

CHAPTER 5

PREVENTION OF PERINATAL HIV TRANSMISSION

The purpose of this document is to provide clinicians with updated information about antiretroviral (ARV) treatments for reducing mother-to-child HIV-1 transmission while maintaining optimal health for women with HIV infection during pregnancy. These guidelines are intended to assist the clinician in both discussing the benefits and risks of treatment with his/her patient and formulating an individualized treatment plan. They are designed to update *Prevention of Perinatal HIV Transmission: Clinical Guidelines*,¹ which was published in 2000, and to be used in concert with the *Antiretroviral Therapy* chapter in *Criteria for the Medical Care of Adults With HIV Infection*, which is also included in this manual as Chapter 1: *Antiretroviral Therapy for Adults*. Appendix II in this manual includes data relevant to the use of ARV agents in pregnancy.

I. BACKGROUND

In February 1994, the National Institutes of Health (NIH)-sponsored Pediatrics AIDS Clinical Trial Group (PACTG) 076 study demonstrated that a regimen with zidovudine given to both mother and newborn could dramatically reduce the risk of mother-to-infant HIV-1 transmission.² The availability of a regimen to reduce the transmission of a fatal pediatric disease led many state and local health departments, including the New York State Department of Health AIDS Institute (NYS-DOH AI)³ and the United States Public Health Service⁴ to develop consensus guidelines for clinicians endorsing the use of zidovudine during pregnancy.

Since that time, rapid advances in the number and efficacy of ARV drugs have resulted in a change in the standard of care for adults with HIV. Highly active antiretroviral therapy (HAART) is used to maximally suppress viral replication and improve clinical outcomes and survival in HIV-infected adults. However, the use of multiple potent drugs has also caused an increase in the toxicities for patients receiving them.

Clinicians caring for HIV-infected pregnant women need to be cognizant of multiple and possibly contradictory treatment goals. These include preventing perinatal HIV transmission, maintaining the well-being of the woman, achieving virological suppression in the woman, and being vigilant for and minimizing drug toxicity in both the woman and the infant. ARV treatment recommendations are based on the principle that therapies of known benefit to women should not be withheld during pregnancy unless they have known adverse effects on the mother, fetus, or infant and unless these adverse effects outweigh the benefit.⁵ In the current absence of such knowledge, pregnant women should be offered the standard of care available for all adults.

II. SCIENTIFIC DATA REGARDING ANTIRETROVIRAL PROPHYLAXIS PREVENTING PERINATAL TRANSMISSION

A. Studies of Zidovudine Alone

Since the publication of the data from ACTG 076, many studies have confirmed the efficacy of zidovudine in preventing perinatal transmission. Both randomized, controlled clinical trials and observational studies have confirmed the effectiveness of the three-part “076” regimen. Other studies have demonstrated the effectiveness of shorter regimens applicable to populations who cannot receive the full 076 regimen.

In November 1996, updated data from 402 mother-infant pairs in the PACTG 076 study confirmed the initial findings. The rate of HIV-1 transmission was 7.6% with zidovudine treatment and 22.6% with placebo.⁶

PACTG 185 showed a similar decrease in perinatal transmission for women with more advanced immunosuppression and previous zidovudine administration. In 379 woman-infant pairs using the 076 regimen and intravenous gammaglobulin with or without specific antibodies against HIV, the mother-to-infant HIV transmission rate was 4.8%.⁷

A Centers for Disease Control and Prevention (CDC)-sponsored study in Thailand showed a transmission rate of 9.4% in infants whose mothers received oral zidovudine from 36 weeks’ gestation through delivery versus a transmission rate of 18.9% for infants whose mothers received placebo. Infants were not given zidovudine and were not breastfed.⁸

An observational study in New York State examined 939 HIV-exposed infants born between 1995 and January 1997.^{9,10} These data demonstrated the benefit of zidovudine prophylaxis when begun prenatally, intrapartum, or within 24 hours postpartum (see Table 1).

TABLE 1
RESULTS OF OBSERVATIONAL STUDY OF
939 HIV-EXPOSED INFANTS IN NEW YORK STATE

Timing of Prophylaxis Initiation	Number Born	Number Infected	Percent HIV Infected
Prenatal	423	26	6.1
Intrapartum	50	5	10.0
Before 48 hours postpartum	86	8	9.3
After 48 hours postpartum	38	7	18.4
No therapy	342	91	26.1

A further analysis of the timing of newborn zidovudine initiation in 21 of the 86 infants who initiated zidovudine within 48 hours post-partum demonstrated that 17/21 initiated zidovudine within 12 hours after birth and all 21 initiated zidovudine within 24 hours after birth.¹⁰

Other observational studies repeatedly confirm the efficacy of zidovudine in decreasing perinatal HIV transmission:

Nationwide, the number of pediatric AIDS cases reported to the CDC declined 67% between 1992 and 1997.^{11,12}

In North Carolina, mother-to-child transmission rates decreased from 25% in 1993 to 3% in 1997 following the use of zidovudine.¹³

In a New York City cohort of 1,080 children followed between 1996 and 1997, the transmission rate was 7% in mother-infant pairs who received any zidovudine compared with 21% in mother-infant pairs who received no zidovudine.^{14,15}

B. Studies of Other Drugs or Combinations

The UNAIDS PETRA study in Africa examined zidovudine and lamivudine administration compared with placebo in the prenatal, intrapartum, and postnatal periods. All women breastfed their infants. HIV transmission was 9.2% in the group treated with prenatal, intrapartum, and postnatal zidovudine/lamivudine and 18.6% in the control group. When zidovudine/lamivudine was initiated during the intrapartum period and administered for 1 week postpartum in both the mother and baby, transmission was 10.8% compared with 17.2% in the placebo group. However, intrapartum zidovudine/lamivudine alone without postpartum prophylaxis was not effective in reducing transmission.¹⁶

The NIH-sponsored HIVNET 012 study in Uganda compared short-course nevirapine and oral zidovudine. Nevirapine was administered as a single dose intrapartum to the mother and a single dose to the newborn at 48 to 72 hours, while zidovudine was administered to the mother every 3 hours from the onset of labor through delivery and then to the infant every 6 hours for 1 week. Almost all of the women breastfed their babies. The HIV transmission rate was 13.1% in the nevirapine group versus 25.1% in the zidovudine group.¹⁷ Of concern, nevirapine-associated mutations in the HIV virus were seen in 19% of the women and in some infants who received a single dose of nevirapine.¹⁸

Controlled comparative trials of HAART for prevention of perinatal HIV transmission are unlikely to be completed. Several observational studies have demonstrated a lower rate of transmission for women receiving HAART. Other studies have shown a distinct but not absolute correlation between plasma viral load and risk of transmission.

