Perinatal Transmission of HIV: Recognition and Treatment Interventions

Jaime Deville, MD, and Yvonne Bryson, MD

Address
UCLA School of Medicine, Mattel Children’s Hospital, 10833 Le Conte Avenue, 22-442 MDCC, Los Angeles, CA 90095-1752, USA.
E-mail: ybryson@mednet.ucla.edu; jdeville@mednet.ucla.edu
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Great strides have been made in the fight against vertical transmission of HIV-1. Improved understanding of mechanisms and timing of transmission of HIV-1 from mother to child have led to the development of effective intervention strategies that have reduced transmission rates to unprecedented low levels, below 2% in developed countries. New reports using shortened, more affordable courses of antiretrovirals prenatally or at the time of delivery have also shown a significant reduction in transmission, over 50% in studies conducted in the developing world. These advances, combined with ongoing studies using simplified effective treatment regimens, have made possible the potential to significantly reduce perinatal transmission worldwide. Future challenges include reduction of breast feeding transmission and the development of an effective HIV-1 vaccine to produce long-lasting protection.

Introduction
There has been a major shift recently in the HIV-1 epidemic in the United States. Minority populations and women now have a larger share of new cases [1–4]. These groups now represent approximately two thirds of new HIV-1 infections and AIDS cases [1]. The highest incidence of HIV-1 infection and AIDS is now reported in African-Americans [1–3]. Over 65,000 women were living with AIDS at the end of 1999 in the United States [5]. Through June of 2000, one in six AIDS cases were in women; most of them (78%) in minority groups [6]. During the early 1990s, approximately 6000 to 7000 HIV-1-infected women delivered children yearly in the United States [7]. Incidence has not been uniform; a rise has been noticed in the Southeast as rates have dropped in the Northeast. Without adequate preventive interventions, one can assume 900 to 2500 HIV-1-infected infants are born each year in the United States [8,9].

Improved understanding of the pathogenesis of HIV-1 transmission has led to effective intervention approaches that have reduced transmission of perinatal HIV-1. Consistent use of antiretroviral treatment, including zidovudine during pregnancy, labor, and early infancy, has led to large declines in transmission rates [10]. The use of multidrug therapy has further reduced transmission to less than 2% in the United States. Guidelines for use of such therapy in pregnancy have been published, and are updated on a regular basis [10–12].

The global picture is radically different. Most new HIV-1 infection cases occur in sub-Saharan Africa, Southeast Asia, India, China, and Latin America. Populations in these areas have had very limited access to treatment. Evaluation of feasible, efficacious, cost-effective therapeutic alternatives is currently in progress [13]. Recent completed trials of abbreviated cost-effective regimens have shown significant reductions in transmission in developing countries. These studies have greatly contributed to the expansion of our understanding of the variables affecting vertical HIV transmission and the relative contributions of routes of transmission including prenatal, intrapartum, and postpartum. We will re-examine some of the most salient issues based on recently published data regarding transmission of HIV-1 from mother to child.

Mother-Infant Transmission Rates
Perinatal transmission rates of HIV-1 vary in different regions of the world; in the US, they ranged from 15% to 30% before the use of antiretrovirals [14–16]. A transmission rate of 25% was confirmed by several cohorts [17•,18,19]. Transmission rates in European countries have been lower, approximately 15% [20,21], whereas rates of 19% to 24% have been reported in Thailand [22•,23] and rates of 40% to 50% reported in Africa [24,25]. These higher rates observed in some early studies in Africa might reflect the difficulties in making an early diagnosis of HIV in the face of a high mortality rate in both infected and uninfected infants. More recