further reduction of transmission with nevirapine added to an established regimen *[83]* and the potential development of resistance, addition of nevirapine during labor for women already receiving antiretroviral therapy is not recommended.

The International AIDS Society-USA Panel and EuroGuidelines Group for HIV-1 Resistance recommend that all pregnant women with detectable HIV-1 RNA levels undergo resistance testing, even if they are antiretroviral naïve, to try to maximize the response to antiretroviral drugs in pregnancy, although data to support an improved maternal outcome or reduced risk of perinatal transmission with routine resistance testing are not available *[163, 164]*. Until further data are available, resistance testing for HIV-1 infected pregnant women should be done for the same indications as for nonpregnant persons:

- those with acute infection;
- those who have virologic failure with persistently detectable HIV-1 RNA levels while receiving antenatal therapy, or sub-optimal viral suppression after initiation of antiretroviral therapy; or
- those with a high likelihood of having resistant virus based on community prevalence of resistant virus, known drug resistance in the woman's sex partner, or other source of infection.

The optimal prophylactic regimen for newborns of women with ZDV resistance is unknown. Therefore, antiretroviral prophylaxis of the infant born to a woman with known or suspected ZDV-resistant HIV-1 should be determined in consultation with pediatric infectious disease specialists.

Recommendations related to antiretroviral drug resistance and drug resistance testing for pregnant women with HIV-1 infection are shown in **Table 6**.

PERINATAL HIV-1 TRANSMISSION AND MODE OF DELIVERY

The studies and data discussed below reflect experience in developed countries. Transmission rates and complications by mode of delivery are not clearly defined in developing countries, and local guidelines for prevention of perinatal transmission should be followed in those settings.

Transmission and Mode of Delivery

Optimal medical management during pregnancy should include antiretroviral therapy to suppress plasma HIV-1 RNA to undetectable levels. Labor and delivery management of HIV-1 infected pregnant women should focus on minimizing the risk for both perinatal transmission of HIV-1 and the potential for maternal and neonatal complications.

Several studies done before viral load testing and combination antiretroviral therapy became a routine part of clinical practice consistently showed that cesarean delivery performed before onset of labor and rupture of membranes (elective or scheduled) was associated with a significant decrease in perinatal HIV-1 transmission compared with other types of delivery, with reductions ranging from 55% to 80%. Data regarding transmission rates according to receipt of ZDV have been summarized in **Table 6**.

The observational data comprised individual patient information from 15 prospective cohort studies, including more than 7,800 mother-child pairs, analyzed in a meta-analysis *[165]*. In this meta-analysis, the rate of perinatal HIV-1 transmission among women undergoing elective cesarean delivery was significantly lower than that among similar women having either nonelective cesarean or vaginal delivery, regardless of whether they received ZDV. In an international randomized trial of mode of delivery, transmission was 1.8% among women randomized to elective cesarean delivery, many of whom received ZDV *[166]*. Although the magnitude of reduction in transmission after elective cesarean versus vaginal delivery among women receiving ZDV in the randomized trial was similar to that seen in untreated women, the overall transmission rates were lower, so this difference was not statistically significant. Additionally, in both studies, nonelective cesarean delivery (performed after onset of labor or rupture of membranes) was not associated with a significant decrease in transmission compared with vaginal delivery. The American College of Obstetricians and Gynecologists' *[167]* Committee on Obstetric Practice, after reviewing these data, has issued a Committee Opinion concerning route of delivery, recommending consideration of scheduled cesarean delivery for HIV-1 infected pregnant women with HIV-1 RNA levels > 1,000 copies/mL near the time of delivery *[168]*.

Transmission, Viral Load, and Combination Antiretroviral Therapy

Since the data on mode of delivery and transmission were generated, the standard of care has evolved to include use of highly active antiretroviral regimens (HAART) for most pregnant women. The potential benefit of scheduled cesarean delivery among women on HAART or with undetectable HIV RNA levels is difficult to determine, especially given current transmission rates among treated women. Recent data from PACTG 316 demonstrated an overall transmission rate of 1.5% among women on antiretroviral therapy during pregnancy, 23% of who were on ZDV, 36% on nucleoside combination regimens, and 41% on combinations including protease inhibitors *[83]*. In this study, 34% of women delivered by elective cesarean, but mode of delivery was not associated with transmission risk. In a study of women with HIV RNA levels below 1000 copies/mL at or near delivery, maternal antiretroviral therapy, primarily ZDV, was the most significant predictor of transmission risk (AOR 0.12, P < 0.001), but any cesarean delivery, scheduled or urgent, was also associated with a reduced risk of transmission (AOR 0.09, p= 0.028) *[104]*. In an Italian study evaluating risk factors for transmission, the risk of transmission was reduced with elective cesarean delivery (AOR 0.54, 95% CI 0.29-1.02) compared to other modes of delivery even after adjustment for type of antiretroviral therapy and other risk factors, but not including HIV RNA levels. Among women receiving any antiretroviral therapy, transmission occurred among 13 (2.4%) of 553 women undergoing elective cesarean delivery and 10 (4.4%) of 229 with other modes of delivery (p=0.13) *[169]*. In the European Collaborative Study, elective cesarean delivery was associated with a reduced risk of transmission (AOR 0.42, 95% CI 0.27-0.67) even after adjustment for antiretroviral therapy (none, incomplete PACTG 076 regimen, complete PACTG 076 regimen, combination) and maternal CD4+ lymphocyte count. HIV RNA levels were not included in the model. Of note, the transmission rate among women on combination antiretroviral therapy regardless of mode of delivery was 1.7% (2/118) *[170]*. In an analysis from the WITS, which adjusted for maternal antiretroviral therapy, HIV RNA level at delivery, and other factors, planned cesarean delivery was associated with a nearly significant reduction in risk of transmission (AOR 0.27, 95% CI 0.06-1.12, p= 0.07), similar to the magnitude of reduction seen with HAART compared to ZDV monotherapy (AOR 0.27, 95% CI 0.08-0.94, p=0.04) *[66]*. Taken together, these studies suggest a benefit from elective cesarean delivery among women on antiretroviral therapy, but the majority of the women in all of these studies were receiving ZDV monotherapy rather than current combination regimens. Where specified, the risk of transmission among women on HAART was under 2%, making it difficult to detect potential differences in transmission by mode of delivery in this subset. In addition, only two studies took into account maternal HIV RNA levels, known to be an important predictor of transmission *[66, 83]*.

