Pregnancy and Optimal Care of HIV-Infected Patients

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Human immunodeficiency virus (HIV) infection during pregnancy is a condition that requires multidisciplinary care. Care must be rendered that is appropriate for both the mother and the fetus. Prevention of mother-to-child transmission of HIV is of paramount concern. To prevent transmission, universal testing for HIV infection in pregnant women is ideal. In the United States and other developed countries, great strides have been made toward decreasing the risk of HIV transmission to infants to <2% with use of a combination of highly active antiretroviral therapy during the antepartum period and during labor and delivery, scheduled cesarean section when appropriate, avoidance of breast-feeding, and 6 weeks of zidovudine prophylaxis for infants. The continuation of antiretroviral therapy after delivery depends on the needs of the mother with regard to treatment of her own health. In resource-limited countries, where simplified and shortened courses of antiretroviral regimens have been used, reduction in mother-to-child transmission has also been shown, although not as effectively as that with highly active antiretroviral therapy. In these settings, exclusive breast-feeding for 6 months is recommended to reduce the risk of postnatal transmission.

When HIV was first found to have the potential for perinatal infection, the prognosis was guarded for both mother and infant [1, 2]. Since that time, great strides have been made in both the care of infected mothers and the prevention of infection of neonates. The risk of perinatal infection has decreased from 25%–30% without intervention to <2% with interventions currently available in the United States and other developed countries [3].

HIV infection can occur during pregnancy, labor and delivery, or with breast-feeding. To avoid perinatal infection, careful attention to universal testing of pregnant women, suitable antiretroviral therapy, scheduled cesarean section when appropriate, and avoidance of breast-feeding when safe and feasible is recommended. With implementation of guidelines aimed at decreasing mother-to-child transmission (MTCT), the absolute numbers of HIV-infected infants in the United States have decreased dramatically (figure 1).

There are a number of factors that impact the rate of MTCT. The Women and Infants Transmission Study examined predictors of MTCT in the United States over time. The most important predictor of transmission appears to be plasma HIV RNA load [4]. Garcia et al. [4] demonstrated that the risk of transmission increased with increasing viral loads, but there was no clear threshold above which all women transmitted the virus. They also found that among women with a viral load <1000 copies/mL, none transmitted the virus to their neonate [4]. However, transmission has been reported among women across all levels of HIV load, including those with HIV RNA loads below detectable levels [5]. Other important risk factors for transmission include the duration of ruptured membranes, mode of delivery, low birth weight, cigarette smoking [6], genital tract infections, substance abuse [7], and unprotected sex with multiple partners [8, 9].

The Women and Infants Transmission Study showed that women were not at greater risk for HIV progression with 2 pregnancies, compared with 1 pregnancy, and even suggested that the benefits gained by receiving care might improve overall maternal health [10]. Tai et al. [11] reported that pregnancy was associated with a lower risk of HIV disease progression in the era of combination antiretroviral therapy. This report will review the role of antiretroviral therapy, mode of delivery, and infant prophylaxis on the prevention of MTCT and discuss concerns related to the prevention of MTCT in resource-limited countries.
ELEMENTS OF PRENATAL CARE AND TIMING OF INITIATION OF ANTIRETROVIRAL THERAPY

Ideally, all HIV-infected women who desire pregnancy should receive preconception care to optimize their health status prior to pregnancy. The care of an HIV-infected pregnant woman is multidisciplinary and involves HIV specialists, obstetricians, and pediatricians, as well as educators and social service providers. Initial assessment of the parturient should include an evaluation of CD4 cell counts, HIV RNA plasma load, determination of the need for prevention of opportunistic infection, and baseline evaluation of general maternal health, including vaccinations, comorbidities, complete blood cell count, and renal and liver function testing. A history of previous exposure to antiretroviral medications and documented resistance is essential. The woman should be counseled about the known benefits and the potential risks of antiretroviral therapy. Women with very low or undetectable viral loads should also be counseled about the use of antiretroviral therapy, because it has been shown to be efficacious, even among this group of women [12]. In addition, risks of maternal toxicities must be considered [13].

