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

Perinatal HIV Guidelines Working Group Members

Revisions to the January 24, 2001 Public Health Service Task Force Recommendations for the 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.

Consultants:

Jean Anderson, M.D.
Johns Hopkins University School of Medicine
Baltimore, MD

Claire Rappoport
Brisbane, CA

I. Celine Hanson, M.D.
Baylor College of Medicine
Houston, TX

Robert Maupin, M.D.
Louisiana State University Health Sciences Center
New Orleans, LA

Howard Minkoff, M.D.
Maimonides Medical Center
Brooklyn, NY

Mary Jo O'Sullivan, M.D.
University of Miami School of Medicine
Miami, FL

Sallie Marie Perryman
New York State Department of Health AIDS Institute
New York, NY

Gwendolyn Scott, M.D.
University of Miami School of Medicine
Miami, FL

Stephen Spector, M.D.
University of California San Diego
La Jolla, CA

Ruth Tuomala, M.D.
Brigham and Women's Hospital
Boston, MA

Nancy Wade, M.D.
The Childrens Hospital at Albany Medical Center
Albany, NY

Patricia Whitley-Williams, M.D.
University of Medicine and Dentistry of New Jersey
New Brunswick, NJ

Catherine Wilfert, M.D.
Elizabeth Glaser Pediatric AIDS Foundation
Chapel Hill, NC

Carmen Zorrilla, M.D.
University of Puerto Rico School of Medicine
San Juan, PR

Federal Government Staff:

Magda Barini-Garcia, M.D.
Health Resources and Services Administration
Rockville, MD

Melisse Baylor, M.D.
Food and Drug Administration
Rockville, MD

Mary Glenn Fowler, M.D.
Centers for Disease Control and Prevention
Atlanta, GA

Federal Government Staff (Cont.):

Eric Goosby, M.D.
Office of HIV/AIDS Policy
Washington, D.C.

Karen Hench, R.N.
Health Resources and Services Administration
Rockville, MD

Denise Jamieson, M.D.
Centers for Disease Control and Prevention
Atlanta, GA

James McNamara, M.D.
National Institutes of Health
Rockville, MD

Lynne Mofenson, M.D. (Executive Secretary)
National Institutes of Health
Rockville, MD

Jose Morales, M.D.
Health Resources and Services Administration
Rockville, MD

Deborah von Zinkernagel, R.N.
Office of HIV/AIDS Policy
Washington, D.C.

D. Heather Watts, M.D.
National Institutes of Health
Rockville, MD

Working Group Coordinating Center Staff:

Carolyn Burr, Ed.D., R.N.
National Pediatric and Family HIV Resource Center
Newark, NJ

Elaine Gross, R.N., M.S., C.N.S.-C.
National Pediatric and Family HIV Resource Center
Newark, NJ

Cheryl Thiemann
National Pediatric and Family HIV Resource Center
Newark, NJ

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Summary

These recommendations update the January 24, 2001 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 as scenarios and the factors influencing treatment considerations are highlighted in this report. It is recognized that strategies to prevent perinatal transmission and concepts related to management of HIV disease in pregnant women are rapidly evolving. The Perinatal HIV Guidelines Working Group will review new data on an ongoing basis and provide regular updates to the guidelines; the most recent information is available on the HIV/AIDS Treatment Information Service (ATIS) website (http://www.hivatis.org).*

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 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. The use of antiretroviral drugs in pregnancy requires unique considerations, including the potential need to alter dosing 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 for 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 to treat HIV-1 infection, to reduce 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 for 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 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 Public Health Service (PHS) task force issued recommendations for the use of ZDV for reduction of perinatal HIV-1 transmission *(2)*, and in July 1995, PHS issued recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with consent for all pregnant women in the United States *(3)*. Following 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 six hours *(10)*. Thus, current therapeutic interventions focus on early initiation of aggressive combination antiretroviral regimens to maximally suppress viral replication, preserve immune function, and reduce the development of resistance *(11)*. New, potent antiretroviral drugs that inhibit the protease enzyme of HIV-1 are now available. When a protease inhibitor is used in combination with nucleoside analogue reverse transcriptase inhibitors, plasma HIV-1 RNA levels may be reduced for prolonged periods to levels that are undetectable using current assays. Improved clinical outcome and survival have been observed in 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")

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 eight-12 hours after birth. (Note: intravenous dosage for infants who can not tolerate oral intake is 1.5 mg/kg body weight intravenously every six hours.)

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, recent 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 important implications for maternal and fetal health. Health-care providers considering the use of antiretrovirals in HIV-1 infected women during pregnancy must take into account two separate but related issues: a) antiretroviral treatment of the woman's HIV infection and b) antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV-1 transmission. The benefits of antiretroviral therapy in a pregnant woman must be weighed against the risk for adverse events to the woman, fetus, and newborn. Although ZDV chemoprophylaxis alone has substantially reduced the risk for perinatal transmission, when considering treatment of pregnant women with HIV infection, antiretroviral monotherapy is now considered suboptimal for treatment; combination drug therapy is the current standard of care *(14)*. This report a) reviews the special considerations regarding the use of antiretroviral drugs in pregnant women, b) updates the results of PACTG 076 and related clinical trials and epidemiologic studies, c) discusses the use of HIV-1 RNA assays during pregnancy, d) provides updated recommendations on antiretroviral chemoprophylaxis for reducing perinatal transmission, and e) 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. The 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 ZDV, access to facilities for safe intravenous infusions among pregnant women during labor, and alternative interventions that may be 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, generally consisting of two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor, is the currently 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, including a) potential 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 many antiretroviral drugs. The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussing the known and unknown benefits and risks to her and her fetus with her health-care provider.

Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby 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 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 about the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Minimal data are available regarding the pharmacokinetics and safety of antiretrovirals other than ZDV during pregnancy. In the absence of data, 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 *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, many drugs commonly used to treat HIV-1 related illnesses may have positive findings on one or more of these screening tests. For example, acyclovir is positive on some *in vitro* carcinogenicity and clastogenicity assays and is associated with some 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).

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

TABLE 2. Preclinical and clinical data relevant to the use of antiretrovirals in pregnancy (see Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy for more detail on drugs)

Antiretroviral drug	Food and Drug Administration (FDA) pregnancy category †	Placental passage (newborn: mother drug ratio)	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside analogue reverse transcriptase inhibitors				
Zidovudine (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent-near lethal dose)
Zalcitabine (HIVID, ddC)	C	Yes (rhesus monkey) [0.30-0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent-hydrocephalus at high dose)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Not completed	Negative (but sternal bone calcium decreases in rodents)
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
Abacavir (Ziagen, ABC)	C	Yes (rats)	Not completed	Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine (Viramune)	C	Yes (human) [~1.0]	Not completed	Negative
Delavirdine (Rescriptor)	C	Unknown	Not completed	Positive (rodent-ventricular septal defect)
Efavirenz (Sustiva)	C	Yes (cynomologus monkey, rat, rabbit) [~1.0]	Not completed	Positive (cynomologus monkey-anencephaly, anophthalmia, microophthalmia)

TABLE 2. Preclinical and clinical data relevant to the use of antiretrovirals in pregnancy - Continued

Protease inhibitors				
Indinavir (Crixivan)	C	Yes (rats, rabbits) [substantial in rats, low in rabbits]	Not completed	Negative (but extra ribs in rodents)
Ritonavir (Norvir)	B	Yes (rats) [mid-term fetus, 1.15; late-term fetus, 0.15-0.64]	Positive (rodent, liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (rats, rabbits)	Not completed	Negative
Nelfinavir (Viracept)	B	Unknown	Not completed	Negative
Amprenavir (Agenerase)	C	Unknown	Not Completed	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Lopinavir/Ritonavir (Kaletra)	C	Unknown	Not Completed	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)

† FDA 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 there is no evidence of risk during later trimesters);

B Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and 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 based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

X Studies in 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.

Combination Antiretroviral Therapy and Pregnancy Outcome

There are limited data concerning combination antiretroviral therapy in pregnancy. A retrospective Swiss report evaluated the pregnancy outcome in 37 HIV-infected pregnant women treated with combination therapy; all received two reverse transcriptase inhibitors and 16 received one or two protease inhibitors *(20)*. Almost 80 percent of women developed 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 pre-term births was noted, as 10 of 30 babies were born prematurely. The pre-term birth rate did not differ between women receiving combination therapy with or without protease inhibitors. The contribution of maternal HIV disease stage and other covariates that might be associated with a risk for prematurity were not assessed. Furthermore, some studies have shown elevated pre-term birth rates in HIV-infected women who have not received any antiretroviral therapy *(21-23)*. To evaluate the baseline rates of adverse pregnancy outcome and risk factors for such outcomes in HIV-infected pregnant women, a meta-analysis of multiple PACTG perinatal trials and cohort studies is in progress. Preliminary analyses do not indicate an elevated risk of pre-term delivery among infants born to women receiving combination antiretroviral therapy with or without protease inhibitors compared to those receiving single drug or no antiretroviral therapy. Until more information is known, it is recommended that HIV-infected pregnant women who are receiving combination therapy for treatment of their HIV infection should continue their provider-recommended regimen. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

Protease Inhibitor Therapy and Hyperglycemia

Hyperglycemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with administration of protease inhibitor antiretroviral drugs in HIV-infected patients *(24-27)*. In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycemia. Clinicians caring for HIV-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 hyperglycemia should be discussed with pregnant women who are receiving protease inhibitors.