Data from 1,492 HIV-infected women who gave birth between 1990 and 2000 in the Women and Infant Transmission Study (WITS) were analyzed to assess the correlation between ARV therapy during pregnancy and rate of HIV transmission. These data showed a transmission rate of 1.1% for women receiving HAART compared to transmission rates of 20.0% for women receiving no ARV therapy, 19.4%

for women receiving zidovudine monotherapy before April 1994 (presumably without the infant receiving the newborn course), 7.8% for women receiving zidovudine monotherapy after April 1994 (presumably with the infant receiving the newborn course), and 3.9% for women receiving combination therapy not defined as HAART.¹⁹

Data from 277 births at 22 sites in the Pediatric Spectrum of HIV Disease and pediatric HIV Surveillance studies in New York City demonstrated a similar transmission of 1% for women who had received combination ARV therapy during pregnancy and both intrapartum and neonatal zidovudine therapy between January 1996 and June 1999.²⁰ These data confirm multiple smaller studies, which have consistently shown transmission rates of <2% in series of 30 and 89 women receiving HAART.^{21,22}

III. OTHER SIGNIFICANT FACTORS ASSOCIATED WITH THE RISK OF TRANSMISSIONS

A. Maternal Plasma Viral Load

A high maternal plasma viral load significantly increases the risk for transmission.²³⁻²⁸ In the PACTG 076 study, the risk of transmission was decreased in women with the lowest maternal plasma RNA levels, but transmission occurred across the entire measurable range of maternal plasma RNA levels.⁶ In two recent reports, the lowest risk of transmission was associated with a viral load <1,000 copies/mL (0/57)²⁹ or <500 copies/mL (0/107).³⁰

B. CD4 cell count

In the PACTG 076 study, the risk of transmission in the placebo group was highest among women with the lowest CD4 counts at study entry.⁶ This is consistent with other reports.^{31,32}

C. Maternal Co-Infections

In a cohort study from Zaire, both funisitis (inflammation of the umbilical cord) and chorioamnionitis were associated with an increased risk of mother-to-child HIV transmission.³³ Similar findings have been reported by the Ariel Project.³⁴ Maternal co-infections with syphilis³⁵ and hepatitis C virus³⁶ may also be associated with an increased risk of transmission.

D. Duration of Rupture of Membranes

Several vertical transmission studies have reported an association between transmission risk and rupture of membranes prior to delivery when the duration of rupture of membranes exceeded 4 hours.^{37,38}

E. Mode of Delivery

Several studies have reported that delivery by cesarean section with intact membranes that occurs prior to the onset of labor is associated with a significantly decreased risk of mother-to-child HIV-1 transmission.³⁹⁻⁴² In an individual patient data meta-analysis from 15 cohort studies in the United States and Europe,³⁹ cesarean section with intact membranes and before the onset of labor was associated with an approximately 50% decrease in transmission, even among women receiving the PACTG 076 regimen. In 7,840 mother/infant pairs, the rate of transmission was 8.2% for women delivering by elective cesarean section compared with 16.8% for women delivering vaginally and 16.2% for women delivering by emergency cesarean section. A randomized clinical trial of elective cesarean section in Europe has replicated these findings.⁴⁰ In this study, women were randomized to either a scheduled cesarean section or vaginal delivery. The transmission rate was 1.8% (3/170) in the elective cesarean section group, 10.5% (21/200) in the vaginal delivery group, and 8.8% (3/31) in women who underwent emergency cesarean section.

F. Breastfeeding

Several studies have demonstrated that HIV can be transmitted by breastfeeding. Although such transmission can occur in infants of any age, the greatest risk of transmission by breastfeeding is shortly after birth, and the risk declines as the infant gets older. Data from one study show that, for infants who breastfed for 24 months, the cumulative additional risk of HIV transmission is 10.3% higher than the risk of intrauterine/intrapartum transmission.⁴³ A randomized clinical trial in Africa demonstrated a transmission rate of 36.7% among breastfed infants compared with 20.5% among formula-fed infants.⁴⁴

IV. POSSIBLE ADVERSE EFFECTS OF ARV IN PREGNANT WOMEN

Many of the common potential adverse effects of ARV drugs are of particular concern for pregnant women. These include hyperglycemia and mitochondrial toxicity, particularly lactic acidosis and hepatic steatosis. Several studies have demonstrated that many of the side effects of ARV agents, including pancreatitis in patients receiving nucleoside analogues and nevirapine-induced hepatitis in patients receiving nucleoside analogues, are more common in women.^{45,46} The nausea and vomiting present during early pregnancy may also confound and delay the diagnosis of side effects caused by ARV medications.

A. Hyperglycemia

Protease inhibitors are known to cause hyperglycemia, new-onset diabetes mellitus, and worsening of pre-existing diabetes.^{47,48} Gestational diabetes is a common occurrence in pregnancy, and a major concern for the mother and her physician. It is not known whether the use of protease inhibitors during the pregnancy will cause an increase in the incidence or severity of gestational diabetes in HIV-infected pregnant women.

