Advances in the Prevention and Treatment of Perinatal HIV Infection

Recent information on the prevention and treatment of perinatal HIV infection was discussed at the Chicago conference by Yvonne J. Bryson, MD, from the University of California, Los Angeles School of Medicine. In her presentation, Dr Bryson highlighted advances in our knowledge of the risk factors associated with vertical transmission and with disease progression in HIV-infected infants.

In the US and around the world, the majority of pediatric HIV infection occurs by maternal-fetal transmission, with transmission rates varying by population and geographic area. In the US and Europe, the transmission rates in women not treated with antiretroviral therapy are estimated at 25% to 30%, and at 13%, respectively. In Africa, HIV transmission rates were estimated at 40% by epidemiological studies earlier in the epidemic; however, more recent studies using better methods for early diagnosis of HIV in infants have reported transmission rates of approximately 25%. Heterosexual transmission of HIV is the most common route of transmission to women worldwide, and at present intravenous drug use is the most common risk factor among HIV-infected pregnant women in the United States. The number of women with HIV disease continues to rise, and as it does, the incidence of perinatal HIV infection is expected to increase if no intervention is employed.

As demonstrated in the AIDS Clinical Trials Group (ACTG) protocol 076, zidovudine given to HIV-infected pregnant women during gestation and at delivery who were previously untreated with antiretroviral drugs and to the infant during the first six weeks of life reduced perinatal transmission by approximately 70%. In this study, the transmission rate was 25.5% in the placebo group and 8.3% in the zidovudine-treated group. The reduction in transmission is most likely achieved by either or both of the following mechanisms: reduction of maternal viral load and prophylaxis of the fetus and infant.

The results of ACTG 076 provided proof of concept that vertical transmission can be significantly reduced with the use of antiretroviral therapy. Zidovudine has become the current antiretroviral drug of choice in the US for pregnant women with HIV to prevent perinatal transmission. Based on this concept, with the recent availability of new and more potent antiretroviral drugs, investigators expect to be able to reduce perinatal transmission even further, with a goal of less than 2% transmission. However, a number of key questions remain: Which specific aspects, if any, of this multifactorial process can be used to help predict those women who are at highest risk for transmitting the virus? Why do more than 70% of infants born to untreated HIV-infected women avoid infection themselves? At what point during gestation and delivery and by what means is transmission most likely to occur? Is there an increased risk associated with early breast-feeding? Ongoing international studies have been designed to address the relative importance of prenatal, intrapartum, and postpartum drug administration and other practical and cost-effective prevention strategies in reducing vertical transmission and the results will help to identify optimal approaches for its prevention.

Risk Factors Associated with Vertical Transmission of HIV

Risk factors and the timing of HIV infection. Viral, immunologic, and clinical factors in both the mother and the infant all play a role in the multifactorial process of vertical transmission of HIV disease. These factors, and, therefore, the efficacy of different interventions vary according to the timing of transmission. There is evidence supporting transmission before birth (in utero), during labor and delivery (intrapartum), and after birth (postpartum: breast-feeding). (See Table 1.) In non–breast-fed infants, the working definition of transmission in utero is based on a positive culture and/or polymerase chain reaction (PCR) assay in infants within 48 hours of life. Intrapartum transmission is defined by a negative culture and DNA-PCR assay in infants within 48 hours of life and by a positive culture and DNA-PCR assay after 48 hours of life and up to 90 days after birth (see Suggested Reading: Bryson et al. *N Engl J Med.* 1992). An HIV-1 DNA-PCR assay was used to assess the relative contribution of intrauterine and intrapartum transmission of HIV in 271 HIV-infected infants. In this study, 38% had a positive DNA-PCR within 48 hours of birth, which is consistent with infection in utero. Within 28 days after birth, 96% of all of the infected infants had a positive DNA-PCR.

Intrauterine HIV transmission. Although the exact timing of in utero infection is unknown, most evidence points to transmission in late gestation in the majority of live-born infants. However, transmission has been documented in the first trimester based on finding HIV in aborted fetuses. A recent study suggested that there may be a higher frequency of HIV infection in spontaneous fetal loss. Risk factors that have been potentially associated with perinatal transmission during gestation include high maternal viral load (see below), decreased CD4+ cell counts, and stage of disease (primary infection and advanced maternal clinical HIV disease). Several small studies have shown that a lack of autologous neutralizing antibody in the mother is associated with a higher risk of perinatal HIV transmission, and that many women who transmit do not have neutralizing antibody to the infant's virus. It is also possible that HIV-infected mothers who do not transmit the virus to their infants may have a broader neutralizing antibody. In a study by Bryson and colleagues, both the presence and titer of autologous neutralizing antibody were decreased in women who transmitted in utero.