Insufficient data exist regarding the teratogenic potential of many of the antiretroviral medications during the first trimester. Efavirenz, a component of a preferred regimen for treatment-naive patients [14], should be avoided during the first trimester of pregnancy because of reports of malformations in cynomolgus monkeys and case reports of fetal open neural tube defects in infants exposed during the first trimester [15].

In developed countries, combination antiretroviral therapy is considered the standard of care for the prevention of perinatal transmission and is recommended to be administered ante-partum and during labor and delivery, regardless of plasma HIV load or CD4 cell count. The US Public Health Service Task Force recommendations for antiretroviral therapy during pregnancy indicate that women who are currently receiving antiretroviral therapy for their own health should continue to receive the treatment regimen if it is effective at suppressing viral load but that efavirenz use should be avoided during the first trimester [13]. This recommendation is based on the concern that the discontinuation of therapy could result in a rebound of plasma viral load and a risk of a decline in immune status leading to an increased risk of perinatal transmission.

Women who are antiretroviral naive at the time of conception should first be evaluated with regard to the need for therapy for their own health. If such women meet standard criteria for the initiation of therapy per the adult treatment guidelines [14], treatment should be started immediately, even during the first trimester. If, on the other hand, the primary reason for therapy is the prevention of MTCT, initiation of therapy can be delayed until after 10–12 weeks of gestation. Frequently, combination...
Table 1. Recommendations for antiretroviral treatment of HIV infection during pregnancy.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Drug class</th>
<th>Entry inhibitor</th>
<th>Integrate inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended</td>
<td>NRTI: Zidovudine, lamivudine</td>
<td>Lopinavir/ritonavir</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>NNRTI: Nevirapine</td>
<td>Indinavir, ritonavir, saquinavir hard gel capsule, nelfinavir</td>
<td>...</td>
</tr>
<tr>
<td>Alternate agents</td>
<td>Didanosine,^a^ emtricitabine, stavudine,^b^ abacavir</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Insufficient data</td>
<td>Tenofovir</td>
<td>Atazanavir, darunavir, fosamprenavir, tipranavir</td>
<td>...</td>
</tr>
<tr>
<td>Not recommended</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
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**NOTE.** NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

^a Should only be used in women with a CD4 cell count >250 cells/mm³ if benefits outweigh the risk of rash-associated hepatotoxicity.

^b Didanosine and stavudine should not be used in combination with one another.

therapy is discontinued following pregnancy in women who do not need therapy for their own health. This decision should be made in consultation with an HIV specialist and should take into consideration adherence issues, current and nadir CD4 cell count, HIV RNA levels, and patient preference. The effects of treatment interruption in pregnant women are unknown. A study of treatment interruption based on CD4 cell count versus continued therapy in nonpregnant adults who required HIV therapy demonstrated higher rates of illness progression and death in the treatment interruption group [16, 17]. CD4 cell counts should be measured every 3 months during pregnancy. Plasma HIV RNA levels should be determined at 2–6 weeks after an initiation or change in therapy, monthly until viral levels are undetectable, and then at least once every 2 months; levels should also be measured at 34–36 weeks of gestation to determine delivery planning. Testing for toxicity should be based on the particular drug regimen the patient is receiving. A standard oral glucose loading test should be performed at 24–28 weeks of gestation. A first-trimester ultrasound is recommended for pregnancy dating to allow for some certainty with regard to delivery timing. Because of the limited data regarding the fetal effects of antiretroviral medications, a detailed assessment of fetal anatomy at 18–20 weeks of gestation should be considered in women who have received combination antiretroviral medications during the first trimester.