Mitochondrial Toxicity and Nucleoside Analogue Drugs

Nucleoside analogue drugs are known to induce mitochondrial dysfunction, as the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction *(28)*. 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), lamivudine (3TC), ZDV and abacavir (ABC) *(29)*. Toxicity related to mitochondrial dysfunction has been reported in infected patients receiving long-term treatment with nucleoside analogues, and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested *(28)*. These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to nucleoside analogue drugs.

Issues in 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 *(30)*. These syndromes have similarities to the rare but life-threatening syndromes of acute fatty liver of pregnancy and hemolysis, elevated liver enzymes and low platelets (the HELLP syndrome) that occur during the third trimester of pregnancy. A number of 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 *(31-33)*. Since the mother would be a heterozygotic carrier of the abnormal gene, there may be an increased risk of liver toxicity due to an inability to properly oxidize both maternal and accumulating fetal fatty acids *(34)*. Additionally, animal studies show that in late gestation pregnant mice have significant reductions (25%-50%) in mitochondrial fatty acid oxidation and that exogeneously administered estradiol and progesterone can reproduce these effects *(35, 36)*; 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 etiology 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 analogue drugs that is thought to be related to mitochondrial toxicity; it has been reported in infected individuals treated with nucleoside analogue drugs for long periods of time (>6 months). Initially, most cases were associated with ZDV, but subsequently other nucleoside analogue drugs have been associated with the syndrome, particularly d4T. In a report from the FDA Spontaneous Adverse Event Program of 106 individuals with this syndrome (60 patients receiving combination and 46 receiving single nucleoside analogue therapy), typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness *(30)*. Metabolic acidosis with elevated serum lactate and elevated hepatic enzymes was common. Patients in this report were predominantly female gender and high body weight. The incidence of this syndrome may be increasing, possibly due to increased use of combination nucleoside analogue therapy or increased recognition of the syndrome. In a cohort of infected patients receiving nucleoside analogue therapy followed at Johns Hopkins University between 1989-1994, the incidence of the hepatic steatosis syndrome was 0.13% per year *(37)*. However, in a report from a cohort of 964 HIV-infected individuals followed in France between 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 *(38)*.

The frequency of this syndrome in pregnant HIV-infected women receiving nucleoside analogue 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 who presented with symptoms and fetal demise at 38 weeks gestation *(39)*. Bristol-Myers Squibb has reported 3 maternal deaths due to lactic acidosis, 2 with and 1 without accompanying pancreatitis, in 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) *(40)*. All cases were in women who 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 demise.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome reported in non-pregnant individuals receiving nucleoside analogue treatment. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other significant disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving nucleoside analogue drugs to be alert for early diagnosis of this syndrome. Pregnant women receiving nucleoside analogue 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-infected pregnant women, clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analogue drug combinations have failed or caused unacceptable toxicity or side effects.

Issues with *in utero* exposure

A French group reported eight cases of uninfected infants with *in utero* and/or neonatal exposure to either ZDV/3TC (four infants) or ZDV alone (four infants) who developed indications of mitochondrial dysfunction after the first few months of life *(41)*. Two of these infants developed severe neurologic disease and died (both of whom had been exposed to ZDV/3TC), three had mild to moderate symptoms, and three had no symptoms but had transient laboratory abnormalities. It is important to note that an association between these findings and *in utero* exposure to antiretroviral drugs has not been established.

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 2 exposed to placebo, and one child in each group had reported spasticity; mortality at 18 months was 1.4% in ZDV-exposed compared to 3.5% in placebo infants *(42)*. In a large database that included 223 deaths in over 20,000 children with and without antiretroviral drug exposure who were born to HIV-infected women followed prospectively in several large cohorts in the United States, no deaths similar to those reported from France were identified *(43)*. 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. Evaluation is ongoing to determine if there is any evidence of mitochondrial dysfunction among any of the living children in these cohorts. Data have been reviewed relating to neurologic adverse events in 1,798 children that participated in PETRA, an African perinatal trial that compared three regimens of ZDV/3TC (before, during and one week postpartum; during labor and postpartum; and during labor only) to placebo for prevention of transmission. No increased risk of neurologic events was observed among children treated with ZDV/3TC compared to placebo, regardless of the intensity of treatment *(44)*. Echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life in 382 uninfected infants born to HIV-infected women; 9% of infants had been exposed to ZDV prenatally *(45)*. No significant differences in ventricular function were observed between infants exposed and unexposed to ZDV.

If the association of mitochondrial dysfunction and *in utero* antiretroviral exposures proves to be real, the development of severe or fatal mitochondrial disease in these infants appears to be extremely rare, and should be compared to the clear benefit of ZDV in reducing transmission of a fatal infection by nearly 70% *(46)*. These data 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

It is strongly recommended that health care providers who are treating HIV-1-infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry is an epidemiological project to collect observational, nonexperimental data on antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtains birth outcome follow-up from the reporting physician. Referrals should be directed to Antiretroviral Pregnancy Registry, 1410 Commonwealth Drive, Wilmington, NC 28403; telephone (800)-258-4263; fax (800) 800-1052.

Update on PACTG 076 Results and Other Studies Relevant to ZDV Chemoprophylaxis of 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 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 *(47)*.

The mechanism by which ZDV reduced transmission in PACTG 076 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 be a substantial component of 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 *(48, 49)*, 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 analogues that have been evaluated (i.e., ddI and ddC) *(50, 51)*. The presence of ZDV-resistant virus was not necessarily associated with failure to prevent transmission. In a preliminary evaluation of genotypic resistance in pregnant women in PACTG 076, ZDV-resistant virus was present at delivery in only one of seven women who had transmitted virus to their newborns, had received ZDV, and had samples that could be evaluated; this woman had ZDV-resistant virus when the study began despite having had no prior ZDV therapy *(52)*. Additionally, the one woman in this evaluation in whom the virus developed genotypic resistance to ZDV during the study period did not transmit HIV-1 to her infant.

In PACTG 076, similar rates of congenital abnormalities occurred in 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 *(53)* Data for uninfected infants from PACTG 076 followed from birth to a median age of 4.2 years (range 3.2-5.6 years) have not indicated any differences in growth, neurodevelopment, or immunologic status among infants born to mothers who received ZDV compared with those born to mothers who received placebo *(54)*. No malignancies have been observed in short-term (i.e., up to six years of age) follow-up of more than 727 infants from PACTG 076 and from a prospective cohort study involving infants with *in utero* ZDV exposure *(55)*. However, follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Long-term follow-up 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 effect of temporary administration of ZDV during pregnancy to reduce perinatal transmission on the induction of viral resistance to ZDV and long-term maternal health requires further evaluation. Data from an analysis of PACTG 288 (a study that followed women enrolled in PACTG 076 postpartum; median follow-up, 4.2 years) indicate no substantial differences in CD4+ T-cell lymphocyte count, time to progression to AIDS, or death in women who received ZDV compared with those who received placebo *(56)*. Limited data regarding the development of genotypic ZDV-resistance mutations (i.e., codons 70 and/or 215) are available from a subset of women in PACTG 076 who received ZDV *(52)*. Virus from one (3%) of 36 women receiving ZDV with paired isolates from the time of study enrollment and the time of delivery developed a ZDV genotypic resistance mutation. However, the population of women in PACTG 076 had low HIV-1 RNA copy numbers, and although the risk for inducing resistance with administration of ZDV chemoprophylaxis alone for several months during pregnancy was low in this substudy, it would likely be higher in a population of women with more advanced disease and higher levels of viral replication.

The efficacy of ZDV chemoprophylaxis for reducing HIV transmission among populations of infected women with characteristics unlike those of the PACTG 076 population has been evaluated in another perinatal protocol (i.e., PACTG 185) and in prospective cohort studies. PACTG 185 enrolled pregnant women with advanced HIV-1 disease and low CD4+ T-lymphocyte counts who were receiving antiretroviral therapy; 24% had received ZDV before the current pregnancy *(57)*. 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 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 combined group transmission rate was only 4.8% and did not substantially differ by whether the women received HIVIG or IVIG or by duration of ZDV use *(57)*. 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, 57)*.

International Antiretroviral Prophylaxis Clinical Trials

In a short-course antenatal/intrapartum ZDV perinatal transmission prophylaxis trial in non-breastfeeding women in Thailand, administration of ZDV 300 mg twice daily for four weeks antenatally and 300 mg every three hours orally during labor was shown to reduce perinatal transmission by approximately 50% compared to placebo *(58)*. Transmission decreased from 19% in the placebo group to 9% in the ZDV group. A second, four-arm factorial design trial in Thailand is comparing administration of ZDV antenatally starting at 28 or 36 weeks gestation, orally intrapartum, and to the neonate for three days or six weeks. At an interim analysis, the transmission rate was 10% in the arm receiving ZDV antenatally starting at 36 weeks and postnatally for three days to the infant, which was significantly higher than for the long-long arm (antenatal starting at 28 weeks and infant administration for six weeks) *(59).* The transmission rate in the short-short arm of this study was similar to the 9% observed with short antenatal/intrapartum ZDV in the first Thai study.

A third trial in Africa (PETRA trial) in breastfeeding HIV-infected women has shown that a combination regimen of ZDV and 3TC administered starting at 36 weeks gestation, orally intrapartum, and for one week postpartum to the woman and infant reduced transmission by approximately 50% compared to placebo at age six weeks *(60).* Transmission at age six weeks was decreased from 17% in the placebo group to 9% 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 *(58).*

Studies have identified two possible intrapartum/postpartum regimens (either ZDV/3TC or nevirapine) that could provide an effective intrapartum/postpartum intervention for those women in whom the diagnosis of HIV is not made until very near to or during labor. The PETRA African ZDV/3TC trial in breastfeeding HIV-infected women also demonstrated that an intrapartum/postpartum regimen, started during labor and continued for one week postpartum in the woman and infant, reduced transmission at age six weeks from 17% in the placebo group to 11% with the two-part ZDV/3TC regimen, a reduction of 38% *(60).* In this trial, oral ZDV/3TC administered solely during the intrapartum period was not effective in lowering transmission. Another study in Uganda, 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 48-72 hours of age reduced transmission by nearly 50% compared to a very short regimen of ZDV given orally during labor and to the infant for one week *(61).* Transmission at age six weeks was 12% in the nevirapine compared to 21% in the ZDV group.

