Special Contribution
Perinatal HIV: Special Considerations

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The percentage of AIDS cases among women—particularly women of color—in the United States is increasing yearly. Despite this increase, there has been a relatively steady decline in the number of AIDS cases occurring perinatally. Regardless of the reasons HIV-infected couples choose to become pregnant, studies indicate that providing support, such as contraceptive counseling and assisted reproduction techniques, can improve the health outcome in the face of HIV-related challenges. Issues specific to antiretroviral therapy, including viral resistance, pregnancy outcomes, and adverse fetal effects, complicate the treatment of perinatal HIV. Postpartum care is yet another area that requires special consideration when supporting HIV-infected parents and children. The growing body of data on pregnancy and HIV may indicate a rising commitment to research of and support for the unique challenges HIV-infected families face. This article was adapted from an IAS–USA interactive, case-based program, Cases on the Web, in November 2003.

According to UNAIDS, a joint United Nations program on HIV/AIDS, there are approximately 19.2 million women living with HIV or AIDS, accounting for nearly half of all infections worldwide. Similarly, an estimated 3.2 million children under the age of 15 are living with HIV or AIDS, the overwhelming majority of whom acquired HIV through perinatal transmission and live in Sub-Saharan Africa. Although this article focuses on the care of the HIV-infected pregnant woman in resource-rich settings, it is crucial to appreciate that the burden of the HIV/AIDS epidemic lies within the developing world.

In the United States, the prevalence of HIV/AIDS among women varies dramatically by geographic region, with the largest share of AIDS cases in the northeast and southeast regions of the country. In 2001, the overall prevalence of AIDS was 9.1 cases per 100,000 women. New York had the highest prevalence with 30.3 AIDS cases per 100,000 women. Moreover, AIDS incidence and the percentage of AIDS cases are increasing yearly among women, particularly among women of color. Although the majority of HIV infections in the United States are among men, an estimated 29% of HIV infections are among women, in those areas with reporting to the Centers for Disease Control and Prevention (CDC).

Epidemiology of Perinatal HIV Transmission

There has been a steady decline in the number of perinatally acquired AIDS cases among infants in the United States, with an estimated incidence of 101 pediatric AIDS cases in 2001, down from a peak of 954 cases in 1992. This change likely represents not only decreased perinatal HIV transmission but also increased use of Pneumocystis carinii pneumonia (PCP; also known as Pneumocystis jiroveci pneumonia) prophylaxis and combination therapy for children, with consequent prolonged AIDS-free survival among perinatally infected infants. It is difficult to estimate perinatal HIV prevalence. Wang-modeled perinatal AIDS surveillance data show an apparent decline in perinatal HIV acquisition in the United States, from 1650 cases in 1991 to 480 cases in 1996. This difference likely represents an increase in the use of zidovudine among HIV-infected pregnant women. Since publication of the landmark AIDS Clinical Trials Group (ACTG) 076 study, prenatal zidovudine use has dramatically increased among pregnant women identified as HIV infected, from 28% in 1994 to 76% in 1997.

The likelihood of perinatal transmission varies dramatically based on numerous risk factors, which will be described below. Nevertheless, most of the early placebo-controlled trials and observational studies conducted in industrialized, non-breast-feeding settings demonstrate a transmission prevalence of approximately 25% without any HIV-specific interventions.

Reproductive Choices Among HIV-Infected Women

Numerous studies have demonstrated that most women and men continue to be sexually active after receiving a diagnosis of HIV infection. The reasons individuals and couples decide to conceive or contracept, or to continue or to terminate a pregnancy, are complex, particularly in the context of HIV infection. Often overlooked by the general HIV provider is a patient’s desire to become pregnant. As people with HIV infection are living longer, healthier lives, and as antiretroviral therapy has dramatically decreased the likelihood of mother-to-child transmission, some HIV-infected women are choosing to become pregnant. Similarly, 1 study found that exposing HIV-infected women to an educational brochure about mother-to-child transmission that included information about zidovudine increased some women’s intentions to continue their current pregnancy and to plan for future pregnancies. In fact, there is a growing body of literature addressing the ethics and science of providing assisted reproduction techniques to HIV-infected pregnant women in settings with full access to antiretroviral therapy. The choices described in this activity may not be applicable to resource-limited settings. For further information on the care of HIV-infected pregnant women in resource-limited settings, please visit: http://www.womenschildrenhiv.org/.
infected women and HIV-serodiscordant couples, both for infertility treatment and for HIV transmission prevention.23,26