B. Mitochondrial Toxicities

Many of the adverse effects associated with nucleoside analogues are manifestations of mitochondrial toxicity. All available nucleoside analogues have a high binding affinity for the mitochondrial gamma-DNA polymerase; relative inhibitory activity is very high for zalcitabine, didanosine, and stavudine, and lower for lamivudine and zidovudine.⁴⁹ Among the clinical presentations of mitochondrial toxicity are cardiomyopathy, hepatic steatosis, lactic acidosis, myopathy, pancreatitis, and peripheral neuropathy. Lactic acidosis and hepatic steatosis caused by ARV therapy are more prevalent in women than in men.⁵⁰

These conditions are of particular concern in pregnant women because of their similarities with acute fatty liver of pregnancy (AFLP) and the HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome of pregnancy. Several investigators have linked these disorders to a recessively

inherited mitochondrial disorder in the fetus. The infant's inability to oxidize mitochondrial fatty acids may contribute to a woman's susceptibility to mitochondrial toxicities of nucleoside analogues.⁵¹⁻⁵³

Lactic acidosis with hepatic steatosis has been reported in HIV-infected people who receive nucleoside analogues for over 6 months. An FDA report identified 106 people with this syndrome. Initial presentation usually included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness. Laboratory abnormalities included metabolic acidosis, elevated serum hepatic enzymes, and elevated serum lactate.⁵⁰

Several severe cases of lactic acidosis leading to death or fetal demise have been reported in pregnant women receiving ARV therapy. Italian researchers reported a case in a pregnant woman receiving lamivudine/stavudine who had a fetal demise at 38 weeks.⁵⁴ The FDA reported three cases of fatal lactic acidosis in pregnant or post-partum women receiving ARV combinations that included both didanosine and stavudine. Two of these women also had pancreatitis. The infants of two of these women died, one *in utero* and one after emergency cesarean section at 36 weeks. Several less severe cases of pancreatitis with or without lactic acidosis and hepatic failure have also been reported in pregnant women receiving combination didanosine/stavudine.⁵⁵ Combination therapy of didanosine and stavudine during pregnancy is thus not recommended and should be used with caution.

For more information on side effects of ARV therapy, refer to Chapter 3: *Side Effects of Antiretroviral Therapy*.

V. POSSIBLE ADVERSE EFFECTS IN INFANTS

Concerns about *in utero* drug toxicity affect a woman's decision regarding ARV therapy and the information and opinions that her physician provides. Although no distinct pattern of long-term toxicity has been identified, potential toxicities include premature birth, manifestations of mitochondrial toxicity, and the potential for cancers or malformations. ARV drugs have not been determined to be carcinogenic or mutagenic in humans; however, that possibility cannot be ruled out until long-term studies of *in utero* ARV-exposed children are completed.

A. Short-Term Toxicities

The only short-term infant toxicity observed in infants on zidovudine in PACTG 076 was a mild, reversible anemia. The nadir was at 6 weeks of age, and the anemia resolved by 12 weeks of age.² The severity and duration of the anemia were not associated with the duration of maternal zidovudine treatment. Among uninfected children aged between 0 and 18 months in the PACTG 076 study, there were no differences between the zidovudine-exposed group and the placebo group in growth patterns, immunologic parameters, or childhood neoplasias.⁵⁶ Among cases reported to the Antiretroviral Pregnancy Registry, a voluntary, collaborative prospective registry supported by pharmaceutical manufacturers, there has not been any reported association between zidovudine exposure and congenital anomalies.⁵⁷

B. Carcinogenicity or Mutagenicity

At the present time, no data exist to suggest that any of the commonly used ARV medications are teratogenic or carcinogenic in humans. Although there are limited animal data for most drugs, it is important to note that of the 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans.⁵⁸ Many of these drugs have a long history of safe use in pregnant women.

Nucleoside analogues such as zidovudine can interfere with DNA synthesis and may be potential carcinogens. One safety concern with zidovudine use during pregnancy is the potential risk of cancer to children following transplacental exposure. In one rodent model, extremely high doses of zidovudine administered during pregnancy were associated with an increased risk of multi-organ tumors in offspring.⁵⁹ Other studies on rodents have not reported similar risks.⁶⁰

Efavirenz teratogenicity studies in monkeys at doses similar to those used in humans resulted in congenital anomalies in 3 of 20 monkeys. These anomalies included microphthalmia in one, anencephaly and unilateral anophthalmia in another, and cleft palate in the third. Because of these outcomes, efavirenz is not recommended for pregnant women.⁶¹ A recent

report of a neural tube defect (sacral myelomeningocele with cerebral ventriculomegaly) in an infant exposed to efavirenz for the first 4.5 weeks of pregnancy highlights this recommendation and emphasizes the need for preconceptional counseling. This infant was born to one of three women who reported that they were taking efavirenz at the time of conception. Each woman discontinued efavirenz before the eighth week of gestation, thus limiting fetal exposure to the drug. Although one of the other two women delivered a healthy child, the other aborted during the first trimester. This neural tube defect is an isolated case to date and causality cannot be established; however, its similarity to the defects found in monkeys causes concern.⁶²

In February 1997, an NIH expert panel composed of clinicians, scientists, and patient advocates reviewed all available animal data and unanimously concluded that the benefits of zidovudine in reducing perinatal HIV infection far outweighed the potential risks.⁶³ This panel also emphasized the importance of informing women of these data and recommended long-term follow-up of all children exposed *in utero* as well as increased clinical and basic research on the topic.

C. Long-Term Safety Studies

Data concerning the long-term safety of zidovudine and other ARV agents continue to be collected. In PACTG 219, 234 uninfected children born to women participating in PACTG 076 (122 in the zidovudine group, 112 in the placebo group) were followed for a median of 4.2 years. No differences have been observed between these two groups when comparing lymphocyte subsets, growth parameters, and cognitive development. There have been no deaths or malignancies. Two zidovudine-exposed children had unexplained but asymptomatic ophthalmic abnormalities; one zidovudine-exposed child had a mild cardiomyopathy detected by echocardiogram but was clinically asymptomatic.⁶⁴ Long-term follow-up of this cohort and others continues.

A report from France described eight infants believed to have mitochondrial dysfunction who

were HIV-uninfected but had *in utero* and/or neonatal exposure to zidovudine/lamivudine or zidovudine alone.⁶⁵ Two infants died from neurologic disorders. Of the other six infants, three were symptomatic and three were asymptomatic but had laboratory abnormalities suggestive of mitochondrial dysfunction. In a subsequent evaluation of >20,000 HIV-exposed infants in the United States, there were 353 deaths, none with symptoms similar to those reported in the French study.⁶⁶ Data regarding neurologic adverse events in 1,798 children who participated in the zidovudine/lamivudine PETRA trial have also been reviewed; no increased risk of neurologic events was observed among children treated with zidovudine/lamivudine compared with placebo, regardless of intensity of the zidovudine/lamivudine exposure.⁶⁷

D. Prematurity

In 1998, Swiss investigators published a report of retrospective data showing that 10 of 30 infants born to women receiving combination ARV therapy (with or without protease inhibitors) were born preterm.⁶⁸ Subsequent data from larger cohort studies have been inconclusive. One large meta-analysis of United States PACTG perinatal trials and other large cohort studies did not find a higher rate of preterm delivery among women who received combination therapy compared with women who did not receive any ARV therapy.⁶⁹ However, a large European cohort study has shown a significantly higher rate of preterm delivery among women who received combination therapy compared with those who received monotherapy or no therapy. The rate of preterm delivery was highest in women who started combination therapy prior to pregnancy.⁷⁰

VI. EFFECTS OF ANTIRETROVIRAL DRUGS ON MATERNAL DISEASE PROGRESSION AND VIRAL RESISTANCE

In PACTG 076, at 6 months postpartum, there were no differences in clinical, immunologic, or virologic disease progression between women who received the zidovudine regimen and those who received placebo.⁵⁷ Data from PACTG 288, a study that followed women from PACTG 076 postpartum (median follow-up, 4.2 years),

indicate no differences in CD4 count or time to progression to AIDS or death in women who received zidovudine compared with those who received placebo.⁷¹

In two separate studies, a single dose of nevirapine administered to both the mother and infant selected for mutations in the HIV genome associated with nevirapine resistance. In ACTG 316, nevirapine in labor was added to a woman's pre-existing ARV regimen, and 8 of 79 (10%) women developed nevirapine-associated resistance mutations.⁷² In HIVNET 012, women received a single dose of nevirapine without other ARV medications; 21 of 111 (19%) women developed resistant virus. This occurred more frequently in women with a high viral load and, in the absence of continued nevirapine therapy, drug resistance disappeared from their viral profiles within 2 years.¹⁸ Although nevirapine resistance was not detected by genotype testing at the subsequent date, the nevirapine-resistant strain is likely to still be present in small amounts. The relative predominance of wild-type virus, as evidenced by the lack of resistance shown by genotyping, suggests that nevirapine may still be effective if used again as a single-dose regimen to reduce viral load at delivery, thereby reducing the risk of perinatal transmission. However, women who have nevirapine-resistant virus detected on an earlier genotyping would likely not achieve complete viral suppression on a nevirapine-containing ARV regimen because of the re-emergence of resistant virus.

In the HIVNET study, 11 of 24 HIV-infected infants who had received nevirapine prophylaxis and were infected by 6 to 8 weeks of age were found to have nevirapine-associated resistance mutations. These often did not correspond to mutations in the maternal viral isolate. In the absence of continued exposure, most of these mutations disappeared by 1 year. In addition, viral isolates from 1 of 9 nevirapine-exposed infants in that study who had late transmission via breastfeeding displayed a resistance mutation.¹⁸

VII. THE IMPORTANCE OF ADHERENCE

The success of ARV therapy in the reduction of perinatal transmission lies in adherence to therapy. The variables that affect adherence to chronic ARV therapy are multiple and complex. The absence of disease symptoms and delayed realization of the benefit of treatment

contribute to incomplete adherence.⁷⁵⁻⁷⁶ The physiologic changes and symptoms of pregnancy present unique challenges to the pregnant woman trying to adhere to a complex ARV regimen. The nausea and abdominal discomfort experienced by most pregnant women may be worsened by ARV medication or may be wrongly attributed to it.

Family and peer pressure also play important roles. The stresses of motherhood, her own treatment, her newborn's treatment, as well as responsibilities toward other family members and sometimes a need for secrecy, may serve as barriers to treatment adherence for a pregnant and newly postpartum woman. An important consideration that should be discussed before delivery is whether to electively discontinue maternal ARV therapy during the adjustment period coinciding with the infant's first few months of life.

Many approaches such as educational programs coupled with individualized counseling, using reminder devices, and buddy systems have been used to enhance HIV medication adherence.⁷⁶ An integrated and multidisciplinary approach that simplifies the regimen, minimizes the side effects, provides patient education, and uses the patient's own support network may provide the best opportunity to improve adherence. For more information on adherence, refer to the New York State Department of Health AIDS Institute's *Promoting Adherence to HIV Antiretroviral Therapy: Best Practices*.⁷⁷

VIII. HIV TESTING OF PREGNANT WOMEN AND NEWBORNS IN NEW YORK STATE

RECOMMENDATIONS:

New York State regulations require HIV counseling with a clinical recommendation to test in all regulated prenatal care settings; NYSDOH recommends this as a standard of care in all other prenatal settings.

In New York State, HIV counseling and consented expedited testing are required if a woman presents in labor with no documented HIV test result from her current pregnancy and is not known to be HIV-infected. If the mother declines testing during labor, the infant should be tested immediately after birth. In this setting, consent for test-

ing the newborn is not required. *HIV test results must be returned as soon as possible and no later than 48 hours after the specimen is obtained* (see Appendix XII).

The meaning of a positive preliminary test result should be discussed with the mother, and based on this discussion, the mother and the physician should decide whether to initiate ARV prophylaxis and whether to advise against breastfeeding.