More recent observational data from PACTG 367 and the European Collaborative Study, evaluating both HIV RNA and maternal antiretroviral therapy along with mode of delivery, do not suggest additional benefit from scheduled cesarean delivery among women with low HIV RNA, but are conflicting regarding benefit for those on HAART with higher HIV RNA *[125, 171]*. Data from PACTG 367, including 2756 women, do not suggest benefit from elective cesarean delivery among women with HIV RNA levels below 1,000 copies/mL or those on multi-agent antiretroviral therapy *[125]*. Women with HIV RNA levels under 1000 copies/mL on multi-agent therapy had transmission rates of 0.8% with elective cesarean delivery and 0.5% with all other delivery modes (OR 1.4, 95% CI 0.2-6.4); those on

single agent therapy, usually ZDV, had a transmission rate of 4.3% after elective cesarean delivery and 1.8% with all other delivery modes (OR 2.5, 95% CI 0.04-50.0). Women on multiagent therapy with HIV RNA levels over 1000 near delivery had a transmission rate of 3.6% with elective cesarean and 2.3% with other delivery modes (OR 1.6, 95% CI 0.6-4.3). Transmission rate among all women on multiagent antiretroviral therapy was 1.3% (34/2539). Conversely, data from 4525 women enrolled in the European Collaborative Study suggested a reduction in perinatal transmission with scheduled cesarean delivery among women on HAART. The overall transmission rate among women on HAART was 10 (1.5%) of 678. However, among the subset of women with undetectable HIV RNA and with logistic regression adjusting for antiretroviral therapy during pregnancy, there was no additional benefit in reduction of transmission with scheduled cesarean delivery *[171]*.

Studies evaluating the potential benefit of scheduled cesarean delivery among women on any antiretroviral therapy have had variable results and included primarily women on ZDV monotherapy. The risk of transmission among women on HAART during pregnancy is low (1.3-1.7%) in all studies, regardless of delivery mode. In a meta-analysis of transmission rates among women with HIV RNA levels under 1,000 copes/mL at delivery, transmission occurred among 1.0% of women on any antiretroviral therapy, primarily ZDV ***[104]***. Current data are preliminary and conflicting regarding further benefit in reduction of transmission with scheduled cesarean delivery among women on HAART, but do not demonstrate benefit with HIV RNA levels below 1,000 copies/mL.

Maternal Risks by Mode of Delivery

Among women not infected with HIV-1, 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 *[172, 173]*. Complications after scheduled cesarean delivery are more common than with vaginal delivery, but less than with urgent cesarean delivery *[174-178]*. 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 between HIV-infected women delivering vaginally or by cesarean. In the European mode of delivery randomized trial among HIV-1 infected pregnant women, no major complications occurred in either the cesarean or vaginal delivery group *[166]*. However, postpartum fever occurred in two (1.1%) of 183 women who delivered vaginally and 15 (6.7%) of 225 who delivered by cesarean delivery (p = 0.002). Substantial postpartum bleeding and anemia occurred at similar rates in the two groups. Among the 497 women enrolled in PACTG 185, only endometritis, wound infection, and pneumonia were increased among women delivered by scheduled or urgent cesarean delivery compared with vaginal delivery *[179]*. Complication rates were within the range previously reported for similar general obstetric populations. An analysis of nearly 1,200 women enrolled in WITS demonstrated increased rate of postpartum fever without documented source of infection among women undergoing elective cesarean delivery compared with spontaneous vaginal delivery, but hemorrhage, severe anemia, endometritis, and urinary tract infections were not increased *[180]*. In the latter two studies, cesarean deliveries before onset of labor and ruptured membranes were done for obstetric indications such as previous cesarean delivery or severe pre-eclampsia and not for prevention of HIV-1 transmission, possibly resulting in higher complication rates than might be observed for scheduled cesarean delivery performed solely to reduce perinatal transmission. In a more recent study including a cohort of HIV-1 infected women with a larger proportion of women undergoing scheduled cesarean delivery specifically for prevention of HIV-1 transmission, fever was increased after cesarean when compared with vaginal delivery *[181]*. In a multivariate analysis adjusted for maternal CD4+ count and antepartum hemorrhage, the relative risk of any postpartum complication was 1.85 (95% CI = 1.00–3.39) after elective cesarean delivery and 4.17 (95% CI = 2.32–7.49) after emergency cesarean delivery, compared with that for women delivering vaginally. Febrile morbidity was increased among women with low CD4+ cell counts.

A study from the European HIV in Obstetrics Group compared outcomes both between HIV-infected women delivering vaginally or by elective cesarean delivery and matched controls of HIV-uninfected women with each mode of delivery *[182]*. Among HIV-infected subjects, minor complications (anemia, fever, wound infection, curettage, endometritis, urinary tract infection) occurred in 16.8% of women delivering vaginally and 48.7% of those with cesarean delivery, and major complications occurred in none of the women with vaginal delivery and 3.2% (5/158) of those with elective cesarean delivery. These frequencies were

increased compared to matched HIV-uninfected women, but the relative difference between vaginal and cesarean deliveries was similar in HIV-infected and HIV-uninfected women.

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 *[183-191]*. Many of these studies were retrospective. Two studies found similar outcomes among HIV-infected women compared to controls *[189, 190]*. Seven studies detected an increased risk of one or more complications among the HIV-infected women. The majority found increases in minor complications such as postoperative fever or mild anemia, but no difference in major complications such as sepsis or hemorrhage requiring transfusion. Cases of pneumonia were seen among HIV-infected women in four of the studies, while no cases occurred in the HIV-negative women. 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 *[180, 181]*.

