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Mother-to-Child Transmission of HIV in the United States

Many HIV-infected women are now planning to have children.
What are the risks to mother and infant?

OVERVIEW: With the rise in the number of HIV-infected women of childbearing age in the United States, nurses are increasingly likely to be caring for such women. Although the exact mechanism of mother-to-child HIV transmission is unknown, experts believe that it can occur during any of three stages: before birth by microtransfusion of maternal blood across the placenta, during labor and delivery by exposure to maternal cervicovaginal secretions and blood, and after birth through breastfeeding. Treating pregnant women with highly active antiretroviral therapy dramatically reduces the risk of such transmission, but little is known about long-term effects of such therapy on the children. This article reviews the literature on the risk of mother-to-child HIV transmission in the United States and the factors that influence that risk, details current practice recommendations, and discusses implications for nursing.

Ramona Sanchez, a 24-year-old woman diagnosed with HIV infection three years ago, arrives at the clinic to begin prenatal care. She is not taking antiretroviral drugs and feels well. Ms. Sanchez and her husband, also HIV positive, planned this pregnancy and are very excited about starting their family.

Theresa Waite, 25 years old and pregnant, comes to the clinic for routine prenatal blood work, which includes HIV testing. She is shocked to learn that her HIV test is positive. Ms. Waite says she has always been healthy; she denies that she has engaged in high-risk behavior, although she also says that she had three partners before this pregnancy and has never used condoms. Her current partner’s HIV test is negative.

Although these cases are fictional, they’re typical of the kinds of patients seen in settings that offer prenatal care to HIV-infected women. Among American women of childbearing age, HIV infection, HIV disease, and AIDS have been increasing:

• Between 2000 and 2004, the estimated number of AIDS cases in adult women and adolescent girls rose 10%.1

• According to the most recent HIV/AIDS Surveillance Report, at the end of 2004 there were an estimated 123,405 adult women and adolescent girls and 6,804 children living with HIV or AIDS in 35 reporting areas (33 states, Guam, and the U.S. Virgin Islands).1 The numbers for the entire United States and its territories are undoubtedly much higher.

• The same report stated that 71% of the adult women and adolescent girls became infected through heterosexual sexual con-
It also stated that 90% of the children were exposed perinatally, although most were infected before current treatment guidelines were issued that increased the use of antiretrovirals: the estimated number of new pediatric AIDS cases in the United States attributed to perinatal transmission dropped from 122 in 2000 to 47 in 2004.

- HIV and AIDS strike racial and ethnic minorities, especially blacks and Hispanics, disproportionately; as of December 2003, of all reported cases of AIDS in adult women and adolescent girls, 67% were black and 16% were Hispanic.

Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, HIV-infected people who receive HAART can live for decades with what is now considered to be a chronic disease.

HAART also significantly reduces the likelihood of perinatal HIV transmission (also called vertical transmission) when it’s combined with good perinatal care of mother and child. Indeed, many HIV-infected women are now planning to have children. In most cases, they are healthy enough to care for themselves and a child either alone or with minimal support from a partner, family member, or friend.

PATHOPHYSIOLOGY OF MOTHER-TO-CHILD HIV TRANSMISSION
HIV is spread through exposure to HIV-infected blood or other body fluids. The primary transmission modes are contact with an infected person’s body fluids during unprotected sex, blood-to-blood exposure (either by direct contact or through needle
sharing among injection drug users), and perinatal transmission from infected mother to child. Most women become infected through unprotected sex with an infected male partner; many women are unaware of their partner’s infection status.7 (For more on HIV infection and how it’s monitored, see HIV Infection, page 59.)

Although the precise mechanisms of perinatal transmission are unknown, it’s believed that it can occur at one or more of three stages: birth by microtransfusion of maternal blood across the placenta, during labor and delivery by exposure to maternal cervicovaginal secretions and blood, or at birth through breastfeeding.8 A literature review exploring the relationship between the “timing” of transmission (when it occurs) and the design of preventive interventions concluded that in 40% to 80% of cases perinatal transmission occurred during the last two months of pregnancy or during labor and delivery.4 Even when HIV infection isn’t discovered until late in a woman’s pregnancy or when prenatal care of an HIV-infected woman is delayed, the benefits of initiating HAART can be substantial.

