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ONLINE EXCLUSIVE

Preventing perinatal transmission of HIV: Your vigilance can pay off

These interventions can keep the risk of mother-to-child transmission at less than 2%.

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PRACTICE RECOMMENDATIONS

› *Approach perinatal HIV transmission comprehensively, from prevention of unintended pregnancies among women with HIV to providing follow-up care to mothers with HIV and to their children.* (C)

› *All HIV-infected pregnant women should be offered highly active antiretroviral therapy (HAART).* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

A long-standing 25-year-old patient of yours reports that a home-pregnancy test proved positive. You confirm the pregnancy. This will be her first child. On routine prenatal testing, her human immunodeficiency virus (HIV) test result is also positive (enzyme-linked immunosorbent assay [ELISA], with confirmatory Western blot). She is concerned that the infection may be transmitted to her child and asks what can be done to prevent it.

With the use of appropriate interventions, the likelihood of her child becoming infected is less than 2%. In the United States today, most infants born to HIV-positive women will remain uninfected. Interventions recommended by the Public Health Service Task Force (US guidelines) include giving antiretroviral medications to the woman during pregnancy; managing the delivery, with the option of vaginal delivery vs cesarean section (to be determined closer to the time of delivery, based on her response to antiretroviral agents); giving a 6-week course of zidovudine (ZDV) to her infant; and avoiding breastfeeding.[1,2]

What heightens the risk?

Perinatal transmission of HIV from mother to child can occur during pregnancy, labor and delivery, or breastfeeding.[3] Risk of transmission is heightened if a mother has a high viral load and low CD4+ cell count or has advanced HIV illness or AIDS; rupture of membranes is prolonged, exceeding 4 hours; or invasive obstetrical procedures are required.[3]

Without intervention, the risk of transmission is 15% to 30%.[4] Approximately 70% of transmission is believed to occur before delivery (20% before 36 weeks' gestation, 50% from 36 weeks through labor), with roughly 30% of transmission occurring during delivery and the infant's passage through the birth canal.[5] Breastfeeding adds 5% to 20% to baseline risk, raising the total modifiable risk to as high as 50%.[5]

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Many HIV-infected women do not receive regular health care, and many do not know they are infected.

A comprehensive approach from WHO

The World Health Organization (WHO) has described a comprehensive approach to preventing perinatal transmission of HIV,[4] which takes into consideration several factors across the spectrum of women's and children's health and assumes the involvement of a range of health care providers, including family physicians. The WHO approach focuses on 4 main areas and their respective interventions:

- Preventing HIV infection among women of childbearing age
- Preventing unintended pregnancies among women with HIV
- Preventing HIV transmission from a mother to her infant
- Providing appropriate care, treatment, and support to mothers with HIV and their children and families.

Preventing HIV infection among women of childbearing age

In 2007, HIV/AIDS was diagnosed in nearly 11,000 American women.[6] African American women are 22 times more likely than white women to become infected, and Hispanic women are 5 times more likely.[6]

More than 80% of women become infected with HIV through high-risk heterosexual contact, including unprotected sex with multiple partners (eg, sex in exchange for money or narcotics), sex with men who have sex with men, and sex with injection drug users.[7]

Injection drug use is associated with 1 in 6 new HIV/AIDS diagnoses in women.[6,7] Young women of childbearing age have a higher risk of becoming HIV infected than older women,[6,7] and pregnancy itself increases a woman's vulnerability to infection.[6,7] In addition, women may not appreciate their male partner's risk factors for HIV infection.[7]

The presence of other sexually transmitted infections (STIs) greatly increases the risk of acquiring and transmitting HIV infection.[8] Poverty, too, is a risk factor for acquiring HIV infection. A study of African American women in North Carolina found that unemployment, receipt of public assistance, and the exchange of sex for money or housing were significantly more likely among HIV-infected women than among uninfected women.[9]

Awareness of these risk factors is important for those who care for minority and disadvantaged populations. In treating at-risk women, consider early referral to social services and reinforce HIV prevention strategies, such as condom use with each sexual contact, to help reduce new HIV infections.[7,10] Screening of young women for gonorrhea and chlamydia and prompt treatment of these and other STIs may also have an impact on HIV transmission.[8,11]

Preventing unintended pregnancies among women with HIV

Many HIV-infected women do not receive regular health care,[12,13] including family planning services. And many do not know they are infected.[12]

The Centers for Disease Control and Prevention (CDC) recommends routine voluntary screening for HIV as a standard part of basic medical care.[14] This is particularly important among higher-risk populations. Family physicians could offer a full range of family planning options for women who choose to undergo screening or otherwise test positive for HIV.