Impact of Pregnancy on HIV

Pregnancy is an immensely complex physiologic and immunologic state, but it does not appear that pregnancy accelerates the course of HIV infection.27 Several investigators have sought to understand the immunology of pregnancy among HIV-infected women. There is evidence, for instance, of altered T-cell function,28 a decline in mean CD4+ cell count,29,30 and altered CD8+ cell count31,32 among HIV-infected pregnant women. However, the immunologic implications of these changes are unclear. Newell and colleagues have demonstrated that, although the absolute CD4+ cell count tends to drop during pregnancy, CD4+ and CD8+ cell percentages appear stable, likely representing the physiologic hemodilution of pregnancy.30 Moreover, a number of studies have now demonstrated that pregnancy itself does not appear to accelerate the progression to AIDS, severe immunosuppression (ie, CD4+ count <100 cells/μL), opportunistic infections, or death.32-36 Furthermore, there does not appear to be an association between pregnancy and increased plasma HIV-1 RNA level.37

Impact of HIV on Pregnancy

Overall, obstetrical outcomes of pregnant women infected with HIV appear to be similar to those of uninfected women. Yet, the Women and Infant Transmission Study (WITS) found an association between significant immunosuppression during pregnancy (<14% CD4+ cells) and delivery of a low birth weight neonate (adjusted odds ratio [OR], 3.81; 95% confidence interval [CI], 1.41-10.28).38 This study also noted a trend toward increased risk of preterm birth (OR, 2.5; 95% CI, 0.98-6.28) in women with a CD4+ cell percentage less than 14.38

Diagnosis of HIV in Pregnancy

Given the many successful interventions now available to prolong AIDS-free survival and to reduce mother-to-child transmission, attention must be turned to ensuring universal HIV testing among pregnant women and access to quality prenatal care among those women known or found to be HIV-infected. Many perinatal HIV cases in the United States represent missed opportunities, in that they lack prenatal care29 and lack HIV testing despite prenatal care.39 Among the 329 children with perinatally acquired AIDS born in 1995 and 1996, 34% were born to women who underwent HIV testing after delivery.40 Similarly, an estimated 40% of US women who delivered HIV-infected infants in 2000 had not been tested for HIV prior to delivery.41

Considerable controversy exists regarding the most effective and ethical approach to HIV testing in pregnant women. The 2 most common strategies are “opt-out” and “opt-in.” In an opt-out approach, women are informed of the inclusion of HIV testing in the standard battery of prenatal labs and may decline such testing. Opt-in strategies use more traditional voluntary HIV counseling and testing techniques, with a specific informed-consent process. The CDC recently documented widely disparate prenatal HIV testing frequencies throughout the United States and Canada.42 Prenatal HIV testing was most common in areas with an opt-out approach, including Tennessee (85%) in the United States and Alberta (98%) and Newfoundland/Labrador (94%) in Canada. Regions using an opt-in approach had testing frequencies as low as 25% (3 counties in the Portland, Oregon, area) and 39% (3 counties in the San Francisco bay area). Similarly, among the 83 pregnancies complicated by HIV infection in the Kaiser Permanente Northern California health care system, only 20% were identified through an opt-in strategy.43

Although the opt-out strategy appears to increase prenatal HIV testing on a population level, it is important to appreciate the implications of testing an individual woman for HIV during her pregnancy. For instance, the overall prevalence of domestic and sexual violence among HIV-infected women is nearly 50% in some studies.44 Some authors report increased risk of domestic violence with disclosure of HIV seropositivity.45,46 although other studies have not found such an association.47

Rapid HIV testing has received much attention due to the increasing availability of reliable technology and a growing body of literature demonstrating the effectiveness of abbreviated intrapartum and neonatal antiretroviral therapy.48 In November 2002, the US Food and Drug Administration (FDA) approved a rapid HIV-1 antibody test. This test is a lateral-flow immunoassay that may be used on whole blood, with results available in approximately 20 to 30 minutes. Reported sensitivity and specificity are 99.6% and 100%, respectively, compared with enzyme-linked immunosorbent assay (ELISA) technology.49 Single Use Diagnostic System for HIV-1 (SUDS), which was approved in 1992, requires centrifugation and immediate confirmatory testing and takes approximately 1 hour overall. SUDS has a sensitivity of 100% and a specificity of 98% as compared with standard ELISA, with a positive predictive value (PPV) of only 33%, reflecting the overall low prevalence of HIV in this cohort.50 Both the new rapid test and SUDS require a confirmatory Western blot or immunofluorescent antibody (IFA).

Rapid HIV testing is cost effective among women presenting in labor with no prenatal care, with an estimated savings of more than $10 million to the US health care system compared with the cost of treating all unregistered women presenting in labor with zidovudine or not treating any unregistered women.51 The Mother Infant Rapid Intervention at Delivery (MIRIAD) study is a multisite study evaluating the feasibility of rapid testing and the effectiveness of intrapartum therapy to reduce mother-to-child transmission.41 As of November 2002, 1771 women in the study had undergone rapid HIV testing. Twelve women had been identified as being infected with HIV, with no false-negative or false-positive tests thus far. Although this technology will bring a new level of perinatal HIV prevention, the social and psychological implications of intrapartum testing will likely be profound. Research on abbreviated antiretroviral therapy regimens abroad raises many ethical issues given the current standard of care of the HIV-infected individual in the resource-rich setting.52,54 Although controversial, the results from these studies offer insight into mechanisms of transmission and may influence decisions about
antiretroviral therapy regimens among HIV-infected, untreated women presenting to labor and delivery.