All HIV-infected pregnant women should be screened for both hepatitis B virus infection (with use of hepatitis B virus surface antigen) and hepatitis C virus infection (with use of a sensitive immunoassay for hepatitis C virus antibodies). The care of hepatitis B virus or hepatitis C virus and HIV coinfected pregnant women is complex because of complications regarding choice of treatment, treatment initiation, and treatment cessation. Care of coinfected women should involve consultation with an expert. Guidance is provided by the Perinatal HIV Guidelines Working Group [13]. Pegylated IFN-α and IFN-α are not recommended for use in pregnant women because of known adverse effects of IFN in pregnant women, and ribavirin is contraindicated in pregnant women [18]. For women who are coinfected with hepatitis B virus or hepatitis C virus, transaminase levels should be evaluated 2 weeks after the initiation of therapy and at least monthly thereafter. The mode of delivery should be based on considerations related to HIV infection alone. There is no proven benefit of a scheduled cesarean section delivery for women infected with hepatitis C virus, although the transmission of both hepatitis C virus and HIV may be more likely in coinfected women [19, 20].

**RECOMMENDED MEDICATION REGIMENS AND REGIMENS TO AVOID**

It is recommended that zidovudine (ZDV) be part of any regimen for treatment of a pregnant woman, unless there is a documented history of severe ZDV-related toxicity or ZDV resistance. For women who have a history of ZDV toxicity or resistance, the regimen should include at least 1 other antiretroviral drug that crosses the placenta to provide the fetus with preexposure prophylaxis [13]. Other antiretroviral drugs that cross the human placenta include didanosine, lamivudine (3TC), tenofovir, nevirapine (NVP), and lopinavir. Several of the protease inhibitors also have variable to minimal placental passage.

When choosing the appropriate regimen for a pregnant woman, combination antiretroviral regimens containing ≥3 drugs are recommended [13]. In general, the guiding principle of therapy for nonpregnant women should be considered. There should be a dual nucleoside reverse-transcriptase inhibitor backbone with an acceptable nonnucleoside reverse-transcriptase inhibitor or protease inhibitor (table 1). Efavirenz is generally avoided during the first trimester of pregnancy because of concerns for teratogenicity. NVP is not recommended for
women with CD4 cell counts $>250$ cells/mm$^3$ because of an increased risk of rash and hepatotoxicity [21]. However, if a woman has been tolerating a NVP-containing regimen prior to pregnancy, this regimen should be continued during pregnancy.

The combination of stavudine and didanosine should be avoided during pregnancy because of the potential for mitochondrial toxicity and lactic acidosis, and reports of fatalities during pregnancy [22, 23]. In general, monotherapy should be avoided during pregnancy because of the potential for development of antiretroviral resistance. The use of time-limited ZDV monotherapy might be a controversial exception to this statement. For women with a very low viral load (i.e., those with HIV RNA loads $<1000$ copies/mL) who are receiving no therapy, a course of therapy similar to that used in Pediatric AIDS Clinical Trial Group (PACTG) 076 during the second and third trimester might be a reasonable option if the patient is averse to the notion of antiretroviral use during pregnancy. This regimen has been shown to not induce clinically significant antiretroviral resistance in the women enrolled in PACTG 076 [24]. A detailed discussion of individual antiretrovirals and their pharmacokinetics during pregnancy is beyond the scope of this article but can be found in the “Public Health Services Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States” [13]. Health care professionals are encouraged to prospectively enroll all women who receive antiretroviral therapy during pregnancy in the Antiretroviral Pregnancy Registry [33].

Intrapartum intravenous ZDV treatment is recommended for all HIV-infected pregnant women unless there is a history of ZDV-related hypersensitivity. The recommended dosage involves a loading dose of 2 mg/kg administered over 1 h, followed by 1 mg/kg/h until delivery. Women who are having a scheduled cesarean section delivery should begin the infusion $\geq 3$ hours before the start of surgery. Other components of the patient’s antiretroviral regimen should be continued orally during labor unless the regimen contains stavudine, which should not be administered during ZDV infusion because of antagonism. The antepartum treatment regimen is recommended to be continued with the usual dosing schedule during labor (with sips of water) to decrease the risk of developing resistance because of missed or erratic doses [13].