Intrapartum HIV transmission. Factors associated with intrapartum transmis-

Table 1. Potential Risk Factors Associated with Perinatal Transmission According to the Timing of Infection.

"In utero" transmission

- Increased maternal viral load (cell-free, cell-associated)
- Advanced maternal clinical disease
- Primary infection during pregnancy
- Lack of neutralizing antibody
- Decreased maternal CD4+ cell count
- Cell-mediated immunity (CTL, CD8+ cell suppression)
- Syncytium-inducing viral phenotype/ tropism
- Placental breaks
- Maternal-fetal transfusion
- HIV or other infection of the placenta
- Spontaneous fetal loss

"Intrapartum" transmission

- High maternal viral load
  - In blood (cell-free, cell-associated)
  - In cervicovaginal secretions
- Prolonged ruptured membranes (>4 h)
- Infant exposure to blood/secretions
  - Swallowing
  - Mucous membranes
  - Maternal-fetal transfusion
- Delivery mode (vaginal vs cesarean section)
- Trauma
- Placental factors
  - Abruption
  - Chorioamnionitis
  - Co-infections
- Infant prematurity
- First-born twin

"Postpartum" transmission

- Breast-feeding
- High risk during primary maternal infection

sion of HIV may also include maternal viral load in both plasma and in cervicovaginal secretions. It is estimated that 30% of HIV-positive women may have virus in cervicovaginal secretions detectable by PCR and/or culture and that these findings may not necessarily correlate with levels of maternal plasma HIV RNA (see Suggested Reading: Nielsen et al. *J Infect Dis.* 1995). HIV has recently been detected in the gastric aspirates of HIV-infected newborns, which may also be a risk factor for infection.

Intrapartum HIV transmission may occur despite the presence of maternal autologous neutralizing antibody. In the study mentioned above, Bryson and colleagues found no significant difference in the mean autologous neutralizing antibody titer in those women transmitting the virus intrapartum compared with that in women who did not receive zidovudine and did not transmit the virus. This suggests that the protective effects of antibody may be overcome and that virus may be transmitted cell to cell or by the oral route. The question of whether the passive transfer of neutralizing antibody can modify viremia and HIV disease course in infants infected intrapartum requires further investigation.

Other factors associated with intrapartum HIV transmission include the mode of delivery, trauma (particularly for premature infants), the duration of ruptured membranes, and placental factors, such as abruption or coinfections. In the European Collaborative Study, the vertical transmission rate was reduced from 17% (127/727) in vaginal deliveries to 12% (21/172) in elective cesarean sections and to 10% (7/67) in emergency cesarean sections. These findings represent an approximately 50% reduction in vertical transmission of HIV for women undergoing a cesarean section ($P = .005$). This study, however, was not randomized, and other studies have not shown the same results. A recently published study by Landesman and colleagues for the Women and Infants Transmission Study (WITS) group showed that in the absence of antiretroviral treatment there was a significantly increased risk of transmission in women who had ruptured membranes for more than 4 hours regardless of the mode of delivery. There is no current recommendation for cesarean section for the prevention of perinatal transmission.

Maternal viral load and risk of perinatal transmission. A number of studies have demonstrated that high levels of HIV in pregnant women as measured by several different assays including ICD p24 antigen, HIV-limiting dilution co-culture, DNA-PCR, and plasma HIV RNA have been associated with an increased risk of vertical HIV transmission. Most recently, plasma HIV RNA assays have been shown to be the most sensitive. Plasma HIV RNA levels greater than or equal to 50,000 copies/mL were associated with a more than 50% risk of vertical HIV transmission in one study and were most highly associated with transmission in utero. In a study by Weiser and colleagues, all women (8/8) transmitting HIV had plasma HIV RNA levels at or above 100,000 copies/mL compared with only 2 of 22 women who did not transmit the virus ($P = .001$).

Dickover and coworkers showed that 75% (15/20) of pregnant women transmitting HIV had plasma HIV RNA levels greater than 50,000 copies/mL compared with 5.3% (4/75) of HIV-infected pregnant women who did not transmit the virus ($P < .0001$). The risk of transmission increased with higher plasma HIV RNA levels (Figure 1). The median plasma HIV RNA level at delivery was 94,054 copies/mL for women who transmitted HIV and 4596 copies/mL for those who did not ($P < .0001$).