**Timing of Mother-to-Child Transmission**

Among non-breast-feeding women, approximately 25% to 35% of transmissions occur during the antepartum period, with 95% of in utero infections appearing to occur in the last 2 months of pregnancy.66-67 One study demonstrated transmission of HIV among late-second-trimester (17-24 weeks) abortus, with a transmission prevalence of 11.1% among women with plasma HIV-1 RNA levels greater than 100,000 copies/mL and 3.1% among women with plasma HIV-1 RNA levels less than 100,000 copies/mL.66 Of the 65% of infections that occur at the time of delivery, the median duration to detectable virus in infants is approximately 10 days (95% CI, 6-14 days).59

**Mother-to-Child Transmission Risk Factors**

There are numerous risk factors that increase the chance of mother-to-child transmission of HIV infection, including maternal, obstetrical, and neonatal variables.

**Maternal Factors**

In most recent studies, maternal HIV-1 RNA level at delivery remains the most consistent predictor of mother-to-child transmission.60-66 However, no threshold HIV-1 RNA level exists below which transmission does not occur or above which transmission always occurs.66,67 Among pregnant women taking zidovudine, each log copies/mL increment in HIV-1 RNA level at delivery was associated with an OR of 3.4 (95% CI, 1.7-6.8).62 Transmission prevalence has been seen as high as 63.3% among women with HIV-1 RNA levels greater than 100,000 copies/mL without zidovudine treatment. Further, an HIV-1 RNA level greater than 1000 copies/mL appears to be particularly predictive of transmission among women with a CD4+ count greater than 500 cells/µL (OR, 2.7; 95% CI, 1.5-5.1 per log10 HIV-1 RNA level).68 Low maternal CD4+ cell count is similarly associated with higher transmission of HIV.65,66,69-73 One study found a decreased CD4+ cell percentage to be associated with increased risk of transmission (OR, 1.4; 95% CI, 1.1-1.7).72 Maternal viral properties, such as viral homogeneity and rapid replication kinetics, have also been linked to increased risk of HIV transmission.74

There is limited and conflicting evidence that viral resistance may increase the likelihood of mother-to-child transmission. Among women receiving zidovudine monotherapy in the early years of the WITS, any reverse transcriptase resistance mutation was associated with increased risk of transmission (OR, 5.16; 95% CI, 1.40-18.97).73 A substudy of ACTG 076 did not note an association between zidovudine resistance and mother-to-child transmission (OR, 4.8; 95% CI, 0.2-131), but, as the wide confidence interval suggests, the study was too small to find such an association.76 Issues of antiretroviral therapy resistance in the perinatal setting will likely only become more troublesome as the prevalence of primary resistance grows in this population. For instance, Juethner and colleagues detected genotypic nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance among 17% of antiretroviral therapy-naive pregnant women in St. Louis, Missouri, between 1999 and 2001.77

**Obstetrical Factors**

Prolonged rupture of membranes (ROM) has been shown to be a risk factor for HIV transmission among women both treated and untreated with antiretroviral therapy during pregnancy.66,72,78 Prolonged ROM appears to be particularly risky among women with low CD4+ cell counts71,73,80 and women at preterm gestation.82 A meta-analysis conducted by the International Perinatal HIV Group found an increased probability of transmission from 8% at 2 hours to 32% at 24 hours after membrane rupture among women with AIDS.80 Among those women without AIDS, the likelihood of transmission increased with prolonged ROM but not significantly so.80 Preterm delivery is an additional risk factor for intrapartum HIV transmission.82 Similarly, chorioamnionitis, an infection of the chorion-aminion space, increases the risk of mother-to-child transmission.81,84 One study found an association between intrapartum fetal scalp electrodes/fetal scalp sampling and transmission to the neonate (OR, 3.5; 95% CI, 1.2-9.6).83 Older studies that do not adjust for plasma HIV-1 RNA level have demonstrated increased transmission with intrapartum maternal hemorrhage,81 maternal sexually transmitted infections, and amniocentesis.81,85

**Neonatal Factors**

Neonatal variables such as premature birth at less than 35 weeks gestation70 and birthweight less than 2500 g66,71,86 are associated with neonatal HIV acquisition. HLA class I maternal-neonatal concordance also appears to increase the risk of transmission (OR, 3.79; 95% CI, 1.14-12.7).84,87 Of note, neonatal CCR5-32 heterozygosity does not appear to confer a protective effect on HIV acquisition.88

**Breast-feeding**

Numerous studies have demonstrated HIV transmission through breast-feeding.89-93 A meta-analysis found a 15% additional risk of transmission due to breast-feeding.94 Nduati and colleagues confirmed these results in a randomized controlled trial of breast-feeding versus bottle-feeding in Kenya, with a documented 16% transmission via breast-feeding.95 In this cohort of women, 44% of mother-to-child transmissions appeared attributable to breast-feeding.