In women who have achieved suboptimal suppression of plasma HIV RNA load and are receiving antepartum therapy, the addition of NVP at the time of labor is not recommended, because there has been no proven benefit for these patients and there is an increased risk of resistance [25, 26]. However, in women who were recently found to be infected with HIV or who have not been receiving antiretrovirals during the antepartum period, the addition of single-dose NVP should be considered. The reason to add single-dose NVP at the time of delivery in women who did not receive the benefit of antepartum therapy is the ability of NVP to rapidly decrease intracellular and extracellular virus levels and to act synergistically with ZDV [27–29]. When single-dose NVP is administered, the risk of resistance must be considered. There is some evidence that continuing a 7-day regimen of ZDV with 3TC after a single dose of NVP can reduce the development of NVP resistance [30]. Chi et al. [31] reported that the addition of a single dose of tenofovir and emtricitabine to a regimen of short-course ZDV and intrapartum NVP effectively reduced the frequency of postpartum resistance to NVP by one-half. The 6-week neonatal ZDV chemoprophylaxis regimen is recommended for all infants who are exposed to HIV. Data are not available to demonstrate whether 6 weeks of ZDV combined with single-dose NVP at birth is superior to 6 weeks of ZDV alone for infants. Short-term toxicity of ZDV prophylaxis in infants has been minimal and has consisted primarily of transient hematologic toxicity (mainly anemia), which generally resolves by 12 weeks of age. Data on the toxicity of exposure to multiple antiretroviral drugs are limited for infants. The latest information on neonatal dosing for antiretroviral drugs can be found in the “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection” [32].

Careful long-term follow-up of infants who were exposed to antiretroviral drugs should persist into adulthood because of the unknown long-term carcinogenic effects of the medications [13]. Health care professionals are encouraged to prospectively enroll all women who receive antiretroviral therapy during pregnancy in the Antiretroviral Pregnancy Registry [33].

**RESISTANCE TESTING AND MONITORING OF VIROLOGIC RESPONSE**

HIV genotypic drug-resistance testing is recommended for all pregnant women who are not currently receiving antiretrovirals before starting treatment and for all pregnant women who are receiving antiretrovirals but achieving suboptimal viral suppression [13]. Start of therapy should begin before receiving the results of the resistance testing for women who require therapy for their own health or for women who are late in
their pregnancy. Adjustments to therapy can be performed after the resistance-test results are obtained. Of note, the plasma HIV RNA load must be ≥1000 copies/mL for genotypic testing to be performed.

To prevent resistance and maximize safety for them and their unborn children, all pregnant women must be counseled about the importance of adherence to the prescribed regimen. There should be a ≥0.5 log₁₀ copies/mL decrease in HIV RNA level at 2–6 weeks after the initiation of therapy. Ideally, plasma HIV RNA load will be undetectable (<50–75 copies/mL, depending on assay) by 16–24 weeks after the initiation of therapy. Any deviation from this expected pattern should prompt drug-resistance testing [14].

MODE OF DELIVERY

Scheduled, prelabor cesarean section delivery has been shown to decrease the risk of MTCT [34]. The American College of Obstetrics and Gynecology recommends that women with detectable virus levels >1000 HIV RNA copies/mL undergo prelabor cesarean section [35]. In a meta-analysis of 15 prospective studies that examined the impact of prelabor cesarean section, risk of transmission was clearly decreased among women who received no antiretroviral therapy or ZDV monotherapy. The odds of MTCT decreased by 50% among women who underwent prelabor cesarean section delivery, compared with other modes of delivery (adjusted OR, 0.43; 95% CI, 0.33–0.56). Among women with plasma HIV RNA loads measuring <1000 copies/mL, whether scheduled cesarean section delivery confers additional benefit is unclear. The Women and Infants Transmission Study found no transmission of HIV among women with a plasma HIV RNA load <1000 copies/mL, but the small number of subjects limits the ability to make conclusions from this finding [4]. A more recent report did find, on univariate analysis, an increased risk of transmission among women with HIV RNA loads of 50–999 copies/mL, compared with women with loads <50 copies/mL, but this risk was not able to be evaluated in a multivariable model because of the low frequency of transmission at these low viral loads [36]. Although the risk of transmission of HIV during vaginal delivery in women with undetectable viral load is probably very small, insufficient data exist regarding how to manage women with plasma viral loads that are detectable but <1000 copies/mL, and decisions should be made on an individual basis.