In summary, data indicate that cesarean delivery is associated with a somewhat greater risk of complications among HIV-1 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-1 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-1 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-1 infected women should be counseled regarding the increased risks and potential benefits associated with cesarean delivery based on their HIV-1 RNA levels and current antiretroviral therapy.

Timing of Scheduled Cesarean Delivery

If the decision is made to perform a scheduled cesarean delivery to prevent HIV-1 transmission, ACOG recommends that it be done at 38 weeks' gestation, determined by the best clinical estimate and avoiding amniocentesis *[168]*. For HIV-1 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 complications in the neonate *[192]*. Cesarean delivery at 38 versus 39 weeks entails a small absolute but substantially increased risk of development of infant respiratory distress requiring mechanical ventilation *[193, 194]*. This increased risk must be balanced against the potential risk for labor or membrane rupture before the woman would reach 39 weeks of gestation. Women should be informed of the potential risks and benefits to themselves and their infants in choosing the timing and mode of delivery.

Intrapartum Management

For a scheduled cesarean delivery, intravenous ZDV should begin 3 hours before surgery, according to standard dosing recommendations *[2]*. Other antiretroviral medications taken during pregnancy should not be interrupted near the time of delivery, regardless of route of delivery. Because maternal infectious morbidity is potentially increased, clinicians should consider perioperative antimicrobial prophylaxis. Although no controlled studies have evaluated the efficacy of antimicrobial prophylaxis specifically for HIV-1 infected women undergoing scheduled operative delivery, use of prophylactic antibiotics at the time of cesarean delivery is generally recommended *[195]*.

Unanswered questions remain regarding the most appropriate management of labor in cases in which vaginal delivery is attempted. Increasing duration of membrane rupture has been demonstrated consistently to be a risk factor for perinatal transmission among women not receiving any antiretroviral therapy *[107, 196-198]*. Among women receiving ZDV, some studies have shown an increased risk of transmission with ruptured membranes for four or more hours before delivery *[9, 93]*, but others have not *[92, 199]*. 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 *[92, 200-202]*. If labor is progressing and membranes are intact, artificial rupture of membranes or invasive monitoring should be avoided. These procedures should be considered only when obstetrically indicated and the length of time for ruptured membranes or monitoring is anticipated to be short. 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.

Recommendations

Considerations related to counseling of the HIV-1 infected pregnant woman regarding risks for vertical transmission of HIV-1 to the fetus/neonate and to the obstetric care of such women include the following:

- Efforts to maximize the health of the pregnant woman, including the provision of highly active combination antiretroviral therapy, can be expected to correlate with both reduction in viral load and low rates of vertical transmission. At a minimum for the reduction of perinatal HIV-1 transmission, ZDV prophylaxis according to the PACTG 076 regimen is recommended unless the woman is intolerant of ZDV.
- Plasma HIV-1 RNA levels should be monitored during pregnancy according to the guidelines for management of HIV-1 infected adults. The most recently determined viral load value should be used when counseling a woman regarding mode of delivery.
- Perinatal HIV-1 transmission is reduced by scheduled cesarean delivery among women with unknown HIV-1 RNA levels who are not receiving antiretroviral therapy or are receiving only ZDV for prophylaxis of perinatal transmission. Plasma HIV-1 RNA levels were not available in these studies to assess the potential benefit among women with low plasma HIV-1 RNA levels.
- Women with HIV-1 RNA levels > 1,000 copies/mL should be counseled regarding the potential benefit of scheduled cesarean delivery in reducing the risk of vertical transmission. The benefit among women on HAART is unproven.
- Data are insufficient to evaluate the potential benefit of cesarean delivery for neonates of antiretroviral-treated women with plasma HIV-1 RNA levels below 1,000 copies/mL. Given the low rate of transmission among this group, it is unlikely that scheduled cesarean delivery would confer additional benefit in reduction of 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-1 RNA level, current antiretroviral therapy, and other clinical factors. It is not clear that cesarean delivery after rupture or onset of labor provides benefit in reducing transmission.
- Women should be informed of the risks associated with cesarean delivery; these risks to the woman should be balanced with potential benefits expected for the neonate.
- Women should be counseled regarding the limitations of the current data. The woman's autonomy to make an informed decision regarding route of delivery should be respected and honored.

Clinical Situations

The following recommendations are based on various hypothetical situations that may be encountered in clinical practice (**Table 7**), with relevant considerations highlighted in the subsequent discussion sections. These recommendations are only guidelines, and flexibility should be exercised according to the patient's individual circumstances.

Scenario A

HIV-1 infected women presenting in late pregnancy (after approximately 36 weeks of gestation), known to be HIV-1 infected but not receiving antiretroviral therapy, and whose results for HIV-1 RNA level and lymphocyte subsets are pending but unlikely to be available before delivery.

Recommendation

Therapy options should be discussed in detail. Antiretroviral therapy, including at least the PACTG 076 ZDV regimen, should be initiated. In counseling, the woman should be informed that scheduled cesarean delivery is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean delivery, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. If cesarean delivery is chosen, the procedure should be scheduled at 38 weeks of gestation, based on the best available clinical information. When scheduled cesarean delivery 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. Options for continuing or initiating combination antiretroviral therapy after delivery should be discussed with the woman as soon as her viral load and lymphocyte subset results are available.