ARV prophylaxis should be initiated as soon as possible during labor or after birth. It is most beneficial prior to birth or within 12 hours after birth and is unlikely to be beneficial if initiated beyond 48 hours after birth (for specific prophylaxis regimens, see Section XV: *Labor and Newborn Management in the Absence of Antenatal Antiretroviral Treatment*).

A confirmatory Western blot assay should be performed as soon as possible after a positive preliminary expedited HIV test result.

The Institute of Medicine recommends a “national policy of universal HIV testing with patient notification as a routine component of prenatal care.”¹⁰ The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists published a joint statement in July 1999 strongly supporting this recommendation.⁷⁸

IX. PRECONCEPTIONAL COUNSELING FOR HIV-INFECTED WOMEN

RECOMMENDATION:

Clinicians should discuss pregnancy planning issues with all HIV-infected women of childbearing age. This should include both a discussion of barrier methods to prevent transmission of HIV and sexually transmitted diseases and information on how to optimize a woman’s chances of having a healthy, HIV-uninfected infant should she wish to become pregnant.

Over the past decade, the number of HIV-infected women of childbearing age has steadily increased. ARV medications and other therapies have simultaneously reduced the risk of mother-to-child transmission and increased the life expectancy for women with HIV. Women’s reproductive choices have become more complex. Early in the epidemic, many women decided

against pregnancy due to fear of having an infected or orphaned child, whereas some are now reconsidering and choosing to become pregnant.

Barrier methods to prevent HIV transmission to an uninfected partner and to protect against other STDs are still recommended for HIV-infected women who choose not to become pregnant. For women who want to become pregnant, however, new concerns should be considered. A woman who chooses to become pregnant should be counseled to avoid known toxic medications, including efavirenz, hydroxyurea, and combination didanosine/stavudine, while maintaining optimal health and virologic suppression. Early identification of pregnancy is essential to minimize first trimester exposure to these drugs and to enable a woman to decide whether to continue or discontinue her ARV regimen.

The recent case reports of neural tube defect and first-trimester abortions in women who conceived while taking efavirenz highlights the need for preconceptional counseling. The occurrence of neural tube defect in the child born to one of these three women causes concern even in cases of very limited early exposure to efavirenz during pregnancy.

X. MONITORING OF HIV-INFECTED WOMEN DURING PREGNANCY

RECOMMENDATIONS:

The monitoring of pregnant HIV-infected women should be similar, if not more attentive, than that for other HIV-infected persons (see Chapter 1: *Antiretroviral Therapy for Adults*).

The provider should assess each HIV-infected pregnant woman early in pregnancy. This assessment should include a classification of clinical, immunologic, and virologic status as well as her support system and her capacity to adhere to medications.

Serum chemistries and complete blood counts should be performed at least every 3 to 4 months, although many experts perform these assays every 4 to 6 weeks, to screen for possible ARV toxicities.

Viral load assessments should be performed at least once a trimester, within 4 weeks after starting or changing ARV therapy. A viral load test should be performed at approximately 33 to 35 weeks' gestation to ensure that the most up-to-date infor-

mation is available for consideration of an elective cesarean section.

Immunologic assessment should be performed every 3 months. Prophylaxis for opportunistic infections should be recommended at the same CD4 cell levels as for non-pregnant adults.

Pneumococcal and influenza vaccines should be given as recommended in non-pregnant adults.

The monitoring of pregnant HIV-infected women should be similar, if not more attentive, than that for other HIV-infected persons. Because the toxicities of ARV therapy mimic the physiologic effects of pregnancy, the clinician should be particularly aware of these symptoms and the accompanying laboratory abnormalities (see Chapter 3: *Side Effects of Antiretroviral Therapy*). Low bicarbonate or hepatic enzyme elevation or increased serum lipase or amylase may help distinguish mitochondrial toxicity from vomiting coincident with pregnancy.

The difficulties in tolerating medication and unique pharmacokinetic parameters affecting maternal drug exposure, especially for protease inhibitors, are additional challenges during pregnancy. The clinician should be vigilant for possible increases in viral load suggestive of difficulties with adherence or developing resistance.

CD4 cell counts are routinely used as surrogate markers to assess the risk of HIV-related disease progression and/or death. Patients who have absolute CD4 cell counts <200 cells/mm³ are at high risk for development of the opportunistic infections that define AIDS. Clinically, CD4 cell counts are used to determine when prophylactic therapies should be initiated.

Routine primary prophylaxis is recommended for *Pneumocystis carinii* when the CD4 cell count decreases to <200 cells/mm³; for *Toxoplasma gondii* when an adult is toxoplasma IgG-seropositive and has a CD4 cell count <100 cells/mm³; and for *Mycobacterium avium* complex (MAC) when a CD4 cell count of <50 cells/mm³ is observed.^{70,79} In addition, because of the morbidity associated with respiratory infections in HIV-infected individuals, pneumococcal vaccination and influenza vaccination should be administered.

However, deferring immunization with these vaccines until after pregnancy is an acceptable option. CDC recommendations for influenza vaccine apply to all HIV-

positive pregnant women after the first trimester. Pregnancy considerations are included in recently published guidelines.^{79,80}

XI. ANTIRETROVIRAL MANAGEMENT FOR PREGNANT WOMEN

RECOMMENDATIONS:

Clinicians should discuss with all patients the use of ARV agents with the dual purposes of preventing mother-to-child transmission and optimizing maternal health. This should include a discussion of the benefits and risks of ARV treatments to both mother and fetus. The provider should be non-coercive and culturally sensitive and should use language and terms that the patient can understand.

The woman should make her final decision about ARV therapy, including which regimen to take, in consultation with an HIV Specialist.

If a woman decides to refuse any level of ARV therapy or care, her provider should not deny her any other aspects of care. The provider should continue to recommend ARV therapy at subsequent visits and should discuss possible barriers to taking it.

The provider should stress the importance of adherence to a treatment regimen. Adherence to therapy should be encouraged and monitored at all antepartum and postpartum visits.