**Antiretroviral Therapy in Pregnancy**

ACTG 076 revolutionized the management of HIV-infected women by demonstrating a nearly 70% decrease in perinatal transmission among non-breast-feeding women from 25.5% (placebo arm) to 8.3% (prenatal/neonatal zidovudine arm).5 Since the publication of this landmark study, other trials have demonstrated the effectiveness of abbreviated regimens of zidovudine, zidovudine/lamivudine, and nevirapine in reducing mother-to-child transmission among both breast-feeding and
non-breast-feeding cohorts. Nonetheless, since the mid-1990s, there has been an increased appreciation of the value of highly active antiretroviral therapy (HAART) in achieving maximum viral suppression and prolonging AIDS-free survival among adults and children. No clinical trial has compared HAART with either zidovudine monotherapy or 2-drug regimens among pregnant women. However, several observational studies have demonstrated remarkably low mother-to-child transmission in the setting of HAART. The lowest transmission prevalence observed is among women with maximally suppressed virus at the time of delivery, and this is certainly most likely to occur among women on HAART. In the WITS cohort, transmission occurred in 20% of women with no pre-natal antiretroviral therapy, 10.4% of women who received zidovudine monotherapy, 3.8% of women who received dual therapy, and 1.2% of women who received HAART. Similarly, the PACTG 367 study found the lowest transmission frequency among women on multiagent regimens (1.8%), compared with those on zidovudine monotherapy (5.3%) and those taking no therapy (20%). The authors reported an overall transmission of only 0.9% among women with HIV-1 RNA levels less than 1000 copies/mL at delivery. Among these women with low delivery HIV-1 RNA levels, transmission prevalence differed, though not significantly, by complexity of regimen (1.8% for monotherapy vs. 0.8% for multiagent). However, PACTG 316 found that the addition of 2-dose intrapartum and neonatal nevirapine to standard antiretroviral therapy does not confer additional protection given the already low risk of transmission (1.6% in placebo arm vs. 1.4% in nevirapine arm).

Even among women with an HIV-1 RNA level less than 1000 copies/mL at the time of delivery, antiretroviral therapy likely protects against mother-to-child transmission. One European and US collaborative study specifically evaluated transmission among women with HIV-1 RNA levels less than 1000 copies/mL at or near delivery. The researchers demonstrated an independent protective effect of antiretroviral treatment (OR, 0.10) among these women with an already low risk of transmission. There is controversy, however, about the optimal regimen for immunocompetent HIV-infected pregnant women with low baseline HIV-1 RNA levels. Some have proposed zidovudine monotherapy as per ACTG 076 given the low risk of transmission, ease of administration, and low maternal and fetal/neonatal toxicity. Zidovudine monotherapy is not without its risks, however. Eastman and colleagues found that 1 of 39 women in a subanalysis of ACTG 076 developed an incident K70R mutation, with no one developing a T215Y/F mutation. The Swiss HIV and Pregnancy Study, on the other hand, reported a 9.6% prevalence of the T215Y/F mutation (6 of 62 women). Of those 6 women, 5 women likely had the mutation emerge after exposure to zidovudine monotherapy, 1 in whom it emerged after only 17 weeks. As we learn more about latent reservoirs and resistance and are able to detect even lower levels of HIV in plasma, the provision of HAART to pregnant women with very low baseline viral loads will likely become standard of care. The initial "hit early, hit hard" paradigm more recently has been tempered by growing evidence of adverse sequelae of long-term HAART. When choosing an antiretroviral regimen for any HIV-infected individual, it is crucial to weigh the full range of issues, including immune status, past regimens, genotypic and phenotypic resistance, medication potency, tolerability, future medication options, comorbidities such as viral hepatitis, pill burden, and risk of medication nonadherence. Additional considerations for pregnant women include maternal, fetal, and neonatal toxic effects, as discussed below. A clinician must also explore the goal of antiretroviral therapy in pregnancy, whether it is for long-term viral suppression or simply for chemoprophylaxis to prevent mother-to-child transmission. Clinicians (or medical providers) must try not to compromise long-term options while seeking to prevent mother-to-child transmission.

Resistance

Resistance most commonly arises in the setting of incomplete viral suppression. Perinatal regimens that include zidovudine monotherapy, dual therapy, or postpartum treatment interruptions may make women vulnerable to acquiring resistance mutations. A substudy of ACTG 076 demonstrated a 6.7% prevalence of K70R at study entry and a 2.6% incidence of K70R. Among 83 pregnant women delivering at Bellevue Hospital in New York between 1995 and 1999, T215Y prevalence was 9.7%. The WITS cohort found 25% zidovudine resistance among women exposed to zidovudine monotherapy between 1989 and 1994. The rapid development of resistance has been noted among pregnant women taking zidovudine/lamivudine, with 80% (4 of 5) of pregnant women developing a M184V mutation prior to delivery and the remaining 20% acquiring an M184V mutation postpartum.

