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U.S. 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

Perinatal HIV Guidelines Working Group Members

Revisions to the 1998 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.

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U.S. 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

Summary

These recommendations update the 1994 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. 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.

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[*] 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 6 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)*. In the 3 years since the results from PACTG 076 became available, epidemiologic studies in the United States and France have demonstrated dramatic decreases in perinatal transmission following incorporation of the PACTG 076 ZDV regimen into general clinical practice *(4-9)*.

Since 1994, advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. The rapidity and magnitude of viral turnover during all stages of HIV-1 infection are greater than previously recognized; plasma virions are estimated to have a mean half-life of only 6 hours *(10)*. Thus, current therapeutic interventions focus on 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 1-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 6 hours) for the first 6 weeks of life, beginning at 8-12 hours after birth. (Note: intravenous dosage for infants who can not tolerate oral intake is 1.5 mg/kg body weight intravenously every 6 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 focuses on antiretroviral chemoprophylaxis for the reduction of perinatal HIV transmission and 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, and d) provides updated recommendations on antiretroviral chemoprophylaxis for reducing 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 and b) 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. 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 - Cont.

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]	Not completed	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)

[†]   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 preterm births was noted, as 10 of 30 babies were born prematurely. The preterm birth rate did not differ between women receiving combination therapy with or without protease inhibitors. The contribution of maternal HIV disease stage and other covariates that might be associated with a risk for prematurity were not assessed. Furthermore, some studies have shown elevated preterm 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

preterm 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). A French group reported 8 cases of uninfected infants with in utero and/or neonatal exposure to either ZDV/3TC (4 infants) or ZDV alone (4 infants) who developed indications of mitochondrial dysfunction after the first few months of life (30). 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 a large database that included 353 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 (31). 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 3 regimens of ZDV/3TC (before, during and 1 week postpartum; during labor and postpartum; and during labor only) to placebo for prevention of transmission. No increased risk of neurologic events were observed among children treated with ZDV/3TC compared to placebo, regardless of intensity of treatment (32). 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% (*33*). These data emphasize the importance of the existing Public Health Service recommendation for long-term follow-up for any infant 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 *(34)*.

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 *(35,36)*, 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) *(37,38)*. 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 *(39)*. 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 *(40)*. 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 *(41)*. No malignancies have been observed in short-term (i.e., up to 6 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 *(42)*. 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 *(43)*. 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 *(39)*. 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 *(44)*. 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 *(44)*. 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 *(6,44)*.

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 4 weeks antenatally and 300 mg every 3 hours orally during labor was shown to reduce perinatal transmission by approximately 50% compared to placebo *(45)*. Transmission decreased from

19% in the placebo group to 9% in the ZDV group. A second, 4-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 3 days or 6 weeks. At an interim analysis, the transmission rate was 10% in the arm receiving ZDV antenatally starting at 36 weeks and postnatally for 3 days to the infant, which was significantly higher than for the long-long arm (antenatal starting at 28 weeks and infant administration for 6 weeks *(46)*. 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. The short-short arm was terminated but the study continues to enroll into the other 3 arms (long-long, short-long and long-short).

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 6 weeks *(47)*. Transmission at age 6 weeks was decreased from 17% in the placebo group to 9% with the 3-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 *(45)*.

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 6 weeks from 17% in the placebo group to 11% with the 2-part ZDV/3TC regimen, a reduction of 38% *(47)*. 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 *(48)*. Transmission at age 6 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 *(6,49,50)*. 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 6 weeks was associated with a significant reduction in transmission if the drug was initiated within 24 hours of birth (the majority of infants started within 12 hours) *(49,50)*. 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% confidence interval [CI]=0.1-0.6) *(51)*.

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 3-4 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 6 months postpartum than during antepartum in many women; this increase was observed in women regardless of ZDV use during and after pregnancy (52).

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 (53). 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 (52,54,55). 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 (34). 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 (34, 56).

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 (45,57-59). 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 (59-61).

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 (62-65). 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 (66). 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 *(67)*. These results are similar to those observed in PACTG 076 *(34)*. 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 *(68,69)*.

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 *(70-74)*, 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 *(3,75)*; 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 *(76-78)*. Comparable clinical response also has been observed in some clinical trials among persons receiving ZDV twice daily *(79-81)*. 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 *(82)*. 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 *(83)*. 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 2 weeks of life; for infants aged 2 6 weeks, the dose is increased to 2 mg/kg body weight every 8 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.

CLINICAL SCENARIOS

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

Recommendation

HIV-1 infected pregnant women 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 should be recommended for all

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HIV-infected pregnant women to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be a) discussed with the woman; b) recommended for infected women whose clinical, immunologic, and virologic status indicate the need for treatment; and c) offered to other infected women (although in the latter circumstance it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefits or risks for the infant). Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' gestation.

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.	HIV-1 infected pregnant women 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 should be recommended for all HIV-infected pregnant women to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be a) discussed with the woman; b) recommended for infected women whose clinical, immunologic, and virologic status indicate the need for treatment; and c) offered to other infected women (although in the latter circumstance it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefits or risks for the infant). 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. 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. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks' gestation. ZDV administration is recommended during the intrapartum period and for the newborn - regardless of the antepartum antiretroviral regimen.

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 6 weeks of ZDV for the newborn; and 4) the 2-dose nevirapine regimen combined with intrapartum intravenous ZDV and 6 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 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 12 24 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.

* 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 whishes 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.

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, and available data are insufficient to justify the substitution of any antiretroviral drug other than ZDV to reduce perinatal transmission. Therefore, if combination antiretroviral therapy is initiated during pregnancy, ZDV should be included as a component of antenatal therapy, and the intrapartum and newborn ZDV parts of the chemoprophylactic regimen should be recommended for the specific purpose of reducing perinatal transmission.

Women should be counseled that combination therapy may have substantial benefit for their own health but is of unknown benefit to the fetus. Potent combination antiretroviral regimens may provide enhanced protection against perinatal transmission, but this benefit is not yet proven. 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) potential drug toxicities and interactions with other drugs; c) the need for adherence to the prescribed drug schedule; and d) pre-clinical, animal, and clinical data relevant to use of the currently available antiretrovirals during pregnancy.

Because the period of organogenesis (when the fetus is most susceptible to potential teratogenic effects of drugs) is during the first 10 weeks of gestation and the risks of antiretroviral therapy during that period are unknown, women 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.

Women for whom initiation of antiretroviral therapy for the treatment of their HIV infection would be considered optional (e.g., those with high CD4+ counts and low or undetectable RNA copy number) should be counseled regarding the potential benefits of standard combination therapy and should be offered such therapy, including the three-part ZDV chemoprophylaxis regimen. Some women may wish to restrict their exposure to antiretroviral drugs during pregnancy but to reduce the risk of transmitting HIV-1 to their infants; the three-part ZDV chemoprophylaxis regimen should be recommended for such women. In these circumstances, the development of resistance should be minimized by the limited viral replication in the patient and the time-limited exposure to ZDV. Because monotherapy with ZDV does not suppress HIV replication to undetectable levels, the use of ZDV chemoprophylaxis alone poses a theoretical concern that such therapy might select for ZDV-resistant viral variants—potentially limiting benefits from combination antiretroviral regimens that include ZDV. Data are insufficient to determine if such use would have adverse consequences for the infected woman during the postpartum period. In some combination antiretroviral clinical trials involving adults, patients with previous ZDV therapy experienced less benefit from combination therapy than those who had never received prior antiretroviral therapy *(84-86)*. However, in these studies, the median duration of prior ZDV use was 12 20 months, and enrolled patients had more advanced disease and lower CD4+ counts than the population of women enrolled in PACTG 076 or for whom initiation of therapy would be considered optional. In one study, patients with <12 months of ZDV responded as favorably to combination therapy as those without prior ZDV therapy *(86)*. In PACTG 076, the median duration of ZDV therapy was 11 weeks; the maximal duration of ZDV (begun at 14 weeks' gestation) would be 6.5 months for a full-term pregnancy.