The maternal use of zidovudine in this cohort significantly reduced maternal plasma HIV RNA levels in the drug-naive women who did not transmit the virus, with a median six- to eightfold reduction from initiation of therapy to the time of delivery. Several patterns of viral load were observed in this cohort. Women who did not receive zidovudine and did not transmit HIV had stable and consistently low plasma HIV RNA levels. Approximately 50% of the untreated transmitters had unexplained increases in plasma HIV RNA prior to delivery, which points out that a low level of plasma HIV RNA early in pregnancy cannot be used to predict a low risk of vertical transmission. This study also revealed that 4 of 22 HIV-infected women given zidovudine did transmit the virus despite treatment,

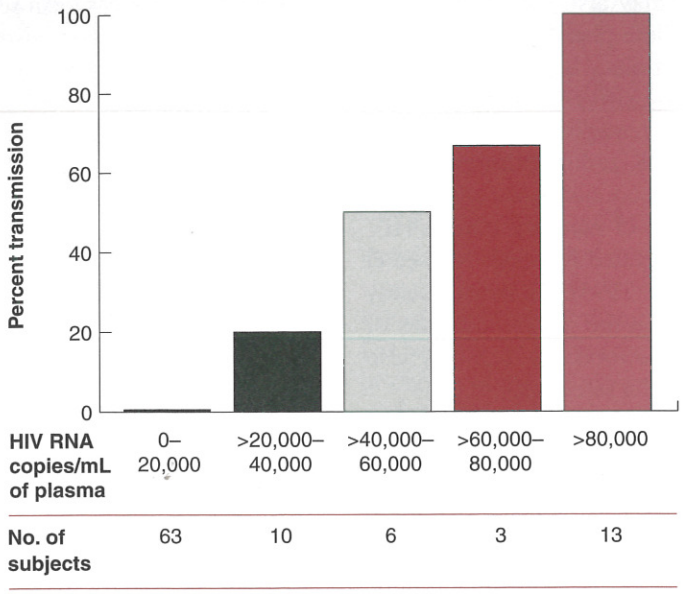

Figure 1. Risk of vertical HIV transmission by maternal plasma HIV RNA level at delivery in a cohort of 95 HIV-infected pregnant women. Adapted with permission from Dickover RE et al. JAMA. 1996; 275: 599–605. Copyright 1996, American Medical Association.

and this finding was associated with high plasma HIV RNA levels at delivery without evidence of zidovudine-resistant virus in maternal or infant samples. According to Dr Bryson, plasma HIV RNA levels in this subgroup were very high and the modest reductions achieved with zidovudine use may not have been enough to significantly reduce maternal viral load or to protect the infant. Since the majority of infants in this study as well as in a recent larger study of more than 180 women did not receive zidovudine after birth, maternal treatment prior to delivery may be most critical.

It is of interest that all of the women with lower plasma HIV RNA levels (less than 50,000 copies/mL) at delivery transmitted intrapartum. Preliminary analysis of plasma HIV RNA levels in women enrolled in the ACTG 076 study revealed that risk of transmission increased with increasing plasma HIV RNA levels; however, transmission occurred in some women with lower plasma HIV RNA levels. At present it is unknown if transmission at lower levels occurred intrapartum and/or resulted from cervicovaginal viral shedding or from other factors related to delivery. The ACTG 076 study also demonstrated that use of zidovudine was associated with reduced vertical HIV transmission in women with all levels of plasma HIV RNA, underscoring the ability of the drug to protect the fetus and infant from infection by a mechanism other than reduction of maternal plasma HIV RNA levels.

Questions remain about the relationship of plasma HIV RNA levels to vertical transmission. Several recent studies have shown that transmission can occur at lower plasma HIV RNA levels. The question is why and if this transmission may be associated with events at the time of delivery or with other viral factors. It is also premature at this time to identify any specific HIV RNA copy number with risk of transmission since plasma HIV RNA measurements vary. The proper collection and processing of blood prior to assay is also important to avoid loss of HIV RNA. Both the choice of anticoagulant and rapid separation of plasma within 4 to 6 hours will help to ensure accurate results. Collection in heparin will result in a 38% decrease in HIV RNA levels compared with baseline levels in EDTA if processed immediately and a greater than 70% decrease in levels will occur if processing is delayed up to 24 hours. Clearly, a high maternal plasma HIV RNA level is an important risk factor, but it is not the only risk factor. According to Dr Bryson, current data support the use of antiretroviral therapy in pregnant HIV-positive women at any level of plasma HIV RNA.