Nevirapine has also been associated with rapid development of the K103N mutation among pregnant women. HIVNET 00617 detected 19% and 20% prevalence of nevirapine resistance, respectively, among women after a single intrapartum dose of nevirapine. Reversion to wild-type virus was seen within 12 to 24 months among these women, who did not receive postpartum antiretroviral therapy. Nonetheless, reemergence of nevirapine resistance is highly likely if those women are ever re-challenged with nevirapine. The PACTG 316 trial evaluated the benefit of adding intrapartum nevirapine to standard perinatal antiretroviral therapy in the United States, Brazil, Bahamas, and Europe. Fifteen percent of women in the nevirapine arm developed nevirapine resistance by 6 weeks postpartum. Development of resistance was not associated with delivery CD4+ cell count, HIV-1 RNA level, or antepartum regimen, although the study was too small to determine such associations. Interestingly, 21% of the women who acquired nevirapine resistance had HIV-1 RNA levels less than 1000 copies/mL at the time of nevirapine exposure. There was no analysis by postpartum continuation versus discontinuation of antiretroviral therapy, and the high incidence of resistance may be explained by the prolonged half-life of nevirapine.

Resistance is an evolving issue among infants as well. Among HIV-1-infected infants in New York state, 6.3% of those born in 1992 to 1994 compared with 33.3% of those born in 1998 to 1999 had a 215 mutation detected. Forty-six percent of infected infants exposed to 2-dose maternal and postpartum neonatal nevirapine in HIVNET 012 demonstrated nevirapine
The transmission of multidrug-resistant HIV-1 from mother to infant has also been documented, with serious consequences for future treatment options.\textsuperscript{120}

**Pregnancy Outcomes**

There are numerous case reports of severe lactic acidosis and hepatic failure among pregnant or postpartum women on nucleoside reverse transcriptase inhibitor (nRTI) therapy.\textsuperscript{121-125} Three women who died of lactic acidosis were taking stavudine and didanosine as part of triple-drug regimens. These cases prompted manufacturer Bristol-Myers Squibb Company to label those medications with specific warnings on their use in pregnancy. It is not entirely clear what role pregnancy, per se, played in those cases, although lactate levels naturally rise in the third trimester and may contribute to an increased risk of serious lactic acidosis. Confounding the diagnosis of lactic acidosis in pregnancy are the many obstetric-related etiologies of hepatic dysfunction, including acute fatty liver of pregnancy; severe preeclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP); and cholestasis of pregnancy.

There are conflicting data regarding the association between antiretroviral therapy and other pregnancy outcomes, including preterm delivery and gestational diabetes. A combined analysis of the European Collaborative Study and Swiss Mother + Child HIV Cohort Study found that women on combination therapy (with or without a protease inhibitor [PI]) were significantly more likely to deliver an infant before 37 weeks gestation than HIV-infected women not receiving any medication (OR, 2.60; 95\% CI, 1.43-4.75 for PI-containing regimens and OR, 1.82; 95\% CI, 1.13-2.92 for PI-sparing regimens).\textsuperscript{126} Importantly, however, the multivariate analysis of data from this study did not include known risk factors for preterm delivery such as tobacco and drug use, low maternal weight, and history of preterm delivery. A more recent study found no such association between antiretroviral therapy and preterm delivery among 2123 HIV-infected pregnant women.\textsuperscript{127} This latter study, however, did find an association between PI-containing regimens and delivery of a very low birth weight infant (OR, 3.56; 95\% CI, 1.04-12.19). Women on PI-containing regimens, however, were more likely to have advanced HIV disease, and researchers did not adjust for stage of disease in the multivariate model. Preliminary data from 1 study reported that the risk of preeclampsia was significantly lower among HIV-infected women who did not receive treatment than among women on triple antiretroviral therapy and HIV-seronegative controls.\textsuperscript{128} The authors suggested that the restoration of preeclampsia risk to that of HIV-seronegative controls might be due to HAART-induced immune reconstitution.

There is evidence of an increased risk of new-onset diabetes among nonpregnant women on PIs.\textsuperscript{129} Moreover, pregnancy is a relatively diabetogenic state. One study demonstrated an increase in glucose tolerance among women on PI-based HAART compared with zidovudine monotherapy historical controls.\textsuperscript{130} Although these women on PI-based HAART had increased initial glucose tolerance screening, there was no increased risk of gestational diabetes on follow-up diagnostic testing compared with non-HIV-infected women. No study has yet definitively documented an increased risk of gestational diabetes among pregnant women on PIs.