Microtransfusion, the passage of small numbers of the mother’s blood cells into the fetus’s circulation, is believed to occur through breaks in the placental epithelium. Microtransfusion is common and happens frequently throughout pregnancy; it probably occurs during childbirth as well, although this has not been confirmed. Conditions associated with placental disruption include, but aren’t limited to, chorioamnionitis, prolonged labor, cigarette smoking, and substance abuse.

During labor and delivery, perinatal transmission can occur when a neonate is exposed to infected blood or cervicovaginal secretions in the genital tract.

The rate of HIV transmission through breastfeeding has been estimated at 14% among HIV-infected mothers and at 29% among those in the acute stage of infection, according to a literature review.9 Higher risk has also been associated with longer duration of breastfeeding.9 The Centers for Disease Control and Prevention (CDC) recommends against breastfeeding by HIV-infected women, regardless of whether they’re receiving antiretroviral therapy.10

**FACTORS INFLUENCING RISK OF PERINATAL TRANSMISSION**

Mother-to-child transmission of HIV involves many factors, including maternal HIV infection status, duration of membrane rupture during labor, and the delivery method, as well as the effectiveness of preventive interventions throughout the perinatal period.

**Maternal HIV infection status.** Several studies have found a correlation between maternal viral load and risk of perinatal transmission; at very low maternal viral loads (less than 1,000 copies/mL), the risk of perinatal transmission of HIV appears to be minimal.11, 12 But the possibility of transmission at any level cannot be ruled out. Perinatal transmission has occurred in mothers with viral loads spanning the possible range, including those with fewer than 1,000 copies/mL.11, 13, 14 And HIV has been found in the cervicovaginal secretions of nonpregnant women, including those whose plasma viral load was fewer than 500 copies/mL15 (a level previously considered undetectable; newer tests can detect levels as low as 40 copies/mL).

That said, HAART appears to minimize the risk of perinatal transmission even in women with very low viral loads.3, 12, 16 A major goal of HAART during pregnancy is to reduce the maternal viral load to lower than 1,000 copies/mL—and if possible, to an undetectable level.

Studies have also shown that a low maternal CD4+ cell count—500/mm3 or less—is independently associated with increased risk of perinatal transmission.17, 18 One recent study found that women with higher CD4+ cell counts were less likely to transmit HIV to their infants.19 That study also identified certain lymphocyte subsets that were associated with increased risk of perinatal transmission. Although more research is needed, the researchers concluded that in the future lymphocyte immunophenotyping may help to identify women who are at higher risk for perinatal transmission despite having a low viral load.

**Maternal genital tract infections** increase viral shedding in cervicovaginal secretions, potentially increasing fetal exposure to HIV during vaginal delivery. In a prospective study of 44 pregnant HIV-infected women and their 53 offspring, researchers found that untreated maternal syphilis was associated with 100% perinatal HIV transmission (n = 4).20 In another study, seropositive mothers who transmitted HIV to their infants had higher incidences of chorioamnionitis and of sexually transmitted infections (STIs) during pregnancy than did seropositive mothers who did not transmit HIV to their infants.21

**Duration of membrane rupture.** A prolonged period (four or more hours before delivery) of amniotic membrane rupture increases the risk of perinatal transmission among women not receiving antiretroviral therapy;22, 23 and there is evidence that it also increases the risk among women receiving monotherapy.24 Analyzing data from a large number of studies, the International Perinatal Group calculated that among women delivering vaginally or by nonelective cesarean section, the risk of transmission increased approximately 2% for every one-hour increment (up to 24 hours) after membrane rupture, regardless of whether the woman had been receiving antiretroviral therapy.24 Recommendations for the management of HIV-infected women during labor specify that if membranes are intact, artificial rupture should be avoided, and that if spontaneous rupture occurs,
interventions to reduce the time to delivery, such as augmenting labor with oxytocin (Pitocin, Syntocinon), should be considered. Other studies indicate that invasive procedures such as internal monitoring with fetal scalp electrodes, fetal scalp pH sampling, amniocentesis, or the use of forceps increase the risk of perinatal HIV transmission through exposure to maternal blood or cervicovaginal secretions.\textsuperscript{23, 26}