No studies have evaluated the use of postpartum antiretroviral prophylaxis alone. Although some epidemiological data do not support efficacy of postnatal ZDV alone, other data indicate that there may be some efficacy if drug is started rapidly following birth *(6, 62, 63).* In a study from North Carolina, the rate of infection in HIV-exposed infants who received only postpartum ZDV chemoprophylaxis was similar to that observed in infants who received no ZDV chemoprophylaxis *(6)*. However, another epidemiological study from New York State, found that administration of ZDV to the neonate for six 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) *(62, 63).* Consistent with a possible preventive effect of rapid postexposure prophylaxis, a retrospective case-control study of health care workers from the United States, France, and the United Kingdom who had nosocomial exposure to HIV-1-infected blood, found that postexposure use of ZDV was associated with reduced odds of contracting HIV-1 (adjusted odds ratio 0.2; 95% CI [CI]=0.1-0.6) *(64).*

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 (e.g., every three to four months or approximately once each trimester). Whether increased frequency of testing is needed during pregnancy is unclear and requires further study. 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 few prospective cohort studies. In one cohort of 198 HIV-1 infected women, plasma HIV-1 RNA levels were higher at six months postpartum than during antepartum in many women; this increase was observed in women regardless of ZDV use during and after pregnancy *(65)*.

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 *(66).* 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 *(65, 67, 68)*. 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 *(47)*. 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 *(47, 69).*

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 antiretroviral treated women *(58, 70-72).* Although the risk of 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 in women with all levels of maternal HIV-1 RNA. Additionally, while HIV-1 RNA may be an important risk factor for transmission, other factors also appear to play a role *(72-74).*

While there is a general correlation between plasma and genital tract viral load, discordance has also been reported, particularly between HIV proviral load in blood and genital secretions *(75-78).* If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, then plasma HIV-1 RNA levels may not always be an accurate indicator of risk. Long-term changes in one compartment (e.g., such as may occur with antiretroviral treatment) may or may not be associated with comparable changes in other select body compartments. Further studies are needed to better define the effect of antiretroviral drugs on genital tract viral load and the association of such effects on the risk of perinatal HIV transmission. In the short-course ZDV Thailand trial, plasma and cervicovaginal HIV-1 RNA levels were reduced by ZDV treatment and each independently correlated with perinatal transmission *(79)*. The use of the full ZDV chemoprophylaxis regimen, including intravenous ZDV during delivery and the administration of ZDV to the infant for the first six weeks of life, alone or in combination with other antiretrovirals, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level.

Whether lowering maternal HIV-1 RNA copy number during pregnancy could reduce the risk for perinatal transmission has not been determined. In one study of 44 HIV-1 infected pregnant women, ZDV was effective in reducing transmission despite minimal effect on HIV-1 RNA levels *(80)*. These results are similar to those observed in PACTG 076 *(47)*. Thus, while determination of HIV-1 RNA copy number is important for decisions related to treatment, because ZDV decreases transmission regardless of maternal HIV-1 RNA level and because transmission may occur when HIV-1 RNA is not detectable, HIV-1 RNA levels should not be the determining factor when deciding whether to use ZDV for chemoprophylaxis. However, it is not known whether an antiretroviral regimen that more substantially suppresses viral replication would be associated with enhanced efficacy in reducing the risk for transmission. Recent epidemiological data suggest that women receiving highly active antiretroviral regimens that effectively reduce viral load may have very low rates of perinatal transmission *(81, 82).*

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

Many women infected with HIV (nearly 60% in some centers) enter pregnancy with a known diagnosis, and nearly half of these women enter the 1st trimester of pregnancy receiving treatment with single or multiagent antiretroviral therapy. Additionally, as many as forty percent of women who have initiated antiretroviral therapy pre-pregnancy, may require adjustment of their therapeutic regimen during their pregnancy course *(83)*.

The American College of Obstetrics and Gynecology advocates extending to all women of childbearing age the opportunity to receive preconceptional counseling as a component of routine primary medical care. It is recognized that unintended pregnancy may occur in > 40% of pregnancies, and that the diagnosis of pregnancy most frequently occurs late in the 1st trimester when organogenesis is nearly completed. The purpose of preconceptional care is to identify risk factors for adverse maternal or fetal outcome (e.g., age, diabetes, hypertension, etc.), provide education and counseling targeted to the patient's individual needs, and treat or stabilize medical conditions prior to conception in order to optimize maternal and fetal outcomes *(84)*.

For women with HIV infection, preconceptional 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.

Recommended components of preconceptional counseling for HIV-infected women include:

- Selection of effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy.
- Education and counseling about perinatal transmission risks and strategies to reduce those risks, and potential effects of HIV or treatment on pregnancy course and outcomes.
- Initiation or modification of antiretroviral therapy prior to conception in order to:
  - Avoid agents with potential reproductive toxicity for the developing fetus (e.g. efaverenz, hydroxyurea). *See Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy
  - Choose agents effective in reducing the risk of perinatal HIV 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 for opportunistic infections and initiate appropriate prophylaxis, and administration of medical immunizations (e.g. influenza, pneumovax, or hepatitis B) as indicated.
- Optimization of maternal nutritional status.
- Institution of the standard recommendations for preconception evaluation and management (e.g. assessment of reproductive and familial genetic history, screening for infectious diseases/STD's and initiation of folic acid supplementation).
- Screening for maternal psychological and substance abuse disorders.
- Planning for perinatal consultation if desired or indicated.

HIV-infected women of childbearing potential engage primary health care services in a variety of 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 preconceptional counseling an integral component of comprehensive primary health care for improving maternal-child health outcomes.

GENERAL PRINCIPLES REGARDING THE USE OF ANTIRETROVIRALS 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 the use of antiretroviral drugs during pregnancy should be made by the woman after discussion with her healthcare 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 antiretroviral regimen. This assessment should include 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 antiretrovirals, decisions regarding alterations in therapy should involve the same parameters as those used for women who are not pregnant. Additionally, use of the three-part ZDV chemoprophylaxis regimen, alone or in combination with other antiretrovirals, should be discussed with and offered to all infected pregnant women to reduce the risk for perinatal HIV 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 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 is recommended in terms of treatment for the health of the HIV-1 infected woman; and c) the efficacy of ZDV for reduction of perinatal HIV transmission. Results from preclinical and animal studies and available clinical information about the use of the various antiretroviral agents during pregnancy also should be discussed. The hypothetical risks of these drugs during pregnancy should be placed in perspective to 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 the use of antiretroviral drugs is the responsibility of the woman. Decisions regarding use and choice of antiretroviral drugs in 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 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 who therefore, following 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. Such discussions 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 specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to assist the infected woman in ensuring adherence to antiretroviral treatment regimens.

General counseling should include information regarding what is known about 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 *(85-89)*, and discontinuing these practices may provide nonpharmacologic interventions that might reduce this risk. In addition, PHS 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, 90)*; 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. Both the efficacy of antiretroviral therapy for the prevention of postnatal transmission of HIV-1 through breast milk and the toxicity of chronic antiretroviral exposure of the infant via breast milk are unknown.

RECOMMENDATIONS FOR ANTIRETROVIRAL CHEMOPROPHYLAXIS TO REDUCE PERINATAL HIV TRANSMISSION

The following recommendations for the use of antiretroviral chemoprophylaxis to reduce the risk for perinatal transmission are based on various scenarios that may be commonly encountered in clinical practice (Table 3), with relevant considerations highlighted in the subsequent discussion sections. These scenarios present only recommendations, and flexibility should be exercised according to the patient's individual circumstances. In the 1994 recommendations *(2)*, six clinical scenarios were delineated based on maternal CD4+ count, gestational age, 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 scenarios by CD4+ count and prior ZDV use are not presented. Additionally, because current data indicate most transmission occurs near the time of or during delivery, ZDV chemoprophylaxis is recommended regardless of gestational age; thus, clinical scenarios by gestational age 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 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 *(91-93)*. Comparable clinical response also has been observed in some clinical trials among persons receiving ZDV twice daily *(94-96)*. 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 enhance maternal adherence.

The recommended ZDV dosage for infants was derived from pharmacokinetic studies performed among full-term infants *(97)*. 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 in clearance may be expected. In a study of 15 premature infants who were 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 *(98)*. 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. Appropriate ZDV dosing for premature infants has not been defined but is being evaluated in a phase I clinical trial in premature infants <34 weeks' gestation. The dosing regimen being studied is 1.5 mg/kg body weight orally or intravenously every 12 hours for the first two weeks of life; for infants aged two to six weeks, the dose is increased to 2 mg/kg body weight every eight hours.

Because subtherapeutic dosing of antiretroviral drugs may be associated with enhanced likelihood for the development of drug resistance, women who must temporarily discontinue therapy because of pregnancy-related hyperemesis should not reinstitute 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.

ANTIRETROVIRAL CLINICAL SCENARIOS

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

Recommendation

Pregnant women with HIV 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, should be recommended for all pregnant women with HIV 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 infection is recommended for infected women whose clinical, immunologic or virologic status requires treatment or who have HIV RNA over 1,000 copies/mL regardless of clinical or immunologic status. 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%. The mechanism by which ZDV reduces transmission is not known. However, protection is likely multifactorial. Pre-exposure prophylaxis of the infant is provided by passage of ZDV across the placenta. Thus, inhibitory levels of the drug are present in the fetus during the birth process. While placental passage of ZDV is excellent, other antiretroviral drugs have variable transplacental passage (Table 2). Therefore, when combination antiretroviral therapy is initiated during pregnancy, ZDV should be included as a component of antenatal therapy whenever possible. Since the mechanism by which ZDV reduces transmission is not known, the intrapartum and newborn ZDV parts of the chemoprophylactic regimen should be administered to reduce perinatal HIV transmission. If a woman does not receive ZDV as a component of her antenatal antiretroviral regimen, intrapartum and newborn ZDV should continue to be recommended.

Women should be counseled 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 women with low or undetectable HIV-1 RNA levels (e.g. <1,000 copies/mL) have extremely low rates of perinatal transmission, particularly when antiretroviral therapy has been received *(70, 71, 81)*. 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 is unknown. Decisions regarding the use and choice of an antiretroviral regimen should be individualized based on discussion with the woman about a) her risk for disease progression and the risks and benefits of delaying initiation of therapy; b) possible benefit of lowering viral load for reducing perinatal transmission; c) potential drug

TABLE 3. Clinical scenarios and recommendations for the use of antiretroviral drugs to reduce perinatal human immunodeficiency virus (HIV) transmission.

Clinical scenario	Recommendations*
Scenario #1 HIV-infected pregnant women who have not received prior antiretroviral therapy.	Pregnant women with HIV 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, should be recommended for all pregnant women with HIV 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 infection is recommended for infected women whose clinical, immunologic or virologic status requires treatment or who have HIV RNA over 1,000 copies/mL regardless of clinical or immunologic status. Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' gestation.
Scenario #2 HIV-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. Recommendations for resistance testing in HIV-infected pregnant women are the same as for non-pregnant patients: acute HIV infection and virologic failure or suboptimal viral suppression after initiation of antiretroviral therapy.

TABLE 3. Clinical scenarios and recommendations for the use of antiretroviral drugs to reduce perinatal human immunodeficiency virus (HIV) transmission - Continued

Clinical scenario	Recommendations*
Scenario #3 HIV-infected women in labor who have had no prior therapy.	Several effective regimens are available (Table 4). These include: 1) single dose nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours; 2) oral ZDV and 3TC during labor, followed by one week of oral ZDV/3TC for the newborn; 3) intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn; 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 is unknown, and appropriate dosing regimens for neonates are incompletely defined. 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.

* 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.

toxicities and interactions with other drugs; d) the need for strict adherence to the prescribed drug schedule to avoid the development of drug resistance; e) unknown long-term effects of in utero drug exposure on the infant; and f) pre-clinical, animal, and clinical data relevant to use of the currently available antiretrovirals during pregnancy**.** Due to the evolving and complex nature of the management of HIV-1 infection, a specialist with experience in the treatment of pregnant women with HIV infection should be involved in their care.

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 who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10-12 weeks' gestation. This decision should be carefully considered and discussed between the health-care provider and the patient; such a discussion should include an assessment of the woman's health status and the benefits and risks of delaying initiation of therapy for several weeks, and the knowledge 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. Hydroxyurea is a potent teratogen in a variety of animal species and should also be avoided during the first trimester (Table 2 and see **SAFETY AND TOXICITY OF INDIVIDUAL ANTIRETROVIRAL DRUGS IN PREGNANCY**).

When initiation of antiretroviral therapy would be considered optional based on current guidelines for treatment of non-pregnant individuals *(14)*, infected pregnant women should be counseled regarding the potential benefits of standard combination therapy 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 below 1,000 copies/mL may substantially lower the risk of perinatal HIV-1 transmission and limit 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 non-pregnant adults *(14)*. Dual nucleoside analogue therapy without the addition of either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor is not recommended due to the potential for inadequate viral suppression and rapid development of resistance *(99)*. If combination therapy is given principally to reduce perinatal transmission and would have been optional for treatment of non-pregnant individuals, consideration may be given to discontinuing therapy postnatally, with the decision to reinitiate treatment based on standard criteria for non-pregnant individuals. If drugs are discontinued postnatally, all drugs should be stopped simultaneously. Discussion regarding the decision to continue or stop combination therapy postpartum should occur prior to initiation of therapy during pregnancy.

Use of antiretroviral prophylaxis has been shown to provide benefit 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 who had infected infants despite having 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 to 9.8% among those receiving no antenatal therapy *(100)*. Therefore, use of antiretroviral prophylaxis is recommended for all pregnant women with HIV infection regardless of antenatal HIV RNA level.

The time-limited use of ZDV alone during pregnancy for chemoprophylaxis of perinatal transmission is controversial. The potential benefits of standard combination antiretroviral regimens for treatment of HIV infection should be discussed with and offered to all pregnant women with HIV infection regardless of viral load, and is recommended for all pregnant women with HIV-1 RNA levels ≥1,000 copies/mL. However, some women may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy but still wish to reduce the risk of transmitting HIV to their infant. 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 due to the limited viral replication existing 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 *(52)*. The use of ZDV chemoprophylaxis alone during pregnancy might be an appropriate option for these women.

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

Recommendation

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. Recommendations for resistance testing in HIV-infected pregnant women are the same as for non-pregnant patients: acute HIV infection and virologic failure or suboptimal viral suppression after initiation of antiretroviral therapy.

Discussion

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

ZDV should be a component of the antenatal antiretroviral treatment whenever possible. However, there may be circumstances where this is not feasible, such as the occurrence of significant ZDV-related toxicity. 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 *(81)*, 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 to the pregnant woman during the intrapartum period whenever feasible. Because ZDV and d4T should not be administered together due to potential pharmacologic antagonsim, options for women receiving oral d4T as part of their antenatal therapy include 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 (e.g., above 1,000 copies/mL) near the time of delivery despite prenatal receipt of ZDV prophylaxis and/or combination antiretroviral therapy, there are currently no data to demonstrate that administration of additional antiretroviral drugs during labor and delivery provides added protection against perinatal transmission. In the HIVNET 012 study in Ugandan women without antenatal antiretroviral therapy, a two-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 to a ultra-short intrapartum/1 week postpartum ZDV regimen *(61)*. In women in the United States, Europe, Brazil and the Bahamas who are receiving antenatal antiretroviral therapy, PACTG 316 is evaluating the addition of the same two-dose intrapartum/postpartum nevirapine regimen to standard therapy compared to the addition of a nevirapine placebo. Final results of PACTG 316 are anticipated in early 2001, but due to an unexpectedly low overall transmission rate, the study will have limited power to address whether nevirapine provides any additional benefit for reducing transmission in women who have received antenatal therapy.

Selection of nevirapine-resistant virus was found at 6 weeks postpartum in pregnant women receiving a single dose of nevirapine during labor. In HIVNET 012, where drugs other than nevirapine were not given, 7 of 31 women (23%) evaluated.developed genotypic resistance mutations at 6 weeks postpartum; these mutations were no longer present in 4 women studied at 13-18 months postpartum *(101, 102)*. In the antiretroviral-treated women in PACTG 316, 4 of 32 women (13%, 95% CI 4-25%) with HIV-1 RNA above 3,000 copies/mL at delivery who received nevirapine developed genotypic nevirapine resistance mutations compared to none of 38 women in the placebo arm *(103)*.

The duration that nevirapine-resistant mutations persist following the removal of the selective pressure induced by the single dose of nevirapine in women with and without antenatal antiretroviral treatment remains unclear. The clinical implications of these findings for future maternal treatment options, especially among women with access to standard combination antiretroviral therapies, remain unknown at present. If the addition of the two-dose nevirapine regimen to existing antiretroviral therapy is considered for a woman currently receiving treatment, the potential implications for future maternal therapy and the unproven benefit in further reducing transmission need to be weighed very carefully and discussed with the woman. Guidelines on decisions related to obstetric interventions to reduce perinatal transmission in antiretroviral-treated women with suboptimal virologic suppression near the time of delivery are outlined in the “Perinatal HIV-1 Transmission and Mode of Delivery” section of this document.

The impact of prior antiretroviral exposure on the efficacy of ZDV chemoprophylaxis is unclear. Data from PACTG 185 indicate that duration of prior ZDV therapy in women with advanced HIV-1 disease, many of whom received prolonged ZDV before pregnancy, was not associated with diminished ZDV efficacy for reduction of transmission *(57)*. Perinatal transmission rates were similar for women who first initiated ZDV during pregnancy and women who had received ZDV prior to pregnancy. Thus, a history of ZDV therapy before the current pregnancy should not limit recommendations for administration of ZDV chemoprophylaxis to reduce perinatal HIV-1 transmission.

Some clinicians have recommended antiretroviral drug resistance testing for all pregnant women, although this is controversial *(104)*. Although perinatal transmission of ZDV-resistant virus has been reported, it is unclear if the presence of genotypic drug resistance mutations increase the risk of transmission, and the utility of resistance testing in pregnant women receiving antitretroviral treatment who have successful virologic control is minimal. In PACTG

076, the prevalence and incidence of ZDV resistance was low (3%) and the presence of resistance did not correlate with transmission *(52)*. However, in a cohort of women with more advanced disease who were receiving antenatal monotherapy with ZDV between 1989-1994 (prior to the results of PACTG 076), the prevalence of ZDV resistance was 24%; in multivariate analysis, the presence of ZDV drug resistance was associated with perinatal transmission *(105)*. Drug-resistant virus may have decreased fitness in terms of perinatal transmission; in a study of the preceding cohort of women that evaluated transmitting mother/infant pairs, only wild-type virus was transmitted to infected infants born to infected women with mixed populations of wild type and low level ZDV resistant virus *(106)*. In a Swiss study in of 62 HIV-infected women, 10% had virus with high level ZDV resistance, but none of the women transmitted HIV-1 to their infant despite receiving only ZDV prophylaxis *(107)*. Antiretroviral resistance testing is expensive, difficult to interpret, and data to support its routine use in pregnancy outside of standard indications in non-pregnant individuals is currently lacking. Further, if a woman's therapeutic regimen is successful (e.g., HIV-1RNA is reduced to <1,000 copies/mL) it both suggests that resistance has not occurred and that transmission will be very unlikely regardless of the results of resistance testing. Therefore, at present, recommendations for resistance testing in HIV-infected pregnant women are the same as for non-pregnant patients: acute HIV infection and virologic failure or suboptimal viral suppression after initiation of antiretroviral therapy *(14)*.

Some women receiving antiretroviral therapy may realize they are pregnant early in gestation, and concern for potential teratogenicity may lead some to consider temporarily stopping antiretroviral treatment until after the first trimester. 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 more of 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 and discussed between the clinician and the pregnant woman. Such considerations include 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 transient discontinuation of therapy is harmful for the woman and/or fetus.

Some health-care providers might consider administration of ZDV in combination with other antiretroviral drugs to newborns of women with a history of prior antiretroviral therapy—particularly in situations where 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. However, the efficacy of this approach is not known. The appropriate dose and short- and long-term safety for most antiretroviral agents other than ZDV are not defined for neonates. The half-lives of ZDV, 3TC, and nevirapine are prolonged during the neonatal period as a result of immature liver metabolism and renal function, requiring specific dosing adjustments when these antiretrovirals are administered to neonates. Data regarding the pharmacokinetics of other antiretroviral drugs in neonates are not yet available, although phase I neonatal studies of several other antiretrovirals are ongoing. The infected woman should be counseled regarding the theoretical benefit of combination antiretroviral drugs for the neonate, the potential risks, and what is known about appropriate dosing of the drugs in newborn infants. She should also be informed that use of antiretroviral drugs in addition to ZDV for newborn prophylaxis is of unknown efficacy for reducing risk for perinatal transmission.

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

Recommendation

Several effective regimens are available (Table 4). These include: 1) single dose nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours; 2) oral ZDV and 3TC during labor, followed by one week of oral ZDV/3TC for the newborn; 3) intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn; 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.

Discussion

While intrapartum antiretroviral drug medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to the time of or during labor and delivery. Pre-exposure prophylaxis can be provided by administration of a drug to the mother that rapidly crosses the placenta to produce systemic antiretroviral drug levels in the fetus during intensive exposure to HIV in maternal genital secretions and blood during birth.

Several intrapartum/neonatal antiretroviral prophylaxis regimens are applicable for women in labor who have had no prior antiretroviral therapy (Table 4). Two regimens, one using a two-dose regimen of nevirapine and the other a combination ZDV and 3TC regimen, were shown to reduce perinatal transmission in randomized clinical trials in breastfeeding settings, while available epidemiologic data suggest efficacy of a third, ZDV-only regimen. The fourth regimen, combining ZDV with nevirapine, is based upon theoretical considerations.

In the HIVNET 012 trial, conducted in Uganda, a single dose of oral nevirapine given to women at the onset of labor and a single dose to the infant at age 48 hours was compared to oral ZDV given to the woman every three hours during labor and postnatally to the infant for seven days (Table 4). At age six weeks, the rates of transmission were 12% (95% CI 8-16%) in the nevirapine arm compared to 21% (95% CI, 16-26%) in the ZDV arm, a 47% reduction (95% CI, 20-64%) in transmission *(61)*. No significant short-term toxicity was observed in either group. Because there was no placebo group, no conclusions can be drawn regarding the efficacy of the intrapartum/one week neonatal ZDV regimen compared to no treatment.

In the PETRA trial, conducted in Uganda, South Africa and Tanzania, ZDV and 3TC were administered orally intrapartum and to the woman and infant for seven days postnatally. Oral ZDV and 3TC were given at the onset of labor and continued until delivery (Table 4). Postnatally, the woman and infant received ZDV and 3TC every 12 hours for seven days. At age six weeks, the rates of transmission were 10% in the ZDV/3TC arm compared to 17% in the placebo arm, a 38% reduction in transmission *(60).* However, no differences in transmission were observed when oral ZDV and 3TC were administered only during the intrapartum period (transmission of 16% in the ZDV/3TC and 17% in the placebo arm), indicating that some post-exposure prophylaxis is needed, at least in breastfeeding settings.

Table 4. Comparison of Intrapartum/Postpartum Regimens for HIV-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
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* *If the mother received nevirapine less than one hour prior to delivery, the infant was given 2 mg/kg oral nevirapine as soon as possible after birth and again at 48-72 hours.	Transmission at six weeks 12% with nevirapine compared to 21% with ZDV, a 47% (95% CI, 20-64%) reduction	Inexpensive Oral regimen Simple, easy to administer Can give directly observed treatment	Unknown efficacy if mother has nevirapine-resistant virus
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 10% with ZDV/3TC compared to 17% with placebo, a 38% reduction	Oral regimen Compliance easier than six weeks of ZDV alone as infant regimen is only one week	Potential toxicity of multiple drug exposure
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% (95% CI, 19-82%) reduction	Has been standard recommendation before clinical trial results	Requires intravenous administration and availability of ZDV intravenous formulation Compliance with six week infant regimen
ZDV and 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 Compliance with six week infant ZDV regimen Unknown efficacy and limited toxicity data

These clinical trials were conducted in Africa, where the majority of women breastfeed their infants. Because HIV can be transmitted by breast milk and the highest risk period for such transmission is the first few months of life *(108),* the absolute transmission rates observed in the African trials may not be comparable to what might be observed with these regimens in HIV-infected women in the U.S., where breastfeeding is not recommended. However, comparison of the percent reduction in transmission at early timepoints (e.g., four to six weeks) may be applicable. In the effective arms of the PETRA trial, antiretrovirals were administered postnatally to the mother as well as the infant to reduce the risk of early breastmilk transmission. 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-infected women are advised not to breastfeed their infants (although ZDV/3TC might be indicated as part of a combination postnatal treatment regimen for the woman).

Epidemiologic data from New York State indicate that intravenous maternal intrapartum ZDV followed by oral ZDV for six weeks to the infant may significantly reduce transmission compared to no treatment (Table 4). Transmission rates were 10% (95% CI [CI], 3-22%) with intrapartum and neonatal ZDV compared to 27% (95% CI, 21-33%) in the absence of ZDV, a 62% reduction in risk (95% CI, 19-82%) *(62, 63).* Similarly, in epidemiologic study in North Carolina, intravenous intrapartum and six week oral neonatal ZDV treatment was associated with a transmission rate of 11%, compared to 31% without therapy *(6)*. However, intrapartum ZDV combined with very short postnatal infant ZDV administration, such as the one-week postnatal infant ZDV course in HIVNET 012 *(61)*, has not proven effective to date. This underscores the necessity of recommending a full six week course of infant treatment when ZDV alone is utilized.

There are currently no data to address the relative efficacy of these three intrapartum/neonatal antiretroviral regimens for prevention of transmission. There is overlap in the 95% CI for the two-dose nevirapine regimen and the maternal intravenous intrapartum/six week infant oral ZDV regimen. 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. The two-dose nevirapine regimen offers the advantage of lower cost, the possibility of directly observed therapy and increased adherence compared to the other two regimens. In South Africa, a clinical trial (SAINT) compared the two-dose nevirapine and the 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 *(109)*.

Whether combining intravenous intrapartum/six week neonatal oral ZDV with the two-dose nevirapine regimen will provide additional benefit over that observed with each regimen alone is unproven. Clinical trial data have clearly established that combination is superior to single drug therapy for treatment of established infection, although data to show superiority of combination treatment when used for prevention of transmission are not available. However, infants born to women in labor who have not received any antiretroviral therapy are at high risk for infection. The two-dose nevirapine regimen had no significant short-term drug-associated toxicity in the 313 mother-infant pairs exposed to the regimen in the HIVNET 012 trial. Nevirapine and ZDV are synergistic in inhibiting HIV replication *in vitro (110),* and both nevirapine and ZDV rapidly cross the placenta to achieve drug levels in the infant nearly equal to those in the mother. In contrast to ZDV, nevirapine can decrease plasma HIV-1 RNA concentration by at least 1.3 log by seven days after a single dose *(111)* and is active immediately against intracellular and extracellular virus *(112).* However, nevirapine resistance can be induced by a single mutation at codon 181, whereas high-level resistance to ZDV requires several mutations.