Discussion

Women in these circumstances are similar to women enrolled in the European randomized trial and those evaluated in the meta-analysis *[165, 166]*. In both studies, the population not receiving antiretroviral therapy was shown to have a significant reduction in transmission with cesarean delivery done before labor or membrane rupture. HIV-1 RNA levels were not

available in these studies. Without current therapy, HIV-1 RNA levels are unlikely to be < 1,000 copies/mL. Even if combination therapy were begun immediately, reduction in plasma HIV-1 RNA to undetectable levels usually takes several weeks, depending on the starting RNA level. ZDV monotherapy could be started, with subsequent antiretroviral therapy decisions made after delivery based on the HIV-1 RNA level, CD4+ count, and the woman's preference regarding initiation of long-term combination therapy. Alternately, a highly active combination antiretroviral regimen could be initiated during pregnancy, with decisions regarding continuation postpartum based on HIV-1 RNA levels, CD4+ lymphocyte count, and patient preference. Scheduled cesarean delivery is likely to provide additional benefit in reducing risk of perinatal transmission of HIV-1 along with the three-part PACTG 076 ZDV regimen or highly active antiretroviral therapy, given initiation so late in pregnancy.

Scenario B

HIV-1 infected women who began prenatal care early in the third trimester, are receiving highly active combination antiretroviral therapy, and have an initial virologic response, but have HIV-1 RNA levels that remain substantially over 1,000 copies/mL at 36 weeks of gestation.

Recommendation

The current combination antiretroviral regimen should be continued because the HIV-1 RNA level is declining appropriately. The woman should be informed that although her HIV-1 RNA level is responding to the antiretroviral therapy, it is unlikely that it will reach < 1,000 copies/mL before delivery. Therefore, scheduled cesarean delivery may provide additional benefit in preventing intrapartum transmission of HIV-1. She should also be informed of the increased risks to her of cesarean delivery, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean delivery, it should be performed at 38 weeks' gestation, and intravenous ZDV should be started at least 3 hours before surgery. Other antiretroviral medications should be continued on schedule as much as possible before and after surgery. The infant should receive oral ZDV for 6 weeks after birth. The importance of adhering to therapy after delivery for her own health should be emphasized

Discussion

Although current combination antiretroviral therapy regimens may be expected to suppress HIV-1 RNA to undetectable levels with continued use, these levels are likely to still be detectable within the period of expected delivery. Scheduled cesarean delivery might further reduce the rate of intrapartum HIV-1 transmission and should be recommended to women with HIV-1 RNA levels > 1,000 copies/mL. Transmission rates among women on HAART have been below 2%, regardless of mode of delivery *[83, 125, 170]* and HIV RNA levels, similar to rates seen among women receiving ZDV and undergoing elective cesarean delivery. It is not clear if the impact on transmission is related to the lowering of maternal plasma HIV-1 RNA levels, pre-exposure prophylaxis of the infant, other mechanisms, or some combination. Until further data are available, women with HIV-1 RNA levels > 1,000 copies/mL should be offered scheduled cesarean delivery regardless of maternal therapy, although a thorough discussion of the uncertain benefit among women on HAART and the potential maternal and infant risks of cesarean delivery must be included.

Regardless of mode of delivery, the woman should receive the PACTG 076 intravenous ZDV regimen intrapartum, and the infant should receive ZDV for 6 weeks after birth. Other maternal drugs should be continued on schedule as much as possible to provide maximal effect and minimize the chance of development of viral resistance. 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 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 with CD4+ counts < 350 cells/mL or HIV-1 RNA levels >100,000 copies/mL before initiation of combination therapy during pregnancy are most likely to benefit from continued antiretroviral therapy after delivery *[14]*. Discussion regarding plans for antiretroviral therapy after delivery should be initiated during pregnancy. If the woman elects to continue therapy after delivery, the importance of continued adherence despite the increased responsibilities of newborn care should be emphasized, and any support available for the woman should be provided.

Scenario C

HIV-1 infected women receiving highly active combination antiretroviral therapy who have an undetectable HIV-1 RNA level at 36 weeks of gestation.

Recommendation

The woman should be informed that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV-1 RNA level is low, probably 2% or less, even with vaginal delivery. Current information suggests that performing a scheduled cesarean delivery will not lower her risk further. Cesarean delivery has an increased risk of complications for the woman compared with vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean delivery in this case.

Discussion

Scheduled cesarean delivery has been beneficial for women either receiving no antiretroviral therapy or receiving ZDV monotherapy, with rates of transmission of HIV-1 of approximately 1%–2% *[165, 166]*. Maternal HIV-1 RNA levels were not evaluated in these studies. Similar rates of transmission have been reported among women receiving antiretroviral therapy, with HIV-1 RNA levels undetectable near delivery *[92, 93, 203]*. Limited and conflicting data are available evaluating transmission rates by mode of delivery among women with undetectable HIV-1 RNA levels on ZDV or other antiretroviral therapy *[66, 104, 125, 170]*. Although a benefit of cesarean delivery in reducing transmission may be present, it would be of small magnitude given the low risk of transmission with vaginal delivery among women with HIV-1 RNA levels < 1,000 copies/mL who are receiving maternal antiretroviral therapy. Any benefit must be weighed against the known increased risks to the woman with cesarean delivery compared with vaginal delivery (i.e., a severalfold increased risk of postpartum infections, including uterine infections and pneumonia; anesthesia risks; and surgical complications). However, given limited data to indicate lack of benefit, if a woman chooses a scheduled cesarean delivery, her decision should be respected and cesarean delivery scheduled.

If vaginal delivery is chosen, the duration of ruptured membranes should be minimized because the transmission rate has been shown to increase with longer duration of membrane rupture among predominantly untreated women *[196-198]* and among ZDV-treated women in some *[9, 93]* but not all studies *[92, 199]*. Fetal scalp electrodes and operative delivery with forceps or the vacuum extractor may increase the risk of transmission and should be avoided *[200, 201]*. Intravenous ZDV should be given during labor, and other maternal antiretroviral drugs should be continued on schedule as much as possible to provide maximal effect and minimize the chance of development of viral resistance; the infant should be treated with ZDV for 6 weeks after birth.

Scenario D

HIV-1 infected women who have elected scheduled cesarean delivery but present in early labor or shortly after rupture of membranes

Recommendation

Intravenous ZDV should be started immediately since the woman is in labor or has ruptured membranes. 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. 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 delivery should be avoided if possible. Other antiretrovirals besides ZDV should be continued orally during labor. The infant should be treated with 6 weeks of ZDV therapy after birth.