For women initiating therapy who have more advanced disease, concerns are greater regarding development of resistance with use of ZDV alone as chemoprophylaxis during pregnancy. Factors that predict more rapid development of ZDV resistance include more advanced HIV-1 disease, low CD4+ count, high HIV-1 RNA copy number, and possibly syncytium-inducing viral phenotype *(87,88)*. Therefore, women with such factors should be counseled that for their own health, therapy with a combination antiretroviral regimen that includes ZDV for reducing transmission risk would be more optimal than use of ZDV chemoprophylaxis alone.

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. 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. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks' gestation. ZDV administration is recommended during the intrapartum period and for the newborn—regardless of the antepartum antiretroviral regimen.

Discussion

Women who have been receiving antiretroviral treatment for their HIV infection should continue treatment during pregnancy. Discontinuation of therapy could lead to rebound in viral load, which theoretically could result in decline in immune status and disease progression, potentially resulting in adverse consequences for both the fetus and the woman. Because the efficacy of non-ZDV containing antiretroviral regimens for reducing perinatal transmission is unknown, ZDV should be a component of the antenatal antiretroviral treatment regimen after 14 weeks' gestation and should be administered to the pregnant woman during the intrapartum period and to the newborn. If a woman does not receive ZDV as a component of her antepartum antiretroviral regimen (e.g., because of prior history of ZDV-related severe toxicity or personal choice), ZDV should continue to be administered to the pregnant woman during the intrapartum period and to her newborn.

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. 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.

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 (44). 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 transmission.

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 6 weeks of ZDV for the newborn; and 4) the 2-dose nevirapine regimen combined with intrapartum intravenous ZDV and 6 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 2-dose

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 1 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 1 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 6 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 3 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 7 days	Transmission at 6 weeks 10% with ZDV/3TC compared to 17% with placebo, a 38% reduction	Oral regimen Compliance easier than 6 weeks of ZDV alone as infant regimen is only 1 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 6 hours for 6 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 6 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 6 hours for 6 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 6 week infant ZDV regimen Unknown efficacy and limited toxicity data

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 3 hours during labor and postnatally to the infant for 7 days (Table 4). At age 6 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 *(48)*. 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/1 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 7 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 7 days. At age 6 weeks, the rates of transmission were 10% in the ZDV/3TC arm compared to 17% in the placebo arm, a 38% reduction in transmission *(47)*. 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.

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 *(89)*, 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., 4-6 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 than intravenous maternal intrapartum ZDV followed by oral ZDV for 6 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%) *(49)*. Similarly, in epidemiologic study in North Carolina, intravenous intrapartum and 6 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 1-week postnatal infant ZDV course in HIVNET 012 *(48)*, has not proven effective to date. This underscores the necessity of recommending a full 6 week course of infant treatment when ZDV alone is utilized.

There are currently no data to address the relative efficacy of these 3 intrapartum/neonatal antiretroviral regimens for prevention of transmission. There is overlap in the 95% confidence intervals for the 2-dose nevirapine regimen and the maternal intravenous intrapartum/6 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 2-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 there is an ongoing clinical trial (SAINT Trial) comparing the 2-dose nevirapine and the intrapartum/postpartum ZDV/3TC regimens. Results from this trial will be available by late 2000, and recommendations will be modified as needed when these become available.

Whether combining intravenous intrapartum/6 week neonatal oral ZDV with the 2-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 2-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 (90),* 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 7 days after a single dose *(91)* and is active immediately against intracellular and extracellular virus *(92).* 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 *(6,39,93,94).* 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 *(94-97).* 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 *(98).* 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 *(94,99,100).* 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 12-24 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.

Discussion

Definitive data are not available to address whether ZDV administered solely during the neonatal period would reduce the risk for perinatal transmission. However, 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 *(51)*. Postexposure prophylaxis also has prevented retroviral infection in some studies involving animals *(101-103)*.

The interval for which benefit may be gained from postexposure prophylaxis is undefined, but 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 *(101-103)*. 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 *(104)*. 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 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 *(105)*. Therefore, initiation of postexposure prophylaxis after the age of 14 days likely would not be efficacious in preventing transmission because infection would already be established in most children.

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.

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 3-4 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 *(106, 107)*. 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 6-week ZDV regimen in the neonate; thus, repeat measurement of hemoglobin is required at a minimum after the completion of the 6-week ZDV regimen. 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.