The mother’s high-risk behaviors such as smoking, illicit drug use (especially injection drug use), and having unprotected sex have been associated with increased risk of perinatal HIV transmission. Although exactly how smoking influences perinatal HIV transmission is unclear, the transmission rate is higher among smokers than nonsmokers, and it’s especially high in smokers with low CD4 cell counts.\textsuperscript{22, 27} Smoking, illicit drug use, and the presence of STIs are each associated with a number of obstetric complications such as premature labor, premature rupture of membranes, chorioamnionitis, and antepartal vaginal bleeding. Cocaine or opiate use has been shown to increase HIV replication,\textsuperscript{28, 29} and both cocaine use and cigarette smoking have been associated with placental damage that might enhance in utero transmission of HIV.\textsuperscript{22, 27, 30}

Whether the mode of delivery affects perinatal HIV transmission has been debated. Several early studies found that elective cesarean section was associated with a lower risk of perinatal HIV transmission than either vaginal or nonelective cesarean delivery.\textsuperscript{22, 27, 30} However, cesarean section increases postpartum morbidity, and it places women with compromised immune systems at higher risk for postoperative complications.\textsuperscript{13} The American College of Obstetricians and Gynecologists Committee on Obstetric Practice has recommended elective cesarean section for HIV–infected pregnant women with a viral load greater than 1,000 copies/mL near the time of delivery.\textsuperscript{34} There is convincing evidence that cesarean section before the onset of labor or membrane rupture is beneficial for women who have not taken antiretroviral drugs during pregnancy.\textsuperscript{24, 31} For women who have achieved undetectable or very low viral loads as a result of HAART, however, elective cesarean section has not been shown to further reduce the risk of perinatal transmission.

TREATMENT WITH AND SAFETY OF ANTIRETROVIRAL DRUGS

Before the development of antiretroviral drugs, perinatal transmission rates averaged 25% to 30% in women with HIV infection in this country; in less developed countries, rates as high as 43% were reported.\textsuperscript{5, 7} But in the mid-1990s, a randomized, double-blind clinical trial conducted in

HIV Infection

Disease course and diagnostic testing.

HIV, a retrovirus, initially attacks the immune system through the CD4+ cells (also known as T helper lymphocytes). Using the enzyme reverse transcriptase, the virus replicates by converting its RNA into DNA. The virus then enters the nucleus of the CD4+ cell and copies its genetic material into the DNA of the host cells. When the infected CD4+ cells replicate, instead of replicating themselves, they produce viral particles that are eventually assembled into new virus. During the acute phase of HIV infection (usually within two to four weeks of exposure), symptoms such as fever, lymphadenopathy, pharyngitis, and rash often accompany a plasma viremia that may peak at greater than 1 million virions/mL, according to one review.\textsuperscript{1}

As HIV replication progresses, the host CD4+ cells die, rapidly depleting the body’s supply. Following the acute phase, the infection continues to progress, although the patient may remain asymptomatic for several years. As the immune system weakens further, HIV symptoms such as oral thrush, chronic diarrhea, prolonged fatigue, and peripheral neuropathy appear. The appearance of such symptoms signals the onset of HIV disease. Eventually, an advanced stage of immunocompromise is reached and opportunistic infections occur. When certain hallmark opportunistic infections (such as Pneumocystis carinii pneumonia or cytomegalovirus disease) or cancers (such as Kaposi sarcoma) manifest, or when the CD4+ cell count falls below 200/mm\textsuperscript{3}, the disease has advanced to AIDS.