Preventing HIV transmission from mother to infant

As many as 40% of HIV-infected infants in the United States are born to mothers unaware of their HIV status at delivery.[15] The CDC emphasizes that it is never too late for pregnant women to be tested, and recommends an "opt out" approach, thereby establishing HIV testing as a routine part of prenatal care.[14] Recommendations also include repeating the HIV screen in the third trimester for women who meet certain criteria (**TABLE 1**);[14] antiretrovirals given to a mother during labor and to the infant after birth can still significantly reduce the risk of perinatal transmission.[16] Accordingly, the use of rapid HIV tests in delivery rooms is recommended for women with unclear HIV status.[15] US guidelines also cover scenarios in which maternal HIV infection is first realized during labor or after a child has been born.[1]

Women known to be living with HIV who

TABLE 1

Repeated HIV screening is recommended for pregnant women in their third trimester who meet these criteria[14]

Women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women ages 15 to 45 years
Women who receive health care in facilities in which prenatal screening identifies at least 1 HIV-infected pregnant woman per 1000 women screened
Women who are known to be at high risk for acquiring HIV
Women who have signs or symptoms consistent with acute HIV infection

NOTE: A second HIV test during the third trimester, preferably <36 weeks of gestation, is cost effective even in areas of low HIV prevalence and may be considered for all pregnant women.

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

wish to become pregnant can be assured that, if current US guidelines are followed, the risk of HIV transmission to their infant is less than 2%.[1] These guidelines include detailed recommendations for antiretroviral drug use by pregnant HIV-infected women that vary by clinical scenario. The guidelines are updated frequently and are available at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.[1] The full package of interventions also includes obstetric measures and a course of ZDV administered to the infant after birth.

Antiretrovirals during pregnancy. Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076) was the first major study of antiretroviral use for perinatal transmission prevention.[17] This randomized, placebo-controlled study evaluated antiretroviral prophylaxis with ZDV monotherapy. ZDV was given to mothers orally, beginning at 14 to 34 weeks of pregnancy, and intravenously during labor and delivery, and to newborns orally for the first 6 weeks of life. Infants were formula fed. At 18 months, HIV transmission occurred with 25.5% of women receiving placebo and 8.3% of women receiving ZDV—a 67.5% relative risk reduction.[17]

Subsequently, it was realized that antiretroviral regimens that use 3 medications are superior to those that use only 1 or 2.[18] Current standard of care in the United States is use of a 3-drug combination during pregnancy (known as highly active antiretroviral therapy, or HAART).[1] HAART generally comprises 2 nucleoside reverse transcriptase inhibitors (ZDV, lamivudine) and either a non-nucleoside reverse transcriptase inhibitor (nevirapine) or a protease inhibitor (lopinavir/ritonavir).

Some women meet criteria for HAART based on their clinical or immunologic status (history of an AIDS-defining condition or severe HIV-associated symptoms, or a CD4+ count <350 cells/mm^3, respectively). However, all pregnant women should be offered HAART, regardless of their immunologic or virologic status, as perinatal transmission may occur even at very low or undetectable viral loads.[1] HIV antiretroviral resistance should be assessed before initiating HAART.[1]

A woman's primary care and obstetric providers are important to the success of antepartum antiretroviral therapy, even though they may not directly manage the regimen. The goal of therapy is an undetectable maternal viral load at delivery,[1] an achievement that depends in large part on adherence to antiretroviral therapy,[19] which may be influenced by the degree to which coordinated care is delivered.[20]

Obstetric interventions. Compared with vaginal delivery, cesarean delivery reduces perinatal HIV transmission.[21,22] To be most effective, a cesarean section must be performed electively, before membranes rupture.[12] For most HIV-infected women, cesarean section is as safe as it is for HIV-negative women. For women with advanced disease or AIDS, cesarean section may carry a higher risk of maternal complications.[23]

All pregnant women should be offered HAART, regardless of immunologic or virologic status.

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HIV-exposed infants should receive routine childhood immunizations according to the usual schedule.

For women with unknown HIV RNA levels (viral load) or a viral load >1000 copies/mL near the time of delivery, US guidelines recommend that scheduled cesarean delivery be performed at 38 weeks' gestation, whether or not they are receiving antepartum antiretroviral drugs.[12] For women taking antiretrovirals who have a viral load of <1000 copies/mL, guidelines advise that data are insufficient to evaluate the potential benefit of cesarean delivery in preventing perinatal transmission.[12] When viral load is <1000 copies/mL, administration of intravenous ZDV followed by vaginal delivery (as in PACTG 076 – 2 mg/kg intravenous load over 1 hour, then 1 mg/kg per hour until delivery) is an option, and is commonly used in the United States.[1,23]

Antiretroviral administration to infants. All HIV-exposed newborns receive ZDV as a standard part of perinatal transmission prevention,[1] initiated as close to delivery as possible. Infants whose gestation was 35 weeks at birth receive an oral dose of 2 mg/kg (or 1.5 mg/kg intravenously if unable to take oral medications) within the first 6 to 12 hours after birth, then every 6 hours until 6 weeks of age. Infants less than 35 weeks' gestation at birth receive 2 mg/kg orally every 12 hours (or 1.5 mg/kg intravenously), advancing to every 8 hours at 2 weeks of age if they were 30 weeks' gestation at birth, or at 4 weeks of age if less than 30 weeks' gestation at birth.