**Adverse Fetal and Neonatal Effects**

Table 1 provides data on placental passage, carcinogenicity, teratogenicity, and FDA pregnancy categories for the various antiretroviral medications used in humans.\textsuperscript{131,132} The Antiretroviral Pregnancy Registry (www.apregistry.com) maintains a voluntary database of birth defects among infants exposed to in utero antiretrovirals.\textsuperscript{133} It has found no difference in birth-defect prevalence among infants with either first-trimester or anytime exposure to antiretrovirals compared with US population-based proportions as monitored by the CDC. Although most antiretrovirals appear to be safe to use during pregnancy, there are a few notable exceptions. Efavirenz has been linked to anencephaly and anophthalmia in monkeys, at doses comparable to those taken by humans.\textsuperscript{134} There has since been a case report of neural tube defects in infants exposed to efavirenz in utero.\textsuperscript{135,136} Amprenavir has been associated with delayed skeletal ossification in rats. High-dose tenofovir is linked to slightly decreased bone porosity among exposed monkeys, though the clinical significance of this finding is uncertain.\textsuperscript{137} Considerable controversy exists regarding the risk of mitochondrial dysfunction among exposed, uninfected infants. Although some reports note a possible association between perinatal exposure and clinically relevant neonatal mitochondrial dysfunction,\textsuperscript{138,139} the largest study failed to find an association.\textsuperscript{140} One recent study noted a decrease in mitochondrial DNA in cord and infant peripheral blood leukocytes among HIV-exposed versus HIV-unexposed infants.\textsuperscript{141} Those HIV-exposed infants who were exposed to zidovudine were at highest risk. The clinical significance of this finding, however, remains to be seen. Although data indicate minimal transplacental passage of PIs, one observational study noted a possible association between PI-containing HAART regimens and very low birth weight (<1500 g).\textsuperscript{142} This may be due to metabolic changes in the mother as opposed to direct in utero effects and certainly warrants further investigation.

**Mode of Delivery**

Significant attention has been paid to the role of delivery mode on the risk of HIV transmission. The European Mode of Delivery Collaboration was a randomized controlled trial of elective cesarean delivery versus trial of labor among 436 HIV-infected women.\textsuperscript{143} Elective cesarean delivery was defined as abdominal delivery at 38 weeks gestation in the absence of labor or ruptured membranes. Transmission occurred in 10.5\% of women in the trial of labor arm compared with 1.8\% in the elective cesarean delivery arm (OR, 0.2; 95\% CI, 0.1-0.6). This difference was only statistically significant, however, in the absence of antepartum zidovudine. The International Perinatal HIV Group performed a meta-analysis of 15 prospective cohort studies, including 8533 mother-child pairs.\textsuperscript{144} Those researchers, too, found a decreased risk of transmission in women undergoing cesarean delivery (OR, 0.43; 95\% CI, 0.33-0.56). This association held even among women with antepartum, intrapartum, or neonatal antiretroviral therapy. However,
### Table 1. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>FDA Pregnancy Category</th>
<th>Placental Passage (model) [newborn: mother drug ratio]</th>
<th>Long-term Animal Carcinogenicity</th>
<th>Animal Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside and nucleotide analogue reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td>C</td>
<td>Yes (human) [0.85]</td>
<td>Positive (rodent, noninvasive vaginal epithelial tumors)</td>
<td>Positive (rodent, near lethal dose)</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>C</td>
<td>Yes (rhesus monkey) [0.30-0.50]</td>
<td>Positive (rodent, thymic lymphomas)</td>
<td>Positive (rodent, hydrocephalus at high dose)</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>B</td>
<td>Yes (human) [0.50]</td>
<td>Negative (no tumors, lifetime rodent study)</td>
<td>Negative</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>C</td>
<td>Yes (rhesus monkey) [0.76]</td>
<td>Positive (mice and rats, at very high dose exposure, liver and bladder tumors)</td>
<td>Negative (but sternal bone calcium decreases in rodents)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>C</td>
<td>Yes (human) [~1.0]</td>
<td>Negative (no tumors, lifetime rodent study)</td>
<td>Negative</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>C</td>
<td>Yes (rat)</td>
<td>Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)</td>
<td>Positive (rodent anasarca and skeletal malformations at 1000 mg/kg [35x human exposure] during organogenesis; not seen in rabbits)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Tenofovir (TDF, PMPA)</td>
<td>B</td>
<td>Yes (rat and monkey)</td>
<td>Not completed</td>
<td>Negative (osteomalacia when given to juvenile animals at high doses)</td>
</tr>
<tr>
<td><strong>Nonnucleoside reverse transcriptase inhibitors</strong></td>
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<td></td>
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<tr>
<td>Nevirapine (NVP)</td>
<td>C</td>
<td>Yes (human) [~1.0]</td>
<td>Positive (hepatocellular adenomas and carcinomas in mice and rats)</td>
<td>Negative</td>
</tr>
<tr>
<td>Delavirdine (DLV)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats; bladder tumors in male mice)</td>
<td>Positive (rodent, ventricular septal defect)</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>C</td>
<td>Yes (cynomologus monkey, rat, rabbit) [~1.0]</td>
<td>Positive (increased hepatocellular adenomas and carcinomas, and pulmonary alveolar/bronchiolar adenomas in female but not male mice)</td>
<td>Positive (cynomologus monkey, anencephaly, anophthalmia, microphthalmia)</td>
</tr>
</tbody>
</table>
### Table 1. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy, Continued