Discussion

No data are available to address the question of whether performing cesarean delivery soon after membrane rupture to shorten labor and avoid vaginal delivery decreases the risk of vertical transmission of HIV-1. 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 *[166, 204]*. When an effect 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 (see **Scenario C**).

If elective cesarean delivery had been planned and the woman presents with a short duration of ruptured membranes or labor, she should be informed that the benefit of cesarean delivery under these circumstances is unclear and be allowed to reassess her decision. If the woman presents after 4 hours of membrane rupture, cesarean delivery is less likely to affect transmission of HIV-1. The woman should be informed that the benefit of cesarean delivery is unclear and that her risks of perioperative infection increase with increasing duration of ruptured membranes. If cesarean delivery is chosen, the loading dose of ZDV should be administered while preparations are made for cesarean delivery; the infusion should continue until cord clamping. Prophylactic antibiotics given after cord clamping have been shown to reduce the rate of postpartum infection among women of unknown HIV-1 status undergoing cesarean delivery after labor or rupture of membranes, and should be used routinely in this setting *[195]*. If vaginal delivery is chosen, intravenous ZDV and other antiretroviral agents the woman is currently taking should be administered and invasive procedures such as internal monitoring avoided. Oxytocin should be used as needed to expedite delivery.

RECOMMENDATIONS FOR MONITORING OF WOMEN AND THEIR INFANTS

Pregnant Woman and Fetus

HIV-1 infected pregnant women should be monitored according to the same standards for monitoring HIV-1 infected persons who are not pregnant. This monitoring should include measurement of $CD4^+$ counts and HIV-1 RNA levels approximately every trimester (i.e., every three to four months) to determine

a. the need for antiretroviral therapy of maternal HIV-1 disease,
b. whether such therapy should be altered, and
c. whether prophylaxis against *Pneumocystis carinii* pneumonia should be initiated.

Changes in absolute $CD4^+$ count during pregnancy may reflect the physiologic changes of pregnancy on hemodynamic parameters and blood volume as opposed to a long-term influence of pregnancy on $CD4^+$ count; $CD4^+$ percentage is likely more stable and might be a more accurate reflection of immune status during pregnancy *[205, 206]*. Long-range plans should be developed with the woman regarding continuity of medical care and antiretroviral therapy for her own health after the birth of her infant.

Monitoring for potential complications of administration of antiretroviral agents during pregnancy should be based on what is known about the side effects of the drugs the woman is receiving. For example, routine hematologic and liver enzyme monitoring is recommended for women receiving ZDV. Because combination antiretroviral regimens have been used less extensively during pregnancy, more intensive monitoring may be warranted for women receiving drugs other than or in addition to ZDV. For example, women receiving protease inhibitors should be monitored for development of hyperglycemia. Women, particularly those with $CD4^+$ counts >250 cells/mm^3, have an increased risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity *[31, 32, 34]*; thus, pregnant women receiving nevirapine should have frequent and careful monitoring of transaminase levels, particularly during the first 18 weeks of treatment (see section, **Nevirapine and Hepatic/Rash Toxicity**).

Antepartum fetal monitoring for women who receive only ZDV chemoprophylaxis should be performed as clinically indicated because data do not indicate that ZDV use in pregnancy is associated with increased risk for fetal complications. Less is known about the effect of combination antiretroviral therapy on the fetus during pregnancy. Thus, more intensive fetal monitoring should be considered for mothers receiving such therapy, including assessment of fetal anatomy with a level II ultrasound and continued assessment of fetal growth and wellbeing during the third trimester.

Neonate

A complete blood count 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; thus, repeat measurement of hemoglobin is required at a minimum after the completion of the 6-week ZDV regimen. If abnormal, repeat measurement should be performed at age 12 weeks, by which time any ZDV-related hematologic toxicity should be resolved. Infants who have anemia at birth or who are born prematurely warrant more intensive monitoring.

Data are limited concerning potential toxicities in infants whose mothers have received combination antiretroviral therapy. More intensive monitoring of hematologic and serum chemistry measurements during the first few weeks of life is advised for these infants.

However, it should be noted that the clinical relevance of lactate levels in the neonatal period to assess potential for mitochondrial toxicity has not been adequately evaluated.

To prevent *P. carinii* pneumonia, all infants born to women with HIV-1 infection should begin prophylaxis at age 6 weeks, after completion of the ZDV prophylaxis regimen *[207]*. Monitoring and diagnostic evaluation of HIV-1 exposed infants should follow current standards of care *[208]*. Data do not indicate any delay in HIV-1 diagnosis in infants who have received the ZDV regimen *[1, 209]*. However, the effect of combination antiretroviral therapy in the mother or newborn on the sensitivity of infant virologic diagnostic testing is unknown. Infants with negative virologic test results during the first 6 weeks of life should have diagnostic evaluation repeated after completion of the neonatal antiretroviral prophylaxis regimen.

Postpartum Follow-Up of Women

Comprehensive care and support services are important for women with HIV-1 infection and their families. Components of comprehensive care include the following medical and supportive care services:

- Primary, obstetric, pediatric and HIV-1 specialty care;
- Family planning services;
- Mental health services;
- Substance-abuse treatment; and
- Coordination of care through case management for the woman, her children, and other family members.

Support services include case management, child care, respite care, assistance with basic life needs (e.g., housing, food, and transportation), and legal and advocacy services. 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-1 specialists. Continuity of antiretroviral treatment when such treatment is required for the woman's HIV-1 infection is especially critical and must be ensured. Concerns have been raised about adherence to antiretroviral regimens during the postpartum period. Women should be counseled about the fact that the physical changes of the postpartum period, as well as the stresses and demands of caring for a new baby, can make adherence more difficult and additional support may be needed to maintain good adherence to their therapeutic antiretroviral regimen during this period *[210, 211]*. The health-care provider should be vigilant for signs of depression, 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 *[212-217]*. Efforts to maintain good 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 *AIDSinfo* Web site (**http://*AIDSinfo*.nih.gov**).