In unusual circumstances, such as when a mother is known to have a high viral load at delivery or an antiretroviral-resistant virus, other antiretroviral agents may be added to ZDV for infant prophylaxis.[1] The decision to use additional antiretrovirals necessitates consultation with a pediatric HIV specialist, preferably before delivery.

With the exception of efavirenz—thought to have potential teratogenicity when administered in the first trimester of pregnancy[1]—antiretrovirals are generally considered safe in pregnancy and for newborns;[7] rarely, significant organ system pathology due to mitochondrial toxicity has been observed in infants exposed to antiretrovirals.[24] Prophylactic ZDV use may be associated with anemia in infants, but this is generally mild and resolves by 12 weeks of age without treatment.[25] Follow-up of the data from PACTG 076 has shown no long-term adverse effects associated with ZDV.[26]

Providing care, Tx, support to mothers with HIV and their newborns

Prevention of perinatal HIV transmission does not end when an infant completes 6 weeks of ZDV therapy. The mother must have postpartum care and ongoing management of HIV infection; the infant must undergo assessment of HIV status and monitoring while receiving ZDV, and receive general infant care. The longitudinal, family-centered approach with family medicine offers an opportunity to optimize the overall wellness of a woman with HIV, including mental health, contraceptive counseling, cervical screening, and a decision on whether to continue antiretroviral therapy, based on clinical status (HIV disease stage) and immunologic (CD4) factors.[1]

In the United States and other developed countries where safe and feasible formula feeding is possible, breastfeeding is not recommended for HIV-infected mothers, due to the risk of virus transmission via breast milk.[1]

Given that maternal antibodies to HIV cross the placenta and are detectable in HIV-exposed infants up to 18 months of age, antibody tests such as HIV ELISA and rapid HIV tests are not suitable for the diagnosis of HIV in infants.[12] Rather, a virologic polymerase chain reaction (PCR) test must be used.[1] While HIV *DNA* PCR is the gold standard for infant diagnosis, HIV *RNA* PCR is also sensitive and specific.[1] HIV-exposed infants should receive routine childhood immunizations according to the usual schedule.[1,27] HIV-infected infants should be referred to a pediatric HIV specialist.

Untreated HIV infection in infants may have a variable course, including rapid progression to AIDS and death.[28] Often the first manifestation of rapid progression is *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia), which may be seen even before HIV diagnosis is realized in an infant who becomes HIV-infected despite prophylaxis.[1,29] Unless there is adequate proof to presumptively exclude HIV infection (negative results on 2 virologic tests conducted

TABLE 2

Follow-up measures for infants exposed to maternal HIV[1,27]

ZDV prophylaxis
From birth to age 6 weeks

Diagnosis of HIV
Virologic test (required for infants <18 months of age; HIV DNA PCR preferred)
At birth (optional), 14 to 21 days, 1 to 2 months, 4 to 6 months

- If positive, repeat immediately on a separate specimen for confirmation; 2 positive HIV DNA PCR tests confirm a diagnosis of HIV infection
- HIV presumptively excluded (nonbreastfed infant): 2 or more negative tests, with 1 at ≥14 days and another at ≥1 month.
- HIV definitively excluded (nonbreastfed infant): 2 negative tests at ≥1 month and ≥4 months of age.

HIV ELISA
18 months. Confirmatory test if HIV DNA PCR tests performed as above are negative

Complete blood count
At birth, when initiating ZDV prophylaxis, and at time of 1st HIV DNA PCR (2-3 weeks)

Prophylaxis against *Pneumocystis* pneumonia
Trimethoprim-sulfamethoxazole beginning at 6 weeks, with discontinuation of ZDV prophylaxis, unless HIV presumptively excluded (see above)

Routine immunizations
As per general US pediatric immunization schedule

DNA, deoxyribose nucleic acid; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; ZDV, zidovudine.

≥2 weeks postpartum, 1 of which must be at least 4 weeks postpartum),[1,29] all HIV-exposed infants should be started at age 6 weeks (after completion of ZDV prophylaxis) on trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra) prophylaxis against *Pneumocystis* pneumonia. TMP-SMX prophylaxis should be continued until 2 virologic tests for HIV yield negative results.[1] If TMP-SMX toxicity develops, dapsone and atovaquone are alternatives.[29] **TABLE 2** outlines the follow-up of HIV-exposed infants, including testing for HIV. JFP

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