Obstetric Care in Patients with HIV Disease

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Appropriate management of pregnant patients who have human immunodeficiency virus (HIV) disease can have a major impact on maternal and infant health. The goals of therapy are to properly manage the pregnancy, treat the maternal HIV infection and minimize the risk of vertical transmission of HIV. Early detection of HIV through aggressive screening programs is necessary to initiate timely therapy. Zidovudine therapy given antepartum and intrapartum to the mother and after birth to the newborn has been shown to decrease the risk of vertical transmission. Evidence suggests that more aggressive antiretroviral therapy for the mother, which allows suppression of viral loads to undetectable levels, may be safe and may provide significant additional benefits. However, treatment needs to be individualized, weighing the possible teratogenic risks against the benefits of decreased transmission. Multiple prospective cohort studies support elective cesarean section as an additional means to decrease vertical transmission, but its role in relation to other therapies has not been determined. As in nonpregnant patients infected with HIV, prevention of opportunistic infections and adequate psychosocial support are essential. (Am Fam Physician 2001:63:107-16,121-2.)

A patient information handout on obstetric care, written by the author of this article, is provided on page 121.

More than 160,000 women of childbearing age in the United States are infected with human immunodeficiency virus (HIV) disease.[1] Perinatal transmission of HIV accounts for more than 90 percent of all pediatric acquired immunodeficiency syndrome (AIDS) cases.[1] Infants infected with HIV at birth are more susceptible to opportunistic infections and rapid progression to AIDS, including a 50 percent chance of developing AIDS by three years of age and a 90 percent chance of dying by 10 years of age.[2] In 1995, AIDS was the leading cause of death in young children in the United States. Fortunately, from 1992 to 1997 the number of pediatric AIDS cases declined 66 percent, despite only a 17 percent decline in the number of births to women infected with HIV.[3] This decline in pediatric AIDS cases is due in part to the use of highly active antiretroviral therapy in infected children and significant advances in the management of infected pregnant women thereby preventing vertical transmission of the virus.

While HIV infection can occur antepartum or postpartum, 65 percent of vertical transmissions occur during labor.[4] Maternal risk factors and multiple intrapartum events can increase the risk of transmission *(Table 1)*.[5-7] Breastfeeding carries a 10 to 20 percent chance of maternal-infant transmission of HIV.[5]

TABLE 1
Factors That Increase the Risk of Vertical Transmission of HIV

Maternal factors
Low CD4+ lymphocyte count
High viral load
Advanced AIDS
Preterm delivery
Placental membrane inflammation
Maternal p24 HIV core antigenemia at birth
Intrapartum events
Events that increase fetal exposure to maternal blood (artificial rupture of membranes, use of fetal scalp monitors, instrumental deliveries, scalp pH testing, DeLee suctioning)
Rupture of membranes more than four hours before delivery

HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Information from references 5, 6 and 7.

Physicians should offer testing to all pregnant patients for human immunodeficiency virus.

In most studies, risks associated with preterm birth, low birth weight and other pregnancy complications were no different in women infected with HIV when compared with those who were not infected. However, several studies of women in Africa who had advanced AIDS showed an increased risk of preterm delivery and of having infants with low birth weights.[8,9] It is unclear why these same results have not been seen in populations in the United States or Europe, but the increased risks may be related to poorer prenatal care or lower socioeconomic status in African women. Overall, HIV infection does not make a pregnancy high risk, and it should not preclude family physicians from caring for these patients.

Screening

In 1995, the U.S. Public Health Service issued a general recommendation[5] that physicians should offer HIV counseling and voluntary testing to all pregnant women. This recommendation was based on the significant decrease in vertical transmission rates when pregnant patients infected with HIV were treated with zidovudine (Retrovir). Currently, the American College of Obstetricians and Gynecologists (ACOG)[10] and the American Academy of Pediatrics (AAP)[11] recommend routine testing for HIV of all pregnant patients after informed consent is obtained.

Multiple reasons exist for screening pregnant patients for HIV, including the importance of early diagnosis and treatment *(Table 2)*.[5] Part of the debate surrounding mandatory screening focuses on concerns that some women may be dissuaded from seeking or continuing prenatal care. Mandatory testing becomes more urgent as interventions and treatments are proven to more effectively prevent perinatal transmission.