All women should receive comprehensive health-care services that continue after pregnancy for their own medical care and for assistance with family planning and contraception. In addition, this is a good time to review immunization status and update vaccines, assess the need for prophylaxis against opportunistic infections, and reemphasize safer sex practices.

Data from PACTG 076 and 288 do not indicate adverse effects through 4 years postpartum among women who received ZDV during pregnancy. Women who have received only ZDV chemoprophylaxis during pregnancy should receive appropriate evaluation to determine the need for antiretroviral therapy during the postpartum period.

Long-Term Follow-Up of Infants

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 *[74, 75]*. As discussed earlier in the section on **Mitochondrial Toxicity and Nucleoside Analog 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 a long-term follow-up study in the Pediatric AIDS Clinical Trials Group (PACTG 219C), 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-1 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 *[56]*. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding potential for carcinogenicity of the nucleoside analog 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 smears.

HIV-1 surveillance databases from states that require HIV-1 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-1 infection in the United States are receiving combination antiretroviral therapy for their own health care along with standard ZDV prophylaxis to reduce perinatal HIV-1 transmission. Additionally, data indicate that antenatal use of potent antiretroviral combinations capable of reducing plasma HIV-1 RNA copy number to very low or undetectable levels near the time of delivery may lower the risk of perinatal transmission to < 2% *[66, 104]*. 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 six week course of ZDV, as well as single-dose nevirapine and single-dose nevirapine in combination with one 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 nevirapine 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 *[132, 134]*. 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 nevirapine or efavirenz for prolonged periods of time (more than 2 weeks) after stopping chronic therapy, as well as after receipt of single-dose nevirapine *[123, 218]*. Nevirapine resistance mutations have been identified postpartum in women who have received single-dose intrapartum nevirapine prophylaxis, as well as in women who have stopped nevirapine-containing combination regimens taken during pregnancy for prevention of mother-to-child transmission *[132, 219]*. In the latter study, nevirapine 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 nevirapine) *[219]*. Preliminary data from a South African study suggest that administration of single-dose nevirapine combined with ZDV/3TC given intrapartum and for 4 or 7 days postpartum may reduce, although not eliminate, the development of resistance compared with administration of single-dose nevirapine alone *[138]*. Further research is needed to assess appropriate strategies for stopping nevirapine-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 nevirapine for prevention of intrapartum transmission. Additionally, research is needed to evaluate the effect of transient nevirapine 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-1 infected persons. Innovative approaches are needed to improve adherence in women with HIV-1 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

Elective cesarean delivery has increased among women with HIV-1 infection since the demonstration that delivery before labor and membrane rupture can reduce intrapartum HIV-1 transmission *[165, 166, 220]*. Further study is needed regarding whether elective 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-1 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 *[221]*. Therefore, further study is also needed to evaluate the role of nonelective 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 *[221]*, more study is needed to determine the appropriate management of pregnant women with HIV-1 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-1 counseling and testing are one of the groups still at high risk for transmitting HIV-1 to their infants. The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study has demonstrated the acceptability and feasibility of offering counseling and rapid HIV-1 testing to women of unknown HIV-1 status who present while in labor *[222]*. Rapid testing during labor can enable pregnant women with undocumented HIV-1 status to learn their HIV-1 infection status so they can receive antiretroviral prophylaxis and be referred for comprehensive medical care and follow-up. A model protocol on implementing rapid HIV testing at labor/delivery is available from CDC at **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-1 infected during delivery, and to identify the optimal antiretroviral prophylaxis regimen for this situation.

Table 1. Pediatric AIDS Clinical Trials Group (PACTG) 076 Zidovudine (ZDV) Regimen

Time of ZDV Administration	Regimen
Antepartum	Oral administration of 100 mg ZDV five times daily*, initiated at 14-34 weeks gestation and continued throughout the pregnancy.
Intrapartum	During labor, intravenous administration of ZDV in a one-hour initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight/hour until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup at 2 mg/kg body weight/dose every six hours) for the first six weeks of life, beginning at 8-12 hours after birth.**

* Oral ZDV administered as 200 mg three times daily or 300 mg twice daily is currently used in general clinical practice and is an acceptable alternative regimen to 100 mg orally five times daily.

** Intravenous dosage for full-term infants who cannot tolerate oral intake is 1.5 mg/kg body weight intravenously every six hours *[119]*. 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 *[121]*.

Table 2. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During 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	Unknown	Not completed	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 (rat and monkey)	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)	C	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)	C	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Unknown	Positive (hepatocellular adenomas in female mice)	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 (humans)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Unknown	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 (humans)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive (liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (humans)	Negative	Negative
Fusion inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

* 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: one of three pages

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 (AZT 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 *[223]*.	No evidence of human teratogenicity *[73]*. 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 *[224]*.	No evidence of human teratogenicity *[73]*. 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 *[225]*.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[53, 54]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine	No 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 *[226]*.	No evidence of human teratogenicity *[73]*. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[53, 54]*.	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*	Phase I/II study in progress.	Hypersensitivity reactions occur in ~5-8% of non-pregnant 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	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy *[227]*. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown *[228, 229]*.	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 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: two of three pages

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			
Recommended agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[230]*.	No evidence of human teratogenicity *[73]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4+ lymphocyte counts > 250/mm^3 when first initiating therapy *[231, 232]*; unclear if pregnancy increases risk.	Nevirapine should be used with caution in pregnant women with CD4+ lymphocyte counts > 250/mm^3 who are starting combination therapy for preventing perinatal transmission but do not require therapy for own health; if used, monitor closely for liver toxicity in first 18 weeks of therapy. Women who enter pregnancy on nevirapine regimens and are tolerating well may continue therapy, regardless of CD4+ lymphocyte count.
Not recommended			
Efavirenz	No studies in human pregnancy.	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 three case reports of neural tube defects in humans after first trimester exposure *[73, 233, 234]*; 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. 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 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).	
Recommended agents			
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1250 mg, given twice daily *[235]*.	No evidence of human teratogenicity *[73]*. Well-tolerated, short-term safety demonstrated for mother and infant. Nelfinavir dosing at 750 mg three times daily produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely 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 compared with atazanavir or nevirapine-based regimens *[236-239]*.
Saquinavir-soft gel capsule [SGC] (Fortovase®) /ritonavir	Adequate drug levels are achieved in pregnant women with saquinavir-SGC 800 mg boosted with ritonavir 100 mg, given twice daily *[240]*. Recommended adult dosing of saquinavir-SGC 1000 mg plus ritonavir 100 mg may be used. No pharmacokinetic data on saquinavir-hard gel capsule [HGC]/ ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.	Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women with saquinavir-SGC given alone at 1200 mg three times daily *[241]*.	Given pharmacokinetic data and moderate experience with use in pregnancy, ritonavir-boosted saquinavir-SGC can be considered a preferred PI for combination regimens in pregnancy.

Table 3: three of three pages

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	Study underway to evaluate pharmacokinetics of indinavir 800 mg with ritonavir 100 mg, given twice daily.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Two studies including six women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen *[242, 243]*.	Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir. May need to give indinavir as ritonavir-boosted regimen to achieve adequate levels during pregnancy.
Lopinavir/ ritonavir	Phase I/II safety and pharmacokinetic study in progress using twice daily lopinavir 400 mg and ritonavir 100 mg.	Limited experience in human pregnancy.	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result is not observed, consult with a specialist with expertise in HIV in pregnancy.
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum *[244]*.	Minimal experience in human pregnancy.	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.
Insufficient data to recommend use			
Amprenavir	No 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.
Fosamprenavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Atazanavir	No studies in human pregnancy.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Fusion inhibitors			
Insufficient data to recommend use			
Enfuvirtide	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

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

\# 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 Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission

SCENARIO #1

HIV-1-infected pregnant women who have not received prior antiretroviral therapy.

- Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed.
- The three-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection regardless of antenatal HIV RNA copy number to reduce the risk for perinatal transmission.
- The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic or virologic status requires treatment or who have HIV-1 RNA over 1,000 copies/mL regardless of clinical or immunologic status, and can be considered for women with HIV-1 RNA < 1,000 copies/mL.
- Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' gestation.

SCENARIO #2

HIV-1-infected women receiving antiretroviral therapy during the current pregnancy.

- HIV-1 infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal antiretroviral treatment regimen after the first trimester whenever possible, although this may not always be feasible.
- For women receiving antiretroviral therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance.
- Regardless of the antepartum antiretroviral regimen, ZDV administration is recommended during the intrapartum period and for the newborn.

SCENARIO #3

HIV-1-infected women in labor who have had no prior therapy.

- Several effective regimens are available (**Table 5**). These include:
  1. intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn;
  2. oral ZDV and 3TC during labor, followed by one week of oral ZDV-3TC for the newborn;
  3. a single dose nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours; and
  4. the two-dose nevirapine regimen combined with intrapartum intravenous ZDV and six week ZDV for the newborn.
- In the immediate postpartum period, the woman should have appropriate assessments (e.g., $CD4^+$ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

SCENARIO #4

Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum.

- The six-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn.
- ZDV should be initiated as soon as possible after delivery - preferably within 6-12 hours of birth.
- Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, 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.
- In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., $CD4^+$ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health.. The infant should undergo early diagnostic testing so that if HIV-infected, treatment can be initiated as soon as possible.

Note: Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care. Use of ZDV should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

Table 5. Comparison of Intrapartum/Postpartum Regimens for HIV-1-Infected Women in Labor Who Have Had No Prior Antiretroviral Therapy (Scenario #3)

Drug Regimen	Source of Evidence	Maternal Intrapartum	Infant Postpartum	Data on Transmission	Advantages	Disadvantages
ZDV	Epidemiologic data, U.S.; compared to no ZDV treatment	2 mg/kg intravenous bolus, followed by continuous infusion of 1 mg/kg/hr until delivery	2 mg/kg orally every six hours for six weeks*	Transmission 10% with ZDV compared to 27% with no ZDV treatment, a 62% reduction (95% CI, 19–82%)	Has been standard recommendation	Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant regimen Reversible, mild anemia with 6 week infant ZDV regimen
ZDV/3TC	Clinical trial, Africa; compared to placebo	ZDV 600 mg orally at onset of labor, followed by 300 mg orally every three hours until delivery AND 3TC 150 mg orally at onset of labor, followed by 150 mg orally every 12 hours until delivery	ZDV 4 mg/kg orally every 12 hours AND 3TC 2 mg/kg orally every 12 hours for seven days	Transmission at six weeks 9% with ZDV-3TC vs. 15% with placebo, a 42% reduction	Oral regimen Adherence easier than six weeks of ZDV	Requires administration of two drugs
Nevirapine	Clinical trial, Africa; compared to oral ZDV given intrapartum and for one week to the infant	Single 200 mg oral dose at onset of labor	Single 2 mg/kg oral dose at age 48–72 hours**	Transmission at six weeks 12% with nevirapine compared to 21% with ZDV, a 47% reduction (95% CI*, 20–64%)	Inexpensive Oral regimen Simple, easy to administer Can give directly observed treatment	Unknown efficacy if mother has nevirapine-resistant virus Transient nevirapine resistance mutations detected at 6 weeks postpartum in 19% of women receiving single-dose intrapartum nevirapine, and 46% of infants who became infected despite receiving nevirapine
ZDV-Nevirapine	Theoretical	ZDV 2 mg/kg intravenous bolus, followed by continuous infusion of 1 mg/kg/hr until delivery AND Nevirapine single 200 mg oral dose at onset of labor	ZDV 2 mg/kg orally every six hours for six weeks AND Nevirapine single 2 mg/kg oral dose at age 48–72 hours**	No data	Potential benefit if maternal virus is resistant to either nevirapine or ZDV Synergistic inhibition of HIV replication with combination in vitro	Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant ZDV regimen Unknown if additive efficacy with combination Transient nevirapine resistance mutations detected at 6 weeks postpartum in 15-25% of women receiving single-dose intrapartum nevirapine with ZDV or other antiretroviral drugs

ZDV, zidovudine; CI, confidence interval; 3TC, lamivudine

* 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 *[121]*.