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<tr>
<th>Antiretroviral Drug</th>
<th>FDA Pregnancy Category</th>
<th>Placental Passage (newborn: mother drug ratio)</th>
<th>Long-term Animal Carcinogenicity</th>
<th>Animal Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>C</td>
<td>Minimal (human)</td>
<td>Positive (thyroid adenomas in male rats at highest dose)</td>
<td>Negative (but extra ribs in rodents)</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>B</td>
<td>Minimal (human)</td>
<td>Positive (rodent, liver adenomas and carcinomas in male mice)</td>
<td>Negative (but cryptorchidism in rodents)</td>
</tr>
<tr>
<td>Saquinavir (SQV)</td>
<td>C</td>
<td>Minimal (human)</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>B</td>
<td>Minimal (human)</td>
<td>Positive (thyroid follicular adenomas and carcinomas in rats)</td>
<td>Negative</td>
</tr>
<tr>
<td>Amprenavir (APV)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in male mice and rats)</td>
<td>Negative (but deficient ossification and thymic elongation in rats and rabbits)</td>
</tr>
<tr>
<td>Atazanavir (ATZ)</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir (LPV/r, ABT-378/r)</td>
<td>C</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (increased benign and malignant liver tumors in male rodents)</td>
<td>Negative (deficient ossification with amprenavir but not fosamprenavir)</td>
</tr>
</tbody>
</table>

| **Fusion inhibitors** |
| Enfuvirtide (T-20) | B | Unknown | Not done | Negative |

**US Food and Drug Administration pregnancy categories:**

**A** Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and 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; 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.

there was no information on HIV-1 RNA levels, and most of the women on antiretroviral therapy in this study were receiving zidovudine monotherapy. More recently, among women with predelivery HIV-1 RNA levels less than 1000 copies/mL, PACTG 367 found no difference in transmission prevalence among women with vaginal deliveries (0.8%), elective cesarean deliveries (0.8%), or nonelective cesarean deliveries (1.1%).^107 Although some studies have found a potential protective role of elective cesarean delivery among women with HIV-1 RNA levels greater than 1000 copies/mL, many study results point to significant morbidity associated with cesarean delivery among HIV-infected women.^144,147 It is crucial also to consider the maternal morbidity associated with subsequent deliveries, whether repeat cesarean deliveries or vaginal births after cesarean delivery.

**Postpartum Care for the Woman and Neonate**

**Immunization**

Although measles-mumps-rubella (MMR) is a live attenuated virus, there has been no evidence of severe or unusual adverse events among HIV-infected individuals without severe immunosuppression who receive MMR vaccination.^148 There is a case report of severe measles pneumonia in a severely immunocompromised adult with AIDS.^149 Therefore, the Advisory Committee on Immunization Practices (ACIP) recommends MMR vaccination for all susceptible, asymptomatic HIV-infected individuals in the absence of severe immunosuppression. ACIP also states that MMR vaccination should be considered for symptomatic HIV-infected individuals in the absence of severe immunosuppression. The CDC defines severe immunosuppression as a CD4+ count below 200 cells/µL or a CD4+ percentage of total lymphocytes of less than 14. Because MMR contains a live attenuated virus, immunization should be deferred until the postpartum period, although there has never been a reported case of vaccine-associated congenital rubella.^151

There are limited data on the safety of varicella vaccination of individuals with HIV infection. PACTG 265 is evaluating the safety and efficacy of varicella vaccination among asymptomatic or mildly symptomatic HIV-infected children (CDC stage N1 or A1). Preliminary data from this study indicate that varicella vaccination is not associated with serious adverse effects, progression of HIV disease, or an increase in HIV-1 RNA level. Furthermore, the vaccine induced immunity in the majority of children studied.

Brady and colleagues reported on the safety of varicella vaccine among HIV-infected adults with CD4+ counts greater than 400 cells/µL who previously had been infected with varicella. There are no data specifically addressing the safety and efficacy of varicella vaccination in HIV-infected, susceptible women in the preconception or postpartum period. As such, varicella-zoster immunoglobulin is recommended for susceptible HIV-infected children and adults in the context of a significant exposure to varicella-zoster virus (VZV), regardless of immune status.^154

**Adherence to Medication**

Medication adherence is the cornerstone of sustained viral suppression. Medication nonadherence is common among all HIV-infected individuals. Adherence may be particularly difficult for postpartum women who juggle many demands, including a 4-times-a-day zidovudine regimen for the neonate. One study found that 41% of women took none of their zidovudine or zidovudine/lamivudine in the first 3 weeks postpartum.^155 Mean postpartum adherence fell to its nadir of 29.3% in the first week postpartum. Demas and colleagues found that 71% of postpartum women self-reported 100% adherence to the neonatal zidovudine regimen. Nearly 18% of infants had no detectable zidovudine in plasma samples drawn within 1 week before the interview. Poor adherence, as defined by low infant zidovudine levels, was associated with maternal asymptomatic HIV disease and poor prenatal maternal medication adherence. For women requiring HAART for their own health postpartum, it is essential for providers to counsel them about medication adherence, with an understanding of the complex social and psychological issues facing those women.