Efavirenz and hydroxyurea should be avoided in pregnant women.

The combination of didanosine and stavudine should be avoided in pregnant women if another alternative is feasible.

Intravenous zidovudine during labor should be strongly recommended for all HIV-infected pregnant women, regardless of which antenatal regimen they received.

The factors that affect the decision of which ARV medications to take are complicated and can sometimes be contradictory. Balancing the need for maximal viral suppression with unknown potential side effects is often challenging.

The choice of HAART is complex and involves an understanding of the pharmacokinetics, toxicities, and drug interactions (see Chapters 1: *Antiretroviral Therapy for Adults*; 3: *Side Effects of Antiretroviral Therapy*; and 4: *HIV Drug-Drug Interactions*).

Normal physiologic processes during pregnancy seem to significantly alter pharmacokinetic parameters. Preliminary data indicate that standard adult dosing of protease inhibitors in pregnant women may lead to significantly subtherapeutic drug concentrations.⁸¹

Pharmacokinetic enhancement with ritonavir to achieve therapeutic levels of protease inhibitors has been successful in non-pregnant adults (see Chapter 4: *HIV Drug-Drug Interactions*) but has not been studied in pregnant women.

Factors to consider in selecting the appropriate HAART regimen in HIV-infected patients include the following:

- Relative ability of available regimens to inhibit HIV-1 replication for prolonged periods of time (potency and durability of the response)
- The potential for the emergence of drug resistance and future treatment failures
- Toxicities associated with prolonged therapy
- The patient's ability to adhere to complex treatment regimens

Pregnancy presents unique treatment considerations including the following:

- Concerns about the infant's drug exposures during the first trimester (the critical time for human organogenesis)
- Both short- and long-term safety for uninfected and infected infants following *in utero* exposures
- Impact of maternal ARV therapy to optimize maternal health and prevent mother-to-child HIV-1 transmission
- Impact of the ARV regimens used during pregnancy on the ability of future ARV regimens to control maternal viremia
- Impact of the ARV regimen used during pregnancy on selection of resistant virus that may or may not be transmitted to the newborn
- Pregnancy-associated symptoms (emesis, heartburn, and depression) that may limit adherence

and potentially increase the risk of drug resistance during pregnancy and in the postpartum period

The goal of ARV therapy is to control viral replication. Women should be counseled that potent ARV regimens are associated with improved clinical, immunologic, and virologic status and provide enhanced protection against perinatal transmission.^{21,82,83} Whether or not these benefits are applicable for patients with low circulating viral loads is currently under investigation.

Therapeutic agents inhibiting different parts of the HIV-1 replication cycle are typically combined in a treatment regimen. It is possible to achieve undetectable plasma viral levels in many patients, although the duration of this response is not known. HAART regimens that include three or more drugs should be used for initial therapy.^{80,83,84} The three-drug combinations most commonly used include two nucleoside reverse transcriptase inhibitors with a protease inhibitor.

For more specific information regarding specific ARV agents or combinations, see Chapter 1: *Antiretroviral Therapy for Adults* and the current federal guidelines.⁸⁵

XII. SPECIFIC ANTIRETROVIRAL ISSUES FOR AN ANTIRETROVIRAL-NAIVE PREGNANT WOMAN

A. Women With Viral Loads >1,000 Copies/mL

RECOMMENDATIONS:

If a woman's viral load is >1,000 copies/mL, the provider should recommend a HAART regimen that includes the three-part zidovudine regimen (see Appendices IX and X).

If a woman chooses not to receive HAART, she should be offered, at a minimum, the three-part zidovudine regimen (see Appendix X).

The provider should recommend that most women who begin ARV therapy during pregnancy start after the first trimester. For women with severe clinical, immunologic, or virologic disease, the urgent need for viral suppression may outweigh the risk of fetal toxicity during the first trimester.

B. Women With Viral Loads <1,000 Copies/mL

RECOMMENDATIONS:

If a woman's viral load is <1,000 copies/mL, the provider should recommend at least the three-part zidovudine regimen (see Appendices IX and X).

The provider should discuss both the increase in potential toxicities and the slightly decreased risk of transmission for women receiving HAART despite a viral load <1,000 copies/mL. The provider should discuss the benefits and risks of HAART for women with viral loads <1,000 copies/mL without making a recommendation.

If a woman with a viral load <1,000 copies/mL strongly desires to receive HAART, the provider should make it available to her.

The provider should recommend that women with a viral load <1,000 copies/mL who begin ARV therapy during pregnancy start after the first trimester.

XIII. SPECIFIC ANTIRETROVIRAL THERAPY ISSUES FOR ANTIRETROVIRAL-EXPERIENCED PREGNANT WOMEN

RECOMMENDATIONS:

Providers should give women the option of continuing or discontinuing their ARV therapy during the first trimester. This decision will involve consideration of its potential effectiveness in suppressing viral load, the tolerability of the regimen, and the potential for toxicity during this period of organogenesis.

For women who choose to temporarily discontinue their regimen, all drugs should be discontinued and then restarted simultaneously.

Providers should recommend alternative regimens for women receiving efavirenz, hydroxyurea, or combination didanosine/stavudine.

Providers should discuss and stress the importance of adherence with all pregnant women receiving ARV therapy.

Resistance testing should be performed for all women who have detectable viral loads despite

adhering to HAART to help determine the most suitable regimen.

Providers should offer alternative regimens for all women who are adhering to ARV therapy but who do not have undetectable levels of virus. Unless contraindicated, these new regimens should contain zidovudine. Regardless of the woman's antenatal regimen, intravenous zidovudine should be recommended during the intrapartum period.

Both the success and toxicity of the current regimen should be evaluated. Factors to consider include first trimester safety during the period of major human organogenesis and other potential maternal or fetal toxicities. Discontinuation of maternal treatment is likely to be associated with rebound viremia and may have potentially adverse effects on maternal health and/or mother-to-child transmission. Discontinuation of a single drug from a successful combination regimen may result in selection of resistant virus. For patients who have had good virologic and clinical responses to their current ARV regimen, the benefits of continuing therapy may outweigh the risks even during the first trimester.