**If the mother received nevirapine less than one hour prior to delivery, the infant should be given 2 mg/kg oral nevirapine as soon as possible after birth and again at 48-72 hours *[245]*.

Table 6. Recommendations Related to Antiretroviral Drug Resistance and Drug Resistance Testing for Pregnant Women with HIV-1 Infection

- All pregnant HIV-1-infected women should be offered highly active antiretroviral therapy to maximally suppress viral replication, reduce the risk of perinatal transmission, and minimize the risk of development of resistant virus.
- For women for whom combination antiretroviral therapy would be considered optional (HIV-1 RNA <1,000 copies/mL) and who wish to restrict their exposure to antiretroviral drugs during pregnancy, monotherapy with the three-part zidovudine (ZDV) prophylaxis regimen (or in selected circumstances, dual nucleosides) should be offered. In these circumstances, the development of resistance should be minimized by limited viral replication (assuming HIV-1 RNA levels remain low) and the time-limited exposure to ZDV. Monotherapy with ZDV does not suppress HIV-1 replication to undetectable levels in most cases, theoretically, such therapy might select for ZDV-resistant viral variants, potentially limiting future treatment options. These considerations should be discussed with the pregnant woman.
- Recommendations for resistance testing for HIV-1-infected pregnant women are the same as for non-pregnant patients: acute HIV-1 infection, virologic failure, sub-optimal viral suppression after initiation of antiretroviral therapy, or high likelihood of exposure to resistant virus based on community prevalence or source characteristics.
- Women who have a history of presumed or documented ZDV resistance and are on antiretroviral regimens that do not include ZDV for their own health should still receive intravenous ZDV intrapartum and oral ZDV for their infants according to the PACTG 076 protocol whenever possible. A key mechanism by which ZDV reduce perinatal transmission is likely through pre- and post-exposure prophylaxis of the infant, which may be less dependent on drug sensitivity than is reduction of viral replication. However, these women are not good candidates for ZDV alone.
- Optimal antiretroviral prophylaxis of the infant born to a woman with HIV-1 known to be resistant to ZDV or other agents should be determined in consultation with pediatric infectious disease specialists, taking into account resistance patterns, available drug formulations, and infant pharmacokinetic data, when available.
- If women receiving combination therapy require temporary discontinuation for any reason during pregnancy, all drugs should be stopped and reintroduced simultaneously to reduce the potential for emergence of resistance.
- Optimal adherence to antiretroviral medications is a key part of the strategy to reduce the development of resistance.
- Because the prevalence of drug-resistant virus is an evolving phenomenon, surveillance is needed to monitor the prevalence of drug-resistant virus in pregnant women over time and the risk of transmission of resistant viral strains.

Table 7. Rate of Perinatal Transmission According to Receipt of Zidovudine During Pregnancy and Mode of Delivery

Study design	Therapy	Transmission rate		Odds ratio (95% CI*)
		Elective CS	Other modes	
Observational data *[165]***	No ZDV	58/559 (10.4%)	1021/5385 (19%)	0.49 (0.4-–0.7)
	ZDV	4/196 (2%)	92/1255 (7.3%)	0.26 (0.07–0.7)
Randomized trial *[166]****	No ZDV	2/51 (4%)	16/82 (20%)	0.20 (0–0.8)
	ZDV	1/119 (1%)	5/117 (4%)	.20 (0–1.7)

* Confidence interval.

** Source: The International Perinatal HIV Group. The Mode of Delivery and the Risk of Vertical Transmission of Human Immunodeficiency Virus Type 1 - a Meta-Analysis of 15 Prospective Cohort Studies. *N Engl J Med*, 1999. 340(13):977-87.

*** Source: The European Mode of Delivery Collaboration. Elective cesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*, 1999. 353(9158):1035-9.

Table 8. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission

Mode of Delivery Clinical Scenario	Recommendations
Scenario A HIV-1-infected women presenting in late pregnancy (after about 36 weeks of gestation), known to be HIV-1-infected but not receiving antiretroviral therapy, and who have HIV-1 RNA level and lymphocyte subsets pending but unlikely to be available before delivery.	Therapy options should be discussed in detail. The woman should be started on antiretroviral therapy including at least the PACTG 076 ZDV regimen. 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 of 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 of gestation based on the best available clinical information. When scheduled cesarean section is performed, the woman should receive continuous intravenous ZDV infusion beginning three hours before surgery and her infant should receive six weeks of ZDV therapy after birth. Options for continuing or initiating combination antiretroviral therapy after delivery should be discussed with the woman as soon as her viral load and lymphocyte subset results are available.
Scenario B HIV-1-infected women who initiated prenatal care early in the third trimester, are receiving highly active combination antiretroviral therapy, and have an initial virologic response, but have HIV-1 RNA levels that remain substantially over 1,000 copies/mL at 36 weeks of gestation.	The current combination antiretroviral regimen should be continued as the HIV-1 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-1 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-1. 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 three hours before surgery. Other antiretroviral medications should be continued on schedule as much as possible before and after surgery. The infant should receive oral ZDV for six weeks after birth. The importance of adhering to therapy after delivery for her own health should be emphasized.
Scenario C HIV-1-infected women on highly active combination antiretroviral therapy with an undetectable HIV-1 RNA level at 36 weeks of gestation.	The woman should be counseled that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV-1 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.
Scenario D HIV-1-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 should be allowed to 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 six weeks of ZDV therapy after birth.

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