Barriers to early detection of HIV include physicians failing to encourage all patients to be tested for the virus and women at high risk for HIV infection waiting too long to initiate prenatal care. Despite these barriers, the number of infants who were perinatally exposed to HIV whose mothers were screened during pregnancy for HIV increased from 70 to 94 percent from 1992 to 1997.[3]

Antiretroviral Therapy

Antiretroviral therapy is now standard practice in the management of pregnant patients with HIV infection. The landmark study[12] that supported this therapy was the AIDS Clinical Trials Group (ACTG) protocol number 076 in 1994 that showed that zidovudine use reduced the relative risk of vertical transmission by more than 66 percent. The maternal-infant HIV transmission rate in the placebo group in this trial was 25.5 percent while the transmission rate in the zidovudine group was 8.3 percent (number needed to treat [NNT] = 5.9). The study population consisted of 477 women with mildly symptomatic HIV infection who

TABLE 2
Reasons to Screen Pregnant Patients for HIV

Assessing future risks
Reinforcing HIV risk-reduction behaviors
Allowing referral to prevention services
Making an early diagnosis
Starting treatment early
Informing patients about reproductive decisions
Preventing transmission to others
Obtaining psychologic and social support services
Reducing perinatal transmission

HIV = human immunodeficiency virus.

Information from Centers for Disease Control and Prevention. U.S. Public Health Service recommendations for human immunodeficiency virus counseling and voluntary testing for pregnant women. MMWR Morb Mortal Wkly Rep 1995;44(RR-7):1-15.

had not previously been receiving antiretroviral therapy. The women in the zidovudine group received what is now a standard regimen of zidovudine *(Table 3)*.[12] The U.S. Food and Drug Administration (FDA) has since approved zidovudine for use during pregnancy and the U.S. Public Health Service has also recommended zidovudine therapy during pregnancy.[13] From 1992 to 1997, the number of pregnant women infected with HIV who received zidovudine therapy increased from 7 to 91 percent.[3] States that require reporting of HIV infections have maternal-infant transmission rates as low as 5 percent in pregnant women who took zidovudine.[14]

Data suggest that more aggressive antiretroviral therapy may provide greater benefits than use of zidovudine alone. In adults infected with HIV who are not pregnant, zidovudine monotherapy is considered inadequate because it does not completely suppress viral replication and allows for rapid development of resistance. Several studies have shown a direct correlation between viral load and rate of vertical transmission, however, there appears to be no threshold value of viral load to discriminate between transmitters and nontransmitters.[15-17] In the New York City Perinatal HIV Transmission Collaborative Study,[16] women with measurable viral load were nearly six times more likely to transmit HIV than were women with an undetectable viral load.

Zidovudine (Retrovir) should be included in the antiretroviral regimen of pregnant patients with human immunodeficiency disease regardless of their viral load or CD4+ cell count.

The most recent recommendations from the Centers for Disease Control and Prevention (CDC)[18] regarding optimal antiretroviral therapy are to treat pregnant women infected with HIV the same as adults infected with HIV who are not pregnant using clinical, virologic and immunologic status to guide treatment decisions. One difference for pregnant women is to include zidovudine in every treatment regimen given the extensive data demonstrating its benefits. A follow-up study[19] from the ACTG 076 trial showed that zidovudine was beneficial independent of its effect on viral load and regardless of the CD4+ lymphocyte count and viral load at the initiation of therapy.[19]

As a result of the CDC's recommendations, regimens consisting of three or four antiretroviral agents are usually prescribed for pregnant patients with a goal of decreasing viral loads to

TABLE 3
Standard Regimens for Pregnant Women and Their Infants in the Use of Zidovudine Therapy

Treatment	*Dosage*
Prenatal zidovudine (Retrovir)	100 mg orally, five times daily,* from 14 weeks of gestation to delivery
Zidovudine during labor	2 mg per kg intravenous load over one hour, then 1 mg per kg per hour
Neonatal zidovudine	2 mg per kg per dose orally every six hours starting within eight hours of birth and continued to six weeks of age

**—Some physicians prescribe a twice daily regimen to increase patient compliance.*

Information from Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994;331:1173-80.

TABLE 4
FDA Pregnancy Categories of Antiretroviral Drugs

Category A	Category C	Approved for patients less than 1 year of age
None	Abacavir (Ziagen)	Abacavir
Category B	Amprenavir (Agenerase)	Didanosine
Didanosine (Videx)	Delavirdine (Rescriptor)	Lamivudine
Nelfinavir (Viracept)	Efavirenz (Sustiva)	Nevirapine
Ritonavir (Norvir)	Indinavir (Crixivan)	Stavudine
Saquinavir (Fortovase)	Lamivudine (Epivir)	Zidovudine
	Nevirapine (Viramune)	
	Stavudine (Zerit)	
	Zalcitabine (HIVID)	
	Zidovudine (Retrovir)	

FDA = U.S. Food and Drug Administration.