The indications for changing an ARV regimen include treatment failure, toxicity, non-adherence, and current use of a suboptimal treatment regimen. Treatment failures are indicated by a significant increase in the HIV RNA levels, failure to achieve the desired reduction in plasma viral load, a declining CD4 cell count, treatment intolerance, or clinical disease progression.

XIV. MODE OF DELIVERY

Although this document focuses primarily on ARV therapy for pregnant women, data demonstrating that elective cesarean section decreases the risk of maternal-infant HIV transmission in certain situations prompts discussion of it as part of a strategy to prevent perinatal transmission of HIV.

RECOMMENDATIONS:

The provider should discuss the risks and benefits of a scheduled cesarean section as opposed to a vaginal delivery with each pregnant woman. This discussion should include the potential increase in morbidity of cesarean section for both the woman and infant contrasted with a

lower rate of transmission of HIV with scheduled cesarean section.

The provider should respect a woman's autonomy to decide which mode of delivery is best for her.

The provider should explain that the anticipated benefit from a cesarean section is dependent on the risk of HIV transmission; when other factors, such as viral suppression and ARV prophylaxis, are optimized, the benefit from a cesarean section is less.

The provider should discuss the benefits and risks of cesarean section with each woman. To help the woman make the most informed decision, the provider should inform her about rates of transmission among women with viral load levels similar to hers and among women receiving the ARV regimen that she is receiving.

Scheduled cesarean section before onset of labor or ruptured membranes is recommended for women with no antenatal ARV therapy or with a viral load >1,000 copies/mL at the time of delivery.

If a woman chooses cesarean section, it should be performed at 38 weeks' gestation. The woman should receive prenatal ARV medications for as long as possible until the surgery and should receive at least 3 hours of intravenous zidovudine prior to the surgery. The newborn should receive one of the ARV regimens listed in Section XV:

Labor and Newborn Management in the Absence of Antenatal Antiretroviral Treatment.

The benefit of cesarean section after onset of labor is unknown. Women in whom labor is rapidly progressing should be allowed to deliver vaginally. Rupture of membranes should be delayed as long as possible. When a provider anticipates a long period of labor and/or possible prolonged rupture of membranes, the clinician and patient should weigh the risks of cesarean section against the benefit of reducing duration of rupture of membranes for women already in labor.

The risk of mother-to-child transmission is extremely low for women with viral loads <1,000 copies/mL, although transmission can still occur at these levels.⁸⁶⁻⁸⁸ One study revealed that women within this viral load

stratum who underwent scheduled cesarean sections had a lower risk of transmission as opposed to women who delivered vaginally.⁸⁸ The risks of cesarean section for both a woman and her infant are well known. The risks and benefits of cesarean section for women with viral loads <1,000 copies/mL or receiving aggressive ARV treatment are not clear; the provider should explain the risks and benefits to allow each woman to make the most informed decision.

XV. LABOR AND NEWBORN MANAGEMENT IN THE ABSENCE OF ANTENATAL ANTIRETROVIRAL TREATMENT

RECOMMENDATION:

For women who have received no antenatal ARV therapy, options for prevention of transmission include the following (see Appendix XI):

- 1) intrapartum intravenous zidovudine followed by 6 weeks of zidovudine to the newborn; or**
- 2) single-dose nevirapine at the onset of labor followed by a single dose of nevirapine to the newborn at 48 hours; or**
- 3) oral zidovudine/lamivudine during labor followed by 1 week of oral zidovudine to the newborn; or**
- 4) the two-dose nevirapine regimen at the onset of labor combined with intrapartum intravenous zidovudine and 6 weeks of zidovudine to the newborn.**

Current scientific data show a significant risk of HIV-1 transmission at the time of labor and delivery. Observational data from New York State support the efficacy of intrapartum/newborn zidovudine therapy and even for newborn zidovudine prophylaxis alone when initiated soon after birth.⁹ Data from HIVNET 012 support the efficacy of single-dose oral nevirapine to the mother in labor combined with one dose to the infant within 72 hours of life.¹⁷ Data from the PETRA study support the efficacy of zidovudine/lamivudine administered in labor and for 1 week to the newborn.¹⁶

XVI. ANTIRETROVIRAL PROPHYLAXIS FOR HIV-EXPOSED INFANTS

RECOMMENDATIONS:

If the mother has not received ARV therapy during pregnancy or labor, 6 weeks of zidovudine for the newborn is still recommended. In such situations, zidovudine should be started immediately after birth or as soon as the child is identified as HIV-exposed. In this circumstance, clinicians may give a single dose of nevirapine to the newborn as soon as possible after birth in addition to the 6-week newborn zidovudine regimen; however, no data yet exist demonstrating the benefits of this approach.

When a mother has not received any antenatal treatment but has received intrapartum treatment, the newborn should receive the same ARV regimen that was given to the mother. Options 1-4 are in Section XV and Appendix XI.

When a mother has received antenatal ARV, the newborn should be given at least the 6-week course of zidovudine.

The efficacy and safety of combining the zidovudine/lamivudine and nevirapine regimens or of giving HAART to newborns to prevent transmission have not been studied. Such regimens should be considered with extreme caution and in consultation with a pediatric HIV Specialist.

Premature infants and newborns unable to tolerate oral medication will require dose modification in conjunction with a pediatric HIV Specialist.

In infants whose mothers have not received ARV prophylaxis, the data from the New York State observational study demonstrate the efficacy of zidovudine prophylaxis when initiated soon after birth.⁹ A CDC retrospective case control study of post-exposure prophylaxis in health care workers supports this intervention, showing a 79% reduction in transmission when given zidovudine after percutaneous exposure to HIV.⁸⁹

Data from both the PETRA study and the CDC study in Thailand demonstrate the importance of a newborn component to the ARV prophylaxis regimen when the mother receives only intrapartum or short prenatal courses of prophylaxis.