Two laboratory tests are important in monitoring the health status of HIV-infected patients and their responses to antiretroviral drugs. The HIV RNA–polymerase chain reaction test measures the number of copies of viral RNA per milliliter of plasma (this is referred to as the viral load). A high viral load (greater than 5,000 copies/mL) indicates that infection is progressing. The CD4+ count is the number of CD4+ cells per cubic micrometer (microliter) of blood; CD4+ cell counts drop as HIV infection progresses. According to the Department of Health and Human Services (DHHS), antiretroviral therapy is indicated for anyone, including pregnant women, whose CD4+ cell count falls below 200/mm\textsuperscript{3}; it’s also indicated for anyone with “a history of an AIDS-defining illness or severe symptoms of HIV disease,” regardless of CD4+ cell count.\textsuperscript{2} For infected pregnant women, the DHHS recommends testing at least once per trimester, and again at 34 to 36 weeks of pregnancy to help determine management of delivery.\textsuperscript{3} In my practice we test every four to six weeks. Testing for viral resistance using phenotypic or genotypic assays is also recommended to help guide the choice of antiretroviral drugs; those in which viral resistance is identified can then be avoided.\textsuperscript{2, 4}—Nancy J. Cibulka

REFERENCES

the United States and France found that treatment of pregnant women with zidovudine (Retrovir) before and during labor and delivery, followed by treatment of the infants with zidovudine for six weeks, reduced perinatal HIV transmission to about 8%. Zidovudine was effective regardless of the mother’s viral load or CD4+ lymphocyte level at the start of treatment. This treatment regimen, known as the Pediatric AIDS Clinical Trials Group Protocol 076, remains in use (see http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf). Although in this country antiretroviral monotherapy—treatment with a single agent, usually zidovudine or nevirapine (Viramune)—is no longer the recommended treatment for HIV infection, it’s sometimes used in pregnant HIV-infected women who’ve needed HAART but have not received it and are now presenting in labor. Monotherapy before, during, and after birth also continues to be used more widely in less developed countries, where the availability of HAART may be limited.

Viral mutation occurs more frequently than was at first recognized, increasing the risk of developing drug resistance. As a result HAART, typically a combination of two nucleoside analog reverse transcriptase inhibitors and a protease inhibitor, is now the recommended treatment for optimal suppression of viral replication in people with HIV, including pregnant women. Adding other antiretrovirals to zidovudine during pregnancy has been found to reduce the rate of transmission to less than 2%. More than 20 drugs are approved by the Food and Drug Administration for the treatment of HIV infection (see Table 1, page 61, for a list of antiretroviral drugs used during pregnancy). The current standard is to treat people who are HIV infected, including women who are pregnant, with at least three antiretrovirals from two or three different classes. Treatment with single-dose agents is now available; these drugs are taken once a day instead of several times and may be included as part of a HAART regimen.

A typical HAART regimen during pregnancy might include lamivudine and zidovudine (formulated together as Combivir). Both drugs are classified as nucleoside analog reverse transcriptase inhibitors. Combivir is usually one of the drugs prescribed, and many different drug combinations are used in practice. For example, Combivir might be given with the protease inhibitors lopinavir and ritonavir (formulated together as Kaletra) or with nevirapine, which is a nonnucleoside analog reverse transcriptase inhibitor. Zidovudine and nevirapine have each been shown to be effective in reducing perinatal transmission risk. However, a warning about nevirapine has recently been issued because of a high incidence (11%) of serious hepatic complications when it’s used by women with a CD4+ cell count above 250/mm3.

All antiretroviral drugs have potentially toxic effects, including neuropathy, cardiomyopathy, ele-
HIV testing of all pregnant women and all those who are planning a pregnancy. CDC guidelines emphasize that HIV testing should be a routine part of prenatal care and recommend that all pregnant women, even those not thought to be at high risk, be tested; testing is voluntary, however, and women have the right to refuse. The CDC also promotes the routine screening of any infant whose mother was not screened during pregnancy. In communities where people are at high risk for infection, a second HIV test in the third trimester has been found to be cost effective. Rapid testing at the time of delivery is available for women who were not tested in pregnancy. Abbreviated antiretroviral regimens and avoidance of breastfeeding have helped reduce the risk of perinatal transmission even when treatment begins during labor and delivery or shortly after birth.

Screening pregnant HIV-infected women for concurrent genital tract infections, especially those that are sexually transmitted, and treatment with appropriate drugs can also reduce the risk of perinatal HIV transmission.