Information from Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and the Henry J. Kaiser Family Foundation. MMWR Morb Mortal Wkly Rep 1998;47:43-82 [Published erratum appears in MMWR Morb Mortal Wkly Rep 1998;47(29):619].

undetectable levels. Protease inhibitors are also being prescribed more frequently for pregnant patients. The safety and effectiveness of antiretroviral agents in the antepartum period and during labor is an area of active research, and recommendations are continually being updated and modified. Physicians who do not have experience in initiating or managing antiretroviral therapy should co-manage patients with an HIV expert.

The primary concern with the use of antiretroviral agents in pregnancy is their safety profile and teratogenic potential. In the ACTG 076 trial,[12] infants were followed to 18 months of age and the only effect seen was a mild and reversible anemia. Further follow-up has shown no adverse effects in the subjects at four years of age.[20]

In the Swiss Collaborative HIV and Pregnancy Study,[21] concerns were raised about complications resulting from the use of antiretroviral agents. In pregnant patients infected with HIV who were treated with two reverse transcriptase inhibitors with or without a protease inhibitor, one or more adverse events occurred in 29 of 37 women and in 14 of 30 infants. Although most complications were minor, one case of intracerebral hemorrhage in a premature infant and one case of biliary tree malformation were reported. No antiretroviral agents are currently rated by the FDA as pregnancy category A medications *(Table 4)*.[22] Despite most antiretroviral agents being rated as category C medications, the benefits likely outweigh the risks. An exception may be efavirenz (Sustiva). Preliminary data in studies of monkeys have shown efavirenz may cause central nervous system malformations. Theoretic concerns also exist about indinavir (Crix-

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ivan) increasing the risk of hyperbilirubinemia and causing renal stones in infants whose mothers used this drug during pregnancy. Furthermore, protease inhibitors have been associated with new-onset diabetes and hyperglycemia in nonpregnant populations and may be amplified during pregnancy. Little additional information is available regarding the safety of protease inhibitors during pregnancy.

During the ACTG 076 trial,[12] zidovudine therapy was initiated at 14 weeks of gestation to minimize the risk of teratogenic effects. Current recommendations, however, are to continue an antiretroviral regimen during the first trimester if the patient was taking antiretroviral agents at the onset of pregnancy. Modifications should be made in the treatment regimen to include zidovudine to increase compliance, optimize viral suppression and provide minimal teratogenic potential. Initiation of antiretroviral therapy can be delayed until the second trimester if the mother is not using antiretroviral therapy at the diagnosis of pregnancy, or use of antiretroviral agents may be delayed until the second trimester if the pregnant patient has early-stage HIV disease.[23]

In patients who do not receive prenatal care and who present with HIV disease during labor, a single dose of nevirapine (Viramune) should be considered.[24] In a recent study of a breast-feeding population in Uganda, a single 200-mg maternal dose of nevirapine taken orally at the onset of labor and an infant dose of 2 mg per kg administered orally 72 hours after birth decreased vertical transmission to 13 percent.[24] This rate is 40 percent lower than when intrapartum and infant zidovudine therapies alone were used.[24]

If antiretroviral therapy is ineffective or ambiguous, consultation with a subspecialist who has expertise in antiretroviral agents and an understanding of recent research on HIV in pregnancy is appropriate. Pregnant patients on antiretroviral therapy should be encouraged to register with the Antiretroviral Pregnancy Registry (800-258-4263). Resources for assistance include the CDC National STD and AIDS Hotline (800-342-2437), the HIV Telephone Consultation Service (also called the AIDS "warm" line; 800-933-3413), the HIV/AIDS Treatment Information Service (ATIS; 800-HIV-0440) and Web site (http://www.hivatis.org) or the Project Inform National HIV/AIDS Treatment Hotline (800-822-7422).

Pregnant patients receiving antiretroviral therapy should be encouraged to register with the Antiretroviral Pregnancy Registry.

Mode of Delivery

In addition to antiretroviral therapy, the mode of delivery can have an impact on vertical transmission of HIV. Approximately 65 percent of transmissions occur during labor.[10] ACOG currently recommends offering an elective cesarean section at 38 weeks of gestation to decrease the risk of transmission.[10] This recommendation is being updated to incorporate information regarding viral load.