A theoretical benefit of combining the intrapartum/neonatal ZDV and nevirapine regimens includes potential efficacy if the woman had acquired infection with HIV that is resistant to either ZDV or nevirapine. Perinatal transmission of antiretroviral drug-resistant virus has been reported but appears to be unusual *(6, 52, 113, 114).* The prevalence of ZDV, nevirapine and other antiretroviral drug resistance among newly infected white homosexual men in the U.S. has varied between 2-16% depending on geographic area and the type of assay (e.g., genotypic or phenotypic) used *(114-117)*. Little data are available relative to the prevalence of drug resistant virus among untreated pregnant women. Mutations associated with ZDV resistance were detected in 19% and nevirapine resistance in 1% of women treated with ZDV during pregnancy between 1991 and 1997 in one study; however, resistant virus was no more likely to be transmitted than wild type virus *(118).* Virus with low level ZDV resistance may be less likely to establish infection than wild type, and transmission may not occur even when maternal virus has high level ZDV resistance *(106, 107, 114, 118).* Since the prevalence of drug-resistant virus is an evolving phenomenon, surveillance is needed to determine the prevalence of drug-resistant virus in pregnant women over time and the risk of transmission of resistant viral strains. The potential benefits of combination prophylaxis with intrapartum/neonatal nevirapine and ZDV must be weighed against the increased cost, possible adherence issues, potential short and long-term toxicity, and the lack of definitive data to show that the combination offers any additional benefit for prevention of transmission compared to use of either drug alone.

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

Recommendation

The 6-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 is unknown, and appropriate dosing regimens for neonates are incompletely defined. 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.

Discussion

Definitive data are not available to address whether ZDV administered solely during the neonatal period would reduce the risk for perinatal transmission. Epidemiologic data from a New York State study suggest a decline in transmission when infants were given zidovudine for the first 6 weeks of life compared to no prophylaxis *(62, 63)*. Transmission rates were 9% (95% CI, 4.1%-17.5%) for newborn only ZDV prophylaxis (initiated within 48 hours after birth) compared to 18% (95% CI, 7.7%-34.3%) when initiated after 48 hours and 27% (95% CI 21%-33%) with no ZDV prophylaxis *(62)*. Epidemiologic data from North Carolina did not demonstrate a benefit of newborn only ZDV compared to no prophylaxis *(6)*. Transmission rates were 27% (95%CI 8-55%) for newborn only prophylaxis and 31% (95%CI 24-39%) for no prophylaxis; the timing of infant prophylaxis initiation was not defined in this study. Data from a case-control study of postexposure prophylaxis of health-care workers who had nosocomial percutaneous exposure to blood from HIV-1 infected persons indicate that ZDV administration was associated with a 79% reduction in the risk for HIV-1 seroconversion following exposure *(64)*. Postexposure prophylaxis also has prevented retroviral infection in some studies involving animals *(119-121)*.

The interval for 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. Most infants initiated prophylaxis within 24 hours in this study *(63)*. Data from studies of animals indicate that the longer the delay in institution of prophylaxis, the less likely that prevention will be observed. In most studies of animals, antiretroviral prophylaxis initiated 24-36 hours after exposure usually is not effective for preventing infection, although later administration has been associated with decreased viremia *(119-121)*. 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 prevent infection *(122)*. The relevance of these animal studies to prevention of perinatal HIV transmission in humans is unknown. HIV-1 infection is established in most infected infants by age 1 to 2 weeks. Of 271 infected infants, HIV-1 DNA polymerase chain reaction (PCR) was positive in 38% of infected infants tested within 48 hours of birth. No substantial change in diagnostic sensitivity was observed within the first week of life, but detection rose rapidly during the second week of life, reaching 93% by age 14 days *(123)*. Initiation of postexposure prophylaxis after the age of 2 days is not likely to be efficacious in preventing transmission, and by 14 days of age infection would already be established in most infants.

When neither the antenatal nor intrapartum parts of the three-part ZDV regimen are received by the mother, 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 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.

PERINATAL HIV-1 TRANSMISSION AND MODE OF DELIVERY

Transmission and Mode of Delivery

Optimal medical management during pregnancy should include antiretroviral therapy to suppress plasma HIV RNA to undetectable levels. Labor and delivery management of HIV-infected pregnant women should focus on minimizing the risk for both perinatal transmission of HIV-1 and the potential for maternal and neonatal complications. In caring for the HIV-infected pregnant woman, she should be provided with the most complete and current information regarding use of antiretroviral therapy, mode of delivery, and other issues and allowed to make her own decisions. The woman's autonomy in decision making should be respected.

Several studies done before routine viral load testing and combination antiretroviral therapy consistently show that cesarean delivery performed before the onset of labor and rupture of membranes (elective or scheduled cesarean) was associated with a significant decrease in perinatal HIV-1 transmission compared to other types of delivery, with reductions ranging from 55-80%. Pertinent data on transmission rates according to receipt of ZDV or not are summarized in Table 5.

Table 5. Rate of perinatal transmission according to receipt of zidovudine during pregnancy and mode of delivery

		Transmission rate		
Study design (reference)	**Therapy**	**Elective CS**	**Other modes**	**Odds ratio(95% CI)**
Observational data *(124)*	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 *(125)*	No ZDV	2/51 (4%)	16/82 (20%)	0.20 (0-0.8)
	ZDV	1/119 (1%)	5/117 (4%)	0.20 (0- 1.7)

The observational data included individual patient data from 15 prospective cohort studies, including more than 7,800 mother-child pairs, analyzed in a meta-analysis *(124)*. In this meta-analysis, the rate of perinatal HIV-1 transmission in women undergoing elective cesarean delivery was significantly decreased compared to similar women having either non-elective cesarean or vaginal delivery, whether or not they received ZDV. In an international randomized trial of mode of delivery, transmission was 1.8% in women randomized to elective cesarean delivery; many of these women received ZDV *(125)*. While the magnitude of the reduction in transmission after elective cesarean section compared to vaginal delivery among women receiving ZDV in the randomized trial was similar to that seen in untreated women, this was not statistically significant. Additionally, in both studies non-elective cesarean delivery (performed after onset of labor and/or rupture of membranes) was not associated with a significant decrease in transmission compared to vaginal delivery. The American College of Obstetricians and Gynecologists' (ACOG) Committee on Obstetric Practice, after reviewing the data, has issued a Committee Opinion concerning route of delivery *(126)*.

Transmission, Viral Load, and Combination Antiretroviral Therapy

The studies above report on data from women not receiving combination antiretroviral therapy or undergoing routine viral load testing and which do not differentiate *in utero* from intrapartum transmission. Whether cesarean delivery offers any benefit to the infants of women receiving highly active combination antiretroviral regimens who have low or undetectable maternal HIV-1 RNA levels is unknown. Studies evaluating vertical transmission rates according to maternal HIV-1 RNA copy number have utilized a variety of assays with different lower limits of detection, and transmission has been reported even when maternal HIV-1 RNA levels were below assay quantification *(47, 67, 127, 128).* There does not appear to be a threshold of HIV RNA levels below which lack of transmission can be assured. Nevertheless, the upper limits of transmission based on the 95% CI of rates reported among women who have undetectable viral load in late pregnancy are similar to the observed rates of vertical transmission in women who receive ZDV and undergo elective cesarean delivery. Transmissions occurred among one (3.4%) of 29, 0 of 32, 0 of 107, and 0 of 198 women with undetectable viral load (500 copies/mL or less) late in pregnancy, 95% of whom were receiving at least ZDV with almost half receiving two or more antiretroviral agents *(70, 71, 129, 130)*. It is unlikely that scheduled cesarean delivery would further reduce this low transmission rate among treated women with undetectable viral loads nor would it prevent *in utero* transmission. Given the variability in quantification of HIV RNA levels at low copy numbers, the variety of lower limits of quantification of the tests, and the similarly low levels of perinatal transmission of HIV at levels below 1,000 copies/mL, ACOG has chosen 1,000 copies/mL as the threshold above which to recommend cesarean delivery as an adjunct for prevention of transmission *(126)*.

Similarly low vertical transmission rates have been observed among limited numbers of women receiving combination antiretroviral therapy during pregnancy. A few small published studies have shown transmission among one (6.7%) of 15, 0 of 30, and 0 of 24 women receiving two or more antiretroviral drugs in combination during pregnancy *(20, 82, 131)*. Additional studies in abstract form reported no transmissions among 153 women receiving highly active combination antiretroviral therapy, while others have reported transmission rates of 1% (two of 187) and 5.8% (three of 52 women) in women receiving triple therapy including a protease inhibitor *(81, 132, 133).* Whether the low transmission rates on combination therapy are due to reduction in HIV-1 RNA to very low or undetectable levels or due to some other mechanism (e.g., transplacental drug passage providing pre-exposure prophylaxis to the infant) is unknown, as HIV-1 RNA levels were not reported. Thus, current data are insufficient to adequately assess whether the impact of combination antiretroviral therapy on vertical transmission is independent from its effect on viral load.

Maternal Risks by Mode of Delivery

Maternal morbidity and mortality are greater after cesarean than vaginal delivery among women not infected with HIV. Complications, especially postpartum infections, are approximately five to seven times more common after cesarean section with labor or membrane rupture compared to vaginal delivery *(134, 135).* Complications after scheduled cesarean delivery are intermediate between those of vaginal delivery and urgent cesarean delivery *(136-140).* Factors that increase the risk of postoperative complications include low socioeconomic status, genital infections, obesity or malnutrition, smoking, and prolonged labor or membrane rupture.

Complications of cesarean delivery among HIV-infected women are similar in frequency and magnitude to those reported among HIV-uninfected women. In the European mode of delivery randomized trial, there were no major complications in either group *(125).* However, postpartum fever occurred in two (1.1%) of 183 women who delivered vaginally and 15 (6.7%) of 225 who delivered by cesarean section (p= 0.002). Substantial postpartum bleeding and anemia occurred at similar rates in the two groups. Among the 497 women enrolled to PACTG 185, only endometritis, wound infection, and pneumonia were increased among women delivered by scheduled or urgent cesarean section, compared to vaginal delivery *(141).* Complication rates were within the range previously reported among similar general obstetric populations. Finally, an analysis among nearly 1,200 women enrolled in the Women and Infants Transmission Study demonstrated a significantly increased rate of postpartum fever without documented source of infection among women undergoing elective cesarean section compared to spontaneous vaginal delivery, but hemorrhage, severe anemia, endometritis or urinary tract infections were not increased *(142).* In the latter two studies, cesareans without labor and ruptured membranes were done for obstetrical indications such as previous cesarean section or severe pre-eclampsia and not for prevention of HIV transmission, potentially resulting in higher complication rates than might be observed for scheduled cesarean section performed solely to reduce perinatal transmission.