**Contraception**

A key component of postpartum care of the HIV-infected woman includes counseling about and provision of contraception. Ideally, a patient will have decided on a plan prior to delivery. Although hormonal contraception offers excellent protection against future pregnancy, there are several issues concerning its use that are relevant to the HIV-infected woman. First, hormonal contraception has been linked to increased genital shedding of HIV-1. In the largest observational study to date, Mostad and researchers found an association between hormonal contraceptives and cervical HIV-1 shedding. In particular, women on high-dose oral contraceptives (50 µg estradiol) had the highest adjusted OR for shedding (12.3; 95% CI, 1.5-101). Researchers also detected a significant association between cervical HIV-1 shedding and both low-dose oral contraceptives (OR, 3.8; 95% CI, 1.4-9.9) and depot medroxyprogesterone acetate (DMPA) (OR, 2.9; 95% CI, 1.5-5.7). More recently, Baeten described an association between DMPA and a higher baseline HIV-1 RNA level as well as an increased risk of viral diversity, suggesting that HIV-infected women taking DMPA may be at risk of faster progression of HIV disease. Furthermore, women taking hormonal contraception may be less likely to concurrently use condoms. Not surprisingly, one study found that HIV-infected women on oral contraceptives were significantly less likely to use condoms, putting them at risk of acquiring sexually transmitted infections and transmitting HIV. Lastly, antiretrovirals that induce CYP3A may decrease plasma levels of hormonal contraceptives. Mildvan and colleagues demonstrated a 29% median decrease in the area under the plasma concentration-time curve (AUC) of hormonal contraceptives among women taking concurrent estradiol/norethindrone and nevirapine. Although there are theoretical concerns about the use of intrauterine devices (IUDs) among HIV-infected women, no study has yet demonstrated an increase in viral shedding or an increase in infectious morbidity associated with their use. Among 98 HIV-infected women in Kenya, there were no changes in HIV-1 DNA cervical shedding before or after IUD insertion. Sinei and researchers found no significant differ-
ferences in overall complications, incident pelvic inflammatory disease, or overall infection-related morbidity between 156 HIV-infected and 493 HIV-uninfected women who underwent IUD insertion. Although it is often difficult to find the ideal method of contraception for any woman, it is crucial to assist the HIV-infected woman in weighing the risks and benefits of all options.

**Neonatal Management**

The standard management of the HIV-exposed neonate includes a 6-week course of zidovudine, laboratory evaluation for HIV infection and medication side effects, and PCP prophylaxis with trimethoprim-sulfamethoxazole from 6 weeks to 4 months of age. The US Department of Health and Human Services maintains living document guidelines at www.aidsinfo.nih.gov. Zidovudine is dosed as 2 mg/kg every 6 hours for the term infant. Ideally, at least 2 of the doses correspond to maternal dosing for those women continuing on antiretroviral therapy postpartum. The infant is weighed weekly for dose adjustments. Laboratory evaluation of the infant includes birth HIV-1 DNA polymerase chain reaction (PCR), complete blood count, and liver function tests. Many providers also obtain a blood-glucose reading on those infants born to women who received antepartum PIs. Because maternal IgG antibodies readily cross the placenta, HIV-1 antibody testing is not considered diagnostic of infant HIV infection and is therefore avoided until the child is 18 months of age. DNA-PCR testing is typically performed at birth (to detect in utero infection), 4 weeks, and 4 to 6 months. An additional PCR may be obtained at 2 weeks, to detect intrapartum exposure in particularly high-risk situations, such as limited or absent maternal antiretroviral medication. Serial DNA-PCR testing increases the sensitivity of HIV detection. Before 1 week of age, the sensitivity of DNA-PCR is approximately 38% to 50%. The sensitivity increases to 96.2% by 4 to 6 weeks and to 100% after 7 weeks of age. HIV infection is diagnosed in the infant by 2 separate positive HIV virologic tests. In the setting of bottle-feeding, HIV is excluded by 2 separate negative HIV virologic tests, 1 at 1 month of age or later and 1 at 4 months of age or later. HIV is also excluded with a negative HIV antibody test at 18 months, though one study found that no additional cases of HIV were identified following 3 negative DNA-PCR tests. Despite initial concerns, zidovudine does not apparently affect the detection of HIV by DNA testing among infants. Little is known, however, about the impact of HAART or non-clade B virus on the sensitivity of PCR testing in the neonate.

**Conclusions**

We are remarkably close to eliminating perinatal HIV in the United States. It is one of the starkest examples of the countless social, political, and economic inequities that exist between the industrialized and resource-poor settings of the world. With our success, we must advocate for women in our own neighborhoods and around the world to have effortless access to contraception and abortion services, supportive prenatal care, and HIV testing and treatment.

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