The most recent comprehensive study addressing elective cesarean section was conducted by the International Perinatal HIV Group,[25] which conducted a meta-analysis of 15 prospective cohort studies that included at least 100 mother-child pairs in North America and Europe. After adjusting for factors known to be associated with vertical transmission, elective cesarean section appeared to decrease the rate of vertical transmission by 50 percent in patients not receiving zidovudine (NNT = 8.5) and by 87 percent in patients on zidovudine therapy (NNT = 9.8). This corresponds with an absolute maternal-infant transmission rate of 10.4 percent and 2.0 percent, respectively, compared with a transmission rate of 19.0 percent for patients who did not take antiretroviral agents or who did not undergo an elective cesarean section. Multiple prospective cohort studies[26-28] within this meta-analysis support the benefits of elective

TABLE 5
Summary Rates of Vertical Transmission of HIV from Major Studies

Name of study	Study date	Rate of vertical transmission in vaginal deliveries (%)		Rate of vertical transmission in elective cesarean sections (%)	
		No zidovudine (Retrovir)	Zidovudine	No zidovudine	Zidovudine
AIDS Clinical Trials Group 076[12]	1994	25.5	8.3	—-	—-
Swiss Neonatal HIV Study Group[28]	1998	20.0	17.0	8.0	0
European Mode of Delivery Collaboration[27]	1999	18.9	3.3	6.8	2.1
French Perinatal Cohort[26]	1998	17.2	6.6	17.2	0.8
International Perinatal HIV Group[25]	1999	19.0	10.4	7.3	2.0

HIV = human immunodeficiency virus.

Information from references 12 and 25 through 28.

cesarean section while others do not[6,29,30] *(Table 5[12,25-28])*. An earlier less comprehensive meta-analysis[31] that included only some of the studies from the International Perinatal HIV Group meta-analysis did not support the benefits of elective cesarean sections.

Several shortcomings exist in the current data on elective cesarean section for women infected with HIV. First, the majority of the information comes from prospective cohort studies that may introduce significant bias as opposed to randomized controlled trials. In cohort studies, patients who take the experimental treatment are often clinically different and managed more aggressively than patients in the comparative group. Randomization removes this confounding factor. Furthermore, many earlier studies contain insufficient information on the use of antiretroviral agents. Finally, most studies are limited by lack of data regarding the benefits of cesarean section in relation to viral load.

With the routine use of aggressive antiretroviral therapy and the possible suppression of viral loads to undetectable levels at the time of delivery, the relationship between mode of delivery, antiretroviral therapy and viral load needs to be studied more objectively. The primary concern with an increase in elective cesarean sections is increased morbidity and mortality, which may be further increased as a patient's immune status declines with HIV progression, compared with vaginal deliveries.[32] The counter argument is that any intervention that decreases transmission has a tremendous benefit to infants born to mothers who have HIV disease. Furthermore, in the European Collaborative Trial,[27] the morbidity related to cesarean section was only 6.7 percent with no serious adverse events reported. Given the overall controversy, physicians should discuss the risks and benefits of different birth options with patients to allow them to make an informed decision regarding mode of delivery.

If the physician and patient decide on a vaginal delivery, every attempt should be made to diminish exposure of the neonate to maternal blood. This includes avoiding artifi-

cial rupture of membranes, use of fetal scalp monitors, delivery using instruments, scalp pH testing, DeLee suctioning and any other event that could cause fetal abrasions. Rupture of membranes more than four hours before delivery has been linked to increased neonatal HIV transmission.[25] Consequently, attempts to expedite delivery after rupture of membranes should be made.[25]

For women with human immunodeficiency virus infection who choose vaginal deliveries, artificial rupture of membranes, the use of fetal scalp monitors, instrumental deliveries and DeLee suctioning should be avoided to reduce the chance of neonatal exposure to maternal blood.