In contrast to the larger cohort studies discussed above, three retrospective and one prospective case-control studies have suggested an increased risk of perioperative complications among HIV-infected compared to uninfected women delivering by cesarean section, often after labor or ruptured membranes *(143-146)*. In the three retrospective studies, the use of postpartum antibiotics was significantly more frequent among HIV-infected compared to HIV-uninfected women, although postpartum endometritis was significantly increased in only one of the three studies. Wound infection was more common among HIV-infected women in two of the studies. Pneumonia occurred only among HIV-infected women in all of the studies. In all three retrospective studies, complication rates were inversely related to CD4+ lymphocyte count or percentage.

The prospective study of 33 HIV-infected women and 168 matched control women again showed an increase in postpartum pneumonia in HIV-infected women undergoing cesarean delivery, but no increase in postpartum fever or blood transfusion *(146)*. More advanced clinical disease (CDC category B or C), but not CD4+ lymphocyte count (in contrast to the retrospective studies), was associated with development of any postpartum complication.

Considering current data, cesarean section compared to vaginal delivery appears to be associated with a similar magnitude of increase of complications among HIV-infected women as observed in HIV-uninfected women. While pneumonia may be more common among HIV-infected women, most data are retrospective and non-randomized and thus may be influenced by differences in diagnosis and patient populations. Complication rates in most studies are within the range reported in populations of HIV-uninfected women with similar risk factors. Risk factors for postpartum morbidity such as poor nutrition and concomitant genital infections may be especially prevalent in HIV-infected women. HIV-infected women with low CD4+ lymphocyte counts may be more prone to complications after cesarean section but also are more likely to have a reduction in transmission with cesarean section. HIV-infected women should be counseled regarding the increased risks for them associated with cesarean section.

Timing of Scheduled Cesarean Section

If the decision is made to perform a scheduled cesarean delivery to prevent HIV transmission, ACOG recommends that it be done at 38 weeks of gestation using clinical and first or second trimester ultrasonographic estimates of gestational age and avoiding amniocentesis *(126).* In HIV-uninfected women, current ACOG guidelines for scheduled cesarean section without confirmation of fetal lung maturity are to wait until 39 completed weeks or the onset of labor to reduce the chance of complications in the neonate *(147)*. Cesarean delivery at 38 compared to 39 weeks entails a small absolute but significantly increased risk of development of infant respiratory distress requiring mechanical ventilation *(148, 149).* This increased risk must be balanced against the potential risk for labor or membrane rupture between 38 and 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 three hours prior to surgery, according to standard dosing *(91)*. Other antiretroviral medications taken during pregnancy should not be interrupted around the time of delivery, regardless of route of delivery. Because maternal infectious morbidity is potentially increased, clinicians may opt to give perioperative antimicrobial prophylaxis**.** There are no controlled data evaluating the efficacy of antimicrobial prophylaxis specifically in HIV-infected women undergoing scheduled operative delivery *(150).*

Unanswered questions remain regarding the most appropriate management of labor in cases where vaginal delivery is to be attempted. Increasing duration of membrane rupture has been demonstrated consistently to be a risk factor for perinatal transmission among women who were not receiving any antiretroviral therapy *(85, 127, 151, 152).* Among women receiving ZDV, some studies have shown an increased risk of transmission with ruptured membranes for four or more hours before delivery *(9, 71)* but others have not *(70, 129).* The additive risk and the critical time of ruptured membranes for perinatal HIV-1 transmission in women receiving antiretroviral therapy and with low viral loads is unknown. Obstetrical 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 *(70, 153-155)*. 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 prior to or early during the course of labor, efforts at active management of labor to decrease the interval to delivery may be employed.

In conclusion, the decision regarding mode of delivery for the HIV-infected woman is complex and influenced by many factors. The decision should be made by the woman after discussing the known and potential benefits and risks to her and her infant with her health care provider. The woman's decision should be respected and optimal care provided for the chosen delivery mode.

Recommendations

Counseling of HIV-infected pregnant women regarding risks for vertical transmission of HIV to the fetus/neonate, should take into consideration 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 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-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 section among women on no antiretroviral therapy or on ZDV for prophylaxis of perinatal transmission with unknown HIV RNA levels. Plasma HIV RNA levels were not available in these studies to assess the potential benefit among women with low plasma HIV RNA levels.
- Women with HIV-1 RNA levels greater than 1,000 copies/mL should be counseled regarding the benefit of scheduled cesarean delivery in reducing the risk of vertical transmission.
- Data are insufficient to evaluate the potential benefit of cesarean section 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 section would confer additional benefit in reduction of transmission.
- Data are insufficient to address the question of whether performing a cesarean section shortly after the onset of labor or after very short duration of membrane rupture to shorten labor and avoid vaginal delivery would decrease the risk of vertical transmission of HIV. Management of women originally scheduled for cesarean section who present with ruptured membranes must be individualized based on duration of rupture, progress of labor, plasma HIV RNA level, current antiretroviral therapy, and other clinical factors.
- Women should be informed of the risks associated with cesarean delivery, and 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.

MODE OF DELIVERY CLINICAL SCENARIOS

The following guidelines are based on various scenarios that may be encountered in clinical practice (Table 6), with relevant considerations highlighted in the subsequent discussion sections. These scenarios are not all inclusive and present only recommendations; flexibility should be exercised according to the patient's individual circumstances.

Scenario A

HIV-infected women presenting in late pregnancy (after about 36 weeks of gestation), known to be HIV-infected but not receiving antiretroviral therapy, and who have HIV RNA level and lymphocyte subsets pending but unlikely to be available before delivery.

Recommendation

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.

Discussion

This woman has characteristics similar to women enrolled to the European randomized trial and those evaluated in the meta-analysis *(124, 125).* In both studies, the population not on antiretroviral therapy was shown to have a significant reduction in transmission with cesarean section done before labor or membrane rupture. HIV RNA levels were not available in these studies. Without current therapy, it is unlikely that the HIV RNA level will be below 1,000 copies/mL. Even if combination therapy were begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the starting RNA level. ZDV monotherapy could be begun with subsequent antiretroviral therapy decisions after delivery based on the HIV RNA level, CD4+ lymphocyte count, and the woman's preference regarding initiation of long term combination therapy. Scheduled cesarean section and the three part PACTG 076 ZDV regimen would be expected to offer the best chance of preventing perinatal HIV transmission in this setting.

Scenario B

HIV-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 RNA levels that remain substantially over 1,000 copies/mL at 36 weeks of gestation.

Recommendation

The current combination antiretroviral regimen should be continued as the HIV RNA level is dropping appropriately. The woman should be counseled that although she is responding to the antiretroviral therapy, it is unlikely that her HIV RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean section may provide additional benefit in preventing intrapartum transmission of HIV. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean section, it should be performed at 38 weeks' gestation according to the best available dating parameters, and intravenous ZDV should be begun at least 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.

Discussion

Current data suggest a rate of vertical transmission of HIV-1 of 1-12% (mean 5.7%) with HIV RNA levels near delivery of 1,000 to 10,000 copies/mL and a rate of 9-29% (mean 12.6%) with an HIV RNA level over 10,000 copies/mL in groups on ZDV therapy with low rates of delivery by scheduled cesarean section *(47, 58, 66, 70, 71, 129)*. Although the woman is currently receiving combination antiretroviral therapy that may be expected to suppress her HIV RNA to undetectable levels with continued use, she is likely to continue to have detectable HIV RNA within the period of expected delivery. Scheduled cesarean section may further reduce the rate of intrapartum HIV transmission and should be recommended to women with HIV RNA levels over 1,000 copies/mL. Although there have been several publications and presentations suggesting low levels of vertical transmission of HIV-1 among pregnant women receiving combination antiretroviral therapy, each has included small numbers of women and has not included adjustment for maternal HIV RNA levels *(82, 131, 132, 156).* Thus, it is not clear if the impact on transmission is related to the lowering of maternal plasma HIV RNA levels, pre-exposure prophylaxis of the infant, other mechanisms, or some combination. Until further data are available to clarify, women with HIV RNA levels above 1,000 copies/mL should be offered scheduled cesarean section regardless of maternal therapy.

Regardless of mode of delivery, the woman should receive the PACTG 076 intravenous ZDV regimen intrapartum and the infant should receive ZDV for six 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 pre-operatively 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 pre-operative period. If maternal antiretroviral therapy must be interrupted temporarily in the peripartum period, all drugs (except for intrapartum intravenous ZDV) should be stopped and re-instituted simultaneously to minimize the chance of resistance developing.

Women with CD4+ lymphocyte counts below 500 cells/mL or HIV RNA levels above 10,000 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 use 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-infected women on highly active combination antiretroviral therapy with an undetectable HIV RNA level at 36 weeks of gestation.

Recommendation

The woman should be counseled that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV RNA level is low, probably 2% or less, even with vaginal delivery. There is currently no information to evaluate whether performing a scheduled cesarean section will lower her risk further. Cesarean section has an increased risk of complications for the woman compared to vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean section in this case.