To prevent *P. carinii* pneumonia, all infants born to HIV-1 infected women should begin prophylaxis at 6 weeks of age, following completion of the ZDV prophylaxis regimen *(108)*. Monitoring and diagnostic evaluation of HIV-1 exposed infants should follow current standards of care *(109)*. Data do not indicate any delay in HIV-1 diagnosis in infants who have received the ZDV regimen *(1,110)*. 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 6 weeks of life should have diagnostic evaluation repeated after completion of the neonatal antiretroviral prophylaxis regimen.

Postpartum Follow-Up of Women

Comprehensive care and support services are required for HIV-1 infected women and their families. Components of comprehensive care include the following medical and supportive care services: a) primary, obstetric, and HIV specialty care; b) family planning services; c) mental health services; d) drug-abuse treatment; and e) coordination of care through case management for the woman, her children, and other family members. Support services include case management, child care, respite care, assistance with basic life needs (e.g., housing, food, and transportation), and legal and advocacy services. This care should begin before pregnancy and should be continued throughout pregnancy and postpartum.

Maternal medical services during the postpartum period must be coordinated between obstetricians 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. 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.

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 from birth through age 18-36 months 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. Continued intensive follow-up through PACTG 219 is ongoing. PACTG 219 also will provide intensive follow-up for infants born to women who receive other antiretroviral drugs as part of PACTG perinatal protocols. Thus, some data regarding follow-up of exposure to other antiretroviral agents alone or in combination will be available in the future.

Innovative methods are needed to provide follow-up to infants with in utero exposure to ZDV or any other antiretrovirals. Information regarding such exposure should be part of the ongoing medical record of the child—particularly for uninfected children. 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 examination of all children exposed to antiretrovirals and for older 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.

FUTURE RESEARCH NEEDS

An increasing number of HIV-1 infected women will be receiving antiretroviral therapy for their own health during pregnancy. Preclinical evaluations of antiretroviral drugs for potential pregnancy- and fetal-related toxicities should 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 in their neonates, particularly when they are used in combination regimens. Results from several phase I studies will be available in the next year; these results will assist in delineating appropriate dosing and will provide data regarding short-term safety of these drugs in pregnant women and their infants. However, the long-term consequences of in utero antiretroviral exposure for the infant are unknown, and mechanisms must be developed to gather information about the long-term outcome for exposed infants. Innovative methods are needed to enable identification and follow-up of populations of children exposed to antiretroviral drugs in utero. Additional studies are needed to determine the long-term consequences of transient use of ZDV chemoprophylaxis during pregnancy for women who do not choose to receive combination therapy antenatally, including the risk for development of ZDV-resistance.

Although more potent antiretroviral combination regimens that dramatically diminish viral load also may theoretically prevent perinatal transmission, no data are available to support this hypothesis. The efficacy of combination antiretroviral therapy to decrease the risk for perinatal HIV-1 transmission needs to be evaluated in ongoing perinatal clinical trials. Additionally, epidemiologic studies and clinical trials are needed to delineate the relative efficacy of the various components of the three-part ZDV chemoprophylactic regimen. Improved understanding of the factors associated with perinatal HIV transmission despite ZDV chemoprophylaxis is needed to develop alternative effective regimens. Because of the dramatic decline in perinatal HIV-1 transmission with widespread implementation of ZDV chemoprophylaxis, an international, collaborative effort is required in the conduct of such epidemiologic studies and clinical trials.

Regimens that are more feasible for implementation in less developed areas of the world are needed. The three-part ZDV chemoprophylactic regimen is complex and may not be a feasible option in many developing countries for the following reasons: a) most pregnant women seek health care only near the time of delivery, b) widespread safe administration of intravenous ZDV infusions during labor may not be possible, and c) the cost of the regimen may be prohibitive and many times greater than the per capita health expenditures for the country. Several studies are ongoing in developing countries that are evaluating the efficacy of more practical, abbreviated modifications of the ZDV regimen. Additionally, several nonantiretroviral interventions also are being studied. Results of these studies will be available in the next few years.

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