Opportunistic Infections

Prevention of opportunistic infections remains an important element of care for AIDS patients during pregnancy because these infections remain a major cause of maternal and fetal morbidity and mortality. *Pneumocystis carinii* pneumonia (PCP) prophylaxis should be initiated if the CD4+ count is less than 200 per mm^3 (200×10^6 per L) or if the patient develops symptoms such as thrush or unexplained fever for more than two weeks.[33] The preferred treatment is a combined daily dosage of trimethoprim-sulfamethoxazole (TMP-SMZ; Bactrim, Septra) at a dose of 160 mg of TMP and 800 mg of SMZ, taken as a single daily dose.[33]

Multiple studies[34] have not supported the concern for neonatal kernicterus from sulfa drug administration in the third trimester. Additional regimens include alternative dosing schedules of TMP-SMZ or, for patients allergic to TMP-SMZ, dapsone or inhaled pentamidine isethionate (Pentam 300). Although teratogenic risks from TMP-SMZ have been minimal compared with the risks of complications from PCP, inhaled pentamidine can be used instead of TMP-SMZ in the first trimester, because pentamidine has little systemic absorption.[33]

All pregnant patients with HIV infection should also undergo tuberculin skin testing as part of their routine prenatal care. If patients test positive but do not have active tuberculosis, chemoprophylaxis with isoniazid (INH) and pyridoxine (vitamin B_6) is recommended after the first trimester.[35] Chemoprophylaxis for *Mycobacterium avium* complex is also recommended after the first trimester for patients with CD4+ cell counts less than 50 per mm^3 (50×10^6 per L).[35] Azithromycin dihydrate (Zithromax) is the drug of choice because of its safety profile. Additional preventative care should include an annual influenza immunization and pneumococcal immunization every five years.[35] Pregnant patients with recurrent or active tuberculosis, toxoplasmosis, cryptococcal disease, histoplasmosis, coccidioidomycosis or cytomegalovirus disease should be treated similarly to nonpregnant patients considering the life-threatening risks to maternal health.[35]

Final Comment

Care for pregnant patients infected with HIV is rapidly evolving with multiple interventions causing a decrease in vertical transmission rates of HIV infection *(Table 6)* and

TABLE 6
Interventions to Decrease the Rate of Vertical Transmission of HIV

Zidovudine therapy
Highly active antiretroviral therapy
Suppressing maternal viral load to undetectable levels
Elective cesarean section at 38 weeks
Prevention of opportunistic infections
Prevention of preterm delivery
Reducing time between rupture of membranes and delivery to less than four hours
Minimizing fetal exposure to maternal blood

HIV = human immunodeficiency virus.

TABLE 7

Summary of Modifications to Care for Obstetric Patients with HIV Infection

First trimester

Screen pregnant patients for HIV infection.

Measure viral load and CD4+ lymphocyte count.

Initiate highly active antiretroviral regimen.

- If antiretroviral naïve, may delay therapy until second trimester.
- Include zidovudine (Retrovir) in antiretroviral regimen.

If CD4+ cell count is less than 200 per mm^3 (200×10^6 per L), initiate PCP prophylaxis.

Update influenza and pneumococcal vaccinations if appropriate.

Obtain necessary social support for patient.

Second trimester

Measure viral load and CD4+ cell count.

Modify antiretroviral regimen based on viral load.

If CD4+ lymphocyte count is less than 50, initiate MAC prophylaxis.

Check PPD status.

- If PPD is positive, administer isoniazid (INH) and pyridoxine (vitamin B_6) prophylaxis.

Third trimester

Measure viral load and CD4+ lymphocyte count.

Modify antiretroviral regimen based on viral load.

Discuss risks and benefits of elective cesarean section.

- If elective cesarean section is planned, perform at 38 weeks of gestation.
- If vaginal delivery is planned, minimize fetal exposure to maternal blood during delivery.
- If vaginal delivery is planned, deliver less then four hours after rupture of membranes.

Infant

Initiate zidovudine therapy.

HIV = human immunodeficiency virus; PCP = Pneumocystis carinii *pneumonia; PPD = purified protein derivative; MAC* = Mycobacterium avium *complex.*

multiple modifications being made to standard obstetric care *(Table 7).* Recommendations are being updated as new research is conducted. Recommendations vary depending on the availability of resources in particular geographic areas. As a means to reduce perinatal transmission, the Institute of Medicine recommends that physicians ensure that pregnant patients have access to prenatal care, are offered HIV counseling and testing, are provided with therapy to reduce the risk of transmission, are advised to avoid breast-feeding and are offered appropriate support services.[36] While antiretroviral agents, especially zidovudine, are clearly beneficial, optimal antiretroviral therapy and its relation to elective cesarean section needs to be studied further. It is likely that future recommendations on mode of delivery will vary depending on the patient's viral load and prior antiretroviral therapy. Future advancements will likely focus on preventing HIV infection, monitoring for emergence of resistance, monitoring potential toxicities of antiretroviral agents and increasing patients' adherence to therapy.

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