For scheduled prelabor cesarean section delivery, the American College of Obstetrics and Gynecology recommends delivery at 38 weeks of gestation [35]. Because of the increased risk of maternal infectious morbidity, it is recommended that HIV-infected women who are undergoing cesarean section delivery receive perioperative prophylactic antibiotics [35, 37]. It is unclear whether there is any benefit to be gained from nonsched-uled cesarean section delivery. That is, if a patient with an elevated viral load presents in labor or with a rupture of membranes for ≥4 h, there may not be any benefit gained from cesarean section delivery [34]. Decisions about mode of delivery are best made on an individual basis.

PREVENTION OF MTCT IN RESOURCE-LIMITED SETTINGS

The risk of MTCT is highest in resource-limited settings because of a higher prevalence of HIV infection among pregnant women and reduced access to prevention measures, including combination antiretroviral therapies. Several international trials have explored the use of simpler antiretroviral regimens in pregnant women, and they have shown that combination antiretroviral therapies are more effective than single-drug regimens and that a longer duration of therapy is more effective [38–40]. In general, the World Health Organization recommends that pregnant women who are not yet eligible for antiretroviral therapy for their own health receive ZDV starting at 28 weeks of gestation or as soon as feasible thereafter, single-dose NVP and ZDV plus 3TC during labor, and ZDV plus 3TC for 7 days postpartum (to prevent NVP resistance); the World Health Organization also recommends that the infant receive single-dose NVP and ZDV for 1 week [41]. In circumstances in which it is not feasible to begin therapy prior to labor, single-dose NVP and ZDV plus 3TC should be given to the mother during labor and ZDV plus 3TC should be administered for 7 days postpartum. The infant should receive single-dose NVP immediately after delivery and should receive ZDV for 4 weeks. The World Health Organization provides recommendations regarding appropriate regimens in a variety of scenarios [42].

In developed countries, the avoidance of breast-feeding is recommended to prevent postnatal transmission of HIV. However, in resource-limited settings, formula feeding has been associated with the same risk of death or HIV infection by 18 months of age as breast-feeding. The Mashi study demonstrated that formula feeding led to reduced vertical transmission but increased mortality, compared with breast-feeding [41, 43]. A study from Cote d’Ivoire showed similar morbidity and mortality at 2 years of age between breast-fed and formula-fed infants [44]. Exclusive breast-feeding has been shown to reduce the risk of postnatal transmission, compared with the predominant practice of mixed feeding [45–47]. The World Health Organization recommends exclusive breast-feeding for the first 6 months of life unless women are in a location where formula feeding is safe and feasible to allow for cessation of all breast-feeding. All breast-feeding should stop once a nutritionally adequate and safe diet without breast milk can be provided. Breast-feeding should be continued, however, among HIV-in-
ected infants, because breast-feeding is associated with a lower rate of mortality for these infants [48].

**SUMMARY**

The first, and perhaps most important, step in preventing MTCT is universal HIV testing of all pregnant women to identify those at risk of transmitting the virus to their infants. In developed countries, combination antiretroviral therapy is recommended during pregnancy regardless of CD4 cell count or viral load to reduce the risk of HIV transmission to the fetus. Scheduled cesarean section is recommended for pregnant women with plasma HIV RNA loads >1000 copies/mL. In the United States and other developed countries, avoidance of breast-feeding is recommended to further decrease the risk of perinatal transmission. In resource-limited countries, simplified and shortened courses of antiretroviral regimens have also reduced MTCT, and exclusive breast-feeding for 6 months is recommended for additional reduction of the risk for postnatal transmission. Optimal therapy for the maternal infection, the pregnancy, and the care of the infant is achieved with a multidisciplinary approach to care for the HIV-infected pregnant woman.

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