Approaches to Preventing Vertical HIV Transmission

At present, antiretroviral therapy is recommended for pregnant HIV-infected women during gestation and delivery, and for infants postpartum. While most research has been conducted with zidovudine monotherapy, proposed trials include studies of a combination of zidovudine/nevirapine during labor and delivery. Phase I trials with a variety of combined antiretroviral drugs are under way, including zidovudine and lamivudine, alone and combined with several of the protease inhibitors, as well as other investigational nucleosides. An efficacy study is planned for early 1997, based on results of these phase I studies. Drug combinations that prove to be safe, well-tolerated, cross the placenta, and maximally reduce maternal viral load will be chosen for this study. Phase I studies of nevirapine have been completed. Owing to its long half-life, a single dose of nevirapine given during labor results in significant drug levels in the infant for 3 days and may help prevent intrapartum transmission. This approach may be very attractive as a practical and cost-effective strategy to reduce intrapartum transmission in developing countries. Outside of the US, various regimens of reduced courses of zidovudine are being evaluated in mother/infant pairs, and in the mother or the infant alone. Studies of zidovudine/lamivudine in combination are also under way in Africa.

Immune-based therapies are also being investigated for use in pregnant HIV-infected women and in infants born to HIV-infected mothers. In the ACTG 185 protocol, pregnant HIV-infected women have been randomized to receive zidovudine and HIV intravenous gamma immunoglobulin (HIVIG) or intravenous gamma immunoglobulin (IVIG). To date, more than 250 women and infants have been enrolled in this efficacy trial. Phase I studies are under way in infants born to HIV-infected women to evaluate broadly-neutralizing monoclonal antibodies, and to evaluate tolerance to and immunogenicity of new vaccines. Studies evaluating a combination of vaccine and antibody therapy are planned.

Local approaches, such as vaginal washing, are also in use outside of the US. A large study in Africa evaluated the effectiveness of vaginal washing at delivery with chlorhexidine in more than 3000 deliveries and found no effect in terms of perinatal transmission. Topical and/or oral treatment of the infant may be other options.

Disease Progression in HIV-infected Infants

Although the majority of perinatally-infected children survive less than eight years, there are long-term pediatric survivors, and significant variation in disease progression and in life span in this population. A number of factors are assumed to effect disease progression, including the timing of perinatal infection, the viral load, the infant's immune response, and the virulence of the virus itself.

In a prospective cohort of 34 HIV-infected infants followed from birth, Dr Bryson and colleagues have conducted ongoing analyses on the risk factors for clinical progression. Rapid progression was defined as the onset of symptoms with disease progression within 6 months, an AIDS diagnosis within 2 years, and a significant and sustained fall in CD4+ cell counts. Slow progression was defined as no symptoms for at least 6 months, stable CD4+ cell counts, and no disease progression for at least 2 years. A third category, intermediate progressors, had early onset of symptoms, a transient fall in CD4+ cell counts, and no disease progression for 2 or more years. Most infants in this latter category received early antiretroviral therapy. Of the 34 infants followed, 18 were infected in utero (PCR- and culture-positive at birth), 13 intrapartum (PCR- and culture-negative at birth), and 3 had no birth samples available.

Early onset of symptoms and rapid progression was associated with high levels of plasma HIV RNA at birth and during the first 6 months of life, rapid and sustained loss of CD4+ cells, and in utero HIV infection. A peak plasma HIV RNA level greater than 10^6 copies/mL was associated with an onset of symptoms within 6 months ($P = .002$); a persistent level of plasma HIV RNA greater than 10^6 copies/mL was associated with early onset of symptoms ($P = .0002$), a diagnosis of AIDS within 2 years ($P = .003$), and a survival time of less than 2 years ($P < .02$). Those infants with CD4+ cell counts less than 1000/μL and those with an age-adjusted CD4+ cell count less than 50% of the normal median were also significantly more likely to experience the onset of symptoms within the first 6 months ($P = .005$).

Early, aggressive antiretroviral therapy in perinatally-infected infants may alter the rate of disease progression, and, subsequently, the long-term prognosis, by reducing viral load and preserving the immune system during this primary infant infection. Studies using the combination of zidovudine/nevirapine, or the triple combination of zidovudine/didanosine/nevirapine, have produced promising early results, including the ability to reduce the viral load below detectable levels for up to 9 months in some infants. Studies of protease inhibitors in children with HIV are currently under way. Studies of treatment of infants upon diagnosis of HIV with potent combinations of antiretroviral drugs including protease inhibitors to maximally reduce viral load during primary infection are planned.

Summary

There is cause for optimism in the prevention of perinatal HIV infection. Effective antiretroviral therapy can significantly reduce the risk of vertical transmission and clinical trials currently under way will help to identify optimal drugs, doses, and timing. In addition, early intervention in neonatal primary infection may potentially alter disease outcome for those infants who are infected with HIV. Raising awareness, providing education, translating scientific advances into clinical practice, and making effective interventions accessible worldwide remain the greatest challenges.

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Suggested Readings

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