In cases in which the risk of transmission is very high, some clinicians may consider more aggressive ARV prophylaxis for the exposed newborn, combining the single-dose nevirapine and the zidovudine/lamivudine regimens listed in Section XV or using HAART.

There are no data regarding safety or efficacy of combining zidovudine and nevirapine for preventing perinatal transmission, nor are there data to either support or reject the use of nevirapine/zidovudine/lamivudine or HAART in this post-exposure setting. Clinical trials of these regimens are planned but are not yet underway. Few studies have been completed describing the pharmacokinetic parameters of ARV agents other than zidovudine or nevirapine in newborns or young infants. The clinician should balance the risk of transmission against the risk of adverse effects from the medications and also consider the history of maternal ARV therapy, viral load, resistance profile, mode of delivery, and duration of rupture of membranes.

The zidovudine dose for full-term infants is 2.0 mg/kg orally every 6 hours or 1.5 mg/kg intravenously every 6 hours if the infant is not able to tolerate oral feedings. The hepatic glucuronidation enzymatic system, the major route of zidovudine metabolism, is relatively immature in newborns and especially in preterm infants. This phenomenon results in delayed zidovudine clearance, resulting in the increased half-life of zidovudine observed in a study of premature infants (26-32 weeks' gestation).⁹⁰ A regimen of oral or intravenous zidovudine dose of 1.5 mg/kg every 12 hours during the first 2 weeks of life followed by a regimen of 2.0 mg/kg every 8 hours until 6 weeks of age is recommended in preterm infants.

XVII. POST-PARTUM MANAGEMENT FOR THE MOTHER AND CHILD

RECOMMENDATIONS:

Proper ARV management requires continuity of care after the mother has delivered and a home environment conducive to giving medication and close medical follow-up. Referrals for case management, visiting nursing, and other services should be made as needed.

The clinician should ensure that a woman's records, in particular her ARV medication history, are transferred both to her primary care doctor

once she is no longer pregnant and to the baby's pediatric primary and pediatric HIV Specialist.

An appointment with a pediatric HIV Specialist should be made before the infant is discharged from the nursery. Precautions to protect the confidentiality of patient information should be ensured.

A woman should be examined by her provider at approximately 2 weeks post-partum.

The provider should ensure that both mother and baby receive an adequate supply of ARV medication to continue the regimen through their post-partum and pediatric visits.

A woman may choose to continue or discontinue ARV medications after she has delivered. This decision is hers and should be made in concert with her primary care provider. The provider should make recommendations that are consistent with the guidelines in Chapter 1: *Antiretroviral Therapy for Adults*.

Breastfeeding by HIV-infected women is not recommended in the United States; if the infant has been breastfeeding, the mother should be counseled to discontinue.

Although anatomical abnormalities have not been reported to date, all infants exposed to ARV agents *in utero* should be examined for congenital abnormalities. If congenital abnormalities are found, they should be reported to the New York State Congenital Malformations Registry.

XVIII. PEDIATRIC FOLLOW-UP

RECOMMENDATIONS:

For newborns exposed to zidovudine, a complete blood count should be obtained at birth and at the completion of the 6-week course of therapy. Some clinicians recommend an additional monitoring visit at 3 to 4 weeks of life to assess the need for dose interruption or modification based on the amount of weight gained by the infant.

Routine evaluations should be performed for the early diagnosis of newborn HIV infection. HIV DNA PCR or HIV cultures are approved diagnostic tests for HIV infection in newborns. Plasma

HIV RNA PCR should not be used as the sole diagnostic assay.

The timing of the first diagnostic test may vary; some clinicians recommend PCR testing as soon as possible after birth, while others may wait 2 or 4 weeks before testing.

For initial HIV testing, clinicians may either use the NYSDOH's Wadsworth Center in Albany, which provides testing at no cost (telephone no.: 518-474-2160) or submit documentation of HIV diagnostic test results from a laboratory with an appropriate New York State permit.

Definitive diagnosis of HIV-1 infection can be made in most infants by 4 months of age using the HIV-DNA PCR assay.⁹² HIV infection can be reasonably excluded in HIV-exposed infants with two or more negative HIV DNA PCR tests, one performed at or after 1 month of age and one at or after 4 months of age. An infected child is defined as a child of any age who has tested positive by PCR on two separate determinations. In PACTG 076, infants who received zidovudine prophylaxis had no delay in the time to establish or exclude definitive diagnosis of their HIV infection status. The length of time to establish HIV status has not been studied in infants born to women receiving other ARV therapy.

HIV-infected infants should receive comprehensive medical and psychosocial care in accordance with the updated NYSDOH/AI guidelines.⁹¹

Consultation with an HIV Specialist is strongly recommended.

ARV prophylaxis should be discontinued once the diagnosis of HIV infection has been established.

An ARV treatment regimen should be initiated in consultation with a pediatric HIV Specialist (see Chapter 2: *Pediatric Antiretroviral Therapy*).

At 4 to 6 weeks of age, prophylaxis to prevent *Pneumocystis carinii* pneumonia should be initiated for HIV-exposed as well as HIV-infected infants.

Clinicians need to develop confidential systems to track and, if necessary, contact ARV-exposed, HIV-uninfected individuals if long-term toxicities are suspected or identified.

The NYSDOH is developing methods to look at long-term follow-up of ARV-exposed infants.

Clinicians should emphasize the need for the child's guardian to share responsibility for transmitting the child's history, including the history of his/her ARV exposure, to future primary care providers.

Adherence to public health guidelines to prevent mother-to-child HIV transmission and the treatment of maternal HIV disease during pregnancy has resulted in a large number of uninfected children with exposures to multiple ARV agents both *in utero*, including during the first trimester, and in early infancy. The possibility of unanticipated, long-term toxicities remains a concern. For these reasons, as these children age, it is critical that information concerning their ARV exposures is transferred to the child's medical record and to the future medical provider.

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