Discussion

Scheduled cesarean section has been shown to be beneficial among women on no antiretroviral therapy or on ZDV monotherapy with rates of transmission of HIV-1 of approximately 1-2% *(124, 125).* Maternal HIV RNA levels were not evaluated in these studies. Similar rates of transmission have been reported among women on antiretroviral therapy with undetectable HIV RNA levels near delivery *(70, 71, 130).* Data evaluating transmission rates among women with undetectable HIV RNA levels by mode of delivery are not currently available. While a benefit of cesarean section in reducing transmission may be present, it would be of small magnitude given the low risk of transmission among women with HIV RNA levels below 1,000 copies/mL on maternal antiretroviral therapy with vaginal delivery and must be weighed against the known increased risks to the woman with cesarean section. Cesarean section carries with it a several fold increased risk of postpartum infections including uterine infections and pneumonia, anesthesia risks, and surgical complications compared to vaginal delivery. These risks must be balanced against an uncertain benefit in reduction of transmission. However, given no data to indicate lack of benefit, if a woman chooses a scheduled cesarean section, her decision should be respected and cesarean scheduled.

If vaginal delivery is chosen, the duration of ruptured membranes should be minimized as the transmission rate has been shown to increase with longer duration of membrane rupture among predominantly untreated women *(127, 151, 152)* and among ZDV treated women in some *(9, 71)* but not all studies *(70, 129)*. Fetal scalp electrodes and operative delivery with forceps or the vacuum extractor may increase the risk of transmission and should be avoided *(153, 154).* Intravenous ZDV should be given during labor, and maternal drugs should be continued on schedule as much as possible to provide maximal effect and minimize the chance of development of viral resistance**,** and the infant should be treated with ZDV for six weeks after birth.

Scenario D

HIV-infected women who have elected scheduled cesarean section 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 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.

Discussion

No data are available to address the question of whether performing cesarean section soon after membrane rupture to shorten labor and avoid vaginal delivery would decrease the risk of vertical transmission of HIV-1. Most studies have shown the risk of transmission with cesarean section done after labor and membrane rupture for obstetrical indications to be similar to that with vaginal delivery, although the duration of ruptured membranes in these women was often longer than four hours *(125, 157).* As discussed in scenario #3, in studies showing an effect, the risk of transmission was twice as high among women with ruptured membranes for four or more hours before delivery compared to those with shorter durations of membrane rupture, although the risk increases continuously with increasing duration of rupture.

In the situation where elective cesarean section 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 section under these circumstances is unclear and be allowed to reassess her decision. If the woman presents after four hours of membrane rupture, it is less likely that cesarean section would impact transmission of HIV-1. The woman should be informed that the benefit of cesarean section is unclear and that her risks of perioperative infection increase with increasing duration of ruptured membranes.

If cesarean section is chosen, the loading dose of ZDV should be administered while preparations are made for cesarean delivery and the infusion continued until cord clamping. Prophylactic antibiotics given after cord clamping have been shown to reduce the rate of postpartum infection among women of unknown HIV-status undergoing cesarean section after labor or rupture or membranes and should be used routinely in this setting *(150).* If vaginal delivery is chosen, intravenous ZDV and other antiretrovirals the woman is currently taking should be administered and invasive procedures such as internal monitoring avoided. Pitocin should be used as needed to expedite delivery.

Table 6. Clinical scenarios and recommendations regarding mode of delivery to reduce perinatal human immunodeficiency virus (HIV) transmission

Mode of Delivery Clinical Scenario	Recommendations
Scenario A HIV-infected women presenting in late pregnancy (after about 36 weeks of gestation), known to be HIV-infected but not receiving antiretroviral therapy, and who have HIV 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-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 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 RNA level is dropping appropriately. The woman should be counseled that although she is responding to the antiretroviral therapy, it is unlikely that her HIV RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean section may provide additional benefit in preventing intrapartum transmission of HIV. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean section, it should be performed at 38 weeks' gestation according to the best available dating parameters, and intravenous ZDV should be begun at least 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.

Table 6. Clinical scenarios and recommendations regarding mode of delivery to reduce perinatal human immunodeficiency virus (HIV) transmission

Mode of Delivery Clinical Scenario	Recommendations
Scenario C HIV-infected women on highly active combination antiretroviral therapy with an undetectable HIV 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 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-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.

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-infected persons who are not pregnant. This monitoring should include measurement of CD4+ T-lymphocyte 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 may be a more accurate reflection of immune status during pregnancy *(158, 159)*. 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 the administration of antiretrovirals 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, and women receiving protease inhibitors should be monitored for the development of hyperglycemia. 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.

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 well being 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 six-week ZDV regimen in the neonate; thus, repeat measurement of hemoglobin is required at a minimum after the completion of the six-week ZDV regimen. Repeat measurement should be performed at 12 weeks of age, 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 in 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 infection should begin prophylaxis at six weeks of age, following completion of the ZDV prophylaxis regimen *(160)*. Monitoring and diagnostic evaluation of HIV-1 exposed infants should follow current standards of care *(161)*. Data do not indicate any delay in HIV-1 diagnosis in infants who have received the

ZDV regimen *(1, 162)*. However, the effect of combination antiretroviral therapy in the mother and/or newborn on the sensitivity of infant virologic diagnostic testing is unknown. Infants with negative virologic tests during the first six 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 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 may include case management, childcare, 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 specialists. Continuity of antiretroviral treatment when such treatment is required for the woman's HIV infection is especially critical and must be ensured**.** Concerns have been raised about adherence to antiretrovirals during the post-partum period. Women should be counseled that the physical changes of the postpartum period, as well as the stresses and demands of caring for a new baby, may make adherence more difficult and additional support may be needed to maintain good adherence to their therapeutic antiretroviral regimen during this period *(163, 164)*. 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 decreased viral control, development of resistance, and decreased long-term effectiveness *(165-170)* The efforts to keep good adherence during the postpartum period might prolong the effectiveness of therapy. See the Adherence section in the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, available at the HIV/AIDS Treatment Information Service (ATIS) website (http://www.hivatis.org).

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 also a good time to review immunization status and update vaccines, assess the need for prophylaxis against opportunistic infections, and re-emphasize safer sex practices.

Data from PACTG Protocols 076 and 288 do not indicate adverse effects through 18 months postpartum among women who received ZDV during pregnancy; however, continued clinical, immunologic, and virologic follow-up of these women is ongoing. 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 *(54, 55)*. Continued evaluation of early and late effects of in utero antiretroviral exposure is ongoing through a number of 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 states and the Centers for Disease Control and Prevention. Since most of the available follow-up data relate to in utero exposure to antenatal ZDV alone and most pregnant women with HIV infection currently receive combination therapy, it is critical that studies to evaluate potential adverse effects of in utero drug exposure continue to be supported in an ongoing fashion.

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 *(41)*. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. Long-term follow-up should include yearly physical examinations of all children exposed to antiretrovirals and for adolescent females, gynecologic evaluation with pap smears.

On a population basis, HIV-1 surveillance databases from states that require HIV-1 reporting provide an opportunity to collect 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

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

Evaluation of Drug Safety and Pharmacokinetics

Many pregnant women with HIV infection in the United States are receiving combination antiretroviral therapy for their own health care as well as standard ZDV prophylaxis to reduce perinatal HIV transmission. Additionally, recent data indicate that antenatal use of potent antiretroviral combinations capable of reducing plasma HIV RNA copy number to very low or undetectable levels near the time of delivery may lower the risk of perinatal transmission to less than 2% *(81, 100)*. While the number of antiretroviral agents and combination regimens used for treatment of infected individuals 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. Additionally, further research is needed on whether there are differing effects of intensive combination treatment on viral load 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/or 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, adolescence, or in adulthood.

Assessment of Drug Resistance

The risk of emerging drug resistance during pregnancy or the postpartum period requires further study. The administration of single drug ZDV 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 for which a single point mutation can confer genotypic resistance, such as nevirapine and lamivudine, to pregnant women with inadequate viral suppression may result in the development of virus with genotypic drug resistance in a significant proportion of the women *(171-173)*. 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 requires further assessment.

Optimizing Adherence

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

Role of Cesarean Section Among Women with Nondetectable Viral Load or with Short Duration of Ruptured Membranes

Elective cesarean delivery has increased among women with HIV infection following the demonstration that delivery prior to labor and membrane rupture can reduce intrapartum HIV transmission *(124, 125, 174)*. Whether elective cesarean delivery provides clinically significant benefit among infected women with low or undetectable viral load on combination antiretroviral therapy, as well as the maternal and infant morbidity and mortality associated with operative delivery, requires further study. Additionally, data from a meta-analysis by the International Perinatal HIV Group indicate that the risk of perinatal transmission increases by 2% for every one hour increase in duration of membrane rupture in infected women with $\leq$24 hours of membrane rupture *(175)*. Therefore, further study is also needed to evaluate the role of non-elective cesarean delivery for reducing perinatal transmission in women with very short duration of ruptured membranes and/or labor.

Management of Premature Rupture of Membranes

With evidence that increasing duration of membrane rupture is associated with an increasing transmission risk *(175)*, more study is needed to define appropriate management of pregnant women with HIV infection who present with ruptured membranes at different points in gestation.

Approaches to offering Rapid Testing at Delivery to Late Presenting Women

One of the groups still at high risk for transmitting HIV to their infants include those women who have not received antenatal care and were not offered HIV counseling and testing. The feasibility of offering counseling and rapid HIV testing to women of unknown HIV status who present in labor requires further study. Additionally, the efficacy and acceptability of intrapartum/postpartum or postpartum infant interventions to reduce the risk of intrapartum transmission by women first identified as infected with HIV during delivery needs to be assessed.

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