Discuss antiretroviral therapy. All HIV-infected women should be offered HAART during pregnancy. It’s important to discuss with them both the importance of adherence to the drug regimen and the risks of antiretroviral therapy. Explain that without antiretroviral therapy, the risk of perinatal HIV transmission is approximately 25%. With HAART, once a very low viral load is achieved (lower than 1,000 copies/mL), the risk is less than 2%. Explain also that no combination of therapies can guarantee that a newborn will not become infected.

Counsel women about safer sex and their lifestyles. Practicing safer sex reduces the risk of HIV transmission to the fetus (as well as to uninfected partners), because it reduces the risk of acquiring other STIs, which have been linked with increased viral shedding in maternal cervicovaginal secretions. HIV-infected women who don’t practice safer sex risk acquiring drug-resistant HIV strains as well. Anyone who is sexually active should be encouraged to use condoms and reminded that mutual monogamy with an uninfected partner is safer than nonmonogamy. Sexual abstinence may be another option.

Women who smoke or use illicit drugs should be counseled to discontinue these practices before becoming pregnant or, if already pregnant, to stop immediately. Offer referrals as needed for nutritional counseling, assistance with smoking cessation, treatment for substance abuse, and safer-sex counseling.

Avoid invasive procedures. Nurses should be aware that invasive procedures, including internal monitoring with fetal scalp electrodes, fetal

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<thead>
<tr>
<th>Antiretroviral Drug or Drug Combination</th>
<th>FDA Pregnancy Category*</th>
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<tbody>
<tr>
<td>abacavir (Ziagen)</td>
<td>C</td>
</tr>
<tr>
<td>didanosine (Videx)</td>
<td>B</td>
</tr>
<tr>
<td>emtricitabine (Emtriva)</td>
<td>B</td>
</tr>
<tr>
<td>abacavir with lamivudine (Epzicom)</td>
<td>C</td>
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<tr>
<td>lamivudine (Epivir)</td>
<td>C</td>
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<tr>
<td>stavudine (Zerit)</td>
<td>C</td>
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<tr>
<td>tenofovir (Viread)</td>
<td>B</td>
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<tr>
<td>zalcitabine (Hivid)</td>
<td>C</td>
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<tr>
<td>zidovudine (Retrovir)</td>
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<tr>
<td>zidovudine with lamivudine (Combivir)</td>
<td>C</td>
</tr>
<tr>
<td>zidovudine with abacavir and lamivudine (Trizivir)</td>
<td>C</td>
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<tr>
<td>tenofovir with emtricitabine (Truvada)</td>
<td>B</td>
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**Table 1. Antiretroviral Drugs Used During Pregnancy**

* FDA = Food and Drug Administration. FDA pregnancy categories: A—Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters). B—Animal reproduction studies fail to demonstrate a risk to the fetus; 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 in pregnant women clearly outweighs any possible benefit.
scant pH sampling, amniocentesis, or the use of forceps, should be avoided if possible, even if the woman is receiving HAART and has an undetectable viral load. Counsel pregnant women with viral loads greater than 1,000 copies/mL regarding the potential benefit of scheduled cesarean delivery in reducing the risk of perinatal HIV transmission.

**Address reproductive decisions.** For women who know they are HIV infected, making decisions about reproduction is complex. Education and counseling regarding HIV infection and its implications for pregnancy should be incorporated into routine care visits before pregnancy occurs, so that reproductive decisions can be based on accurate information, health status, and access to recommended care. The risks of perinatal HIV transmission, the safety of antiretroviral drugs, and the importance of adherence to antiretroviral therapy are essential topics. For some women the desire for a child is so strong that they’re willing to accept some risk. However, if a woman’s immune system has been severely compromised, she may not be healthy enough to bear or raise children. It can be helpful to include partners and significant family members in these discussions.

Besides providing education and counseling, nurses may need to coordinate social services. Tasks such as obtaining housing and job training, accessing mental health and dental care services, and deciding whether and how to disclose HIV status to sexual partners and family members can be particularly complex. Referral to a social worker or case manager may be appropriate. ▼

**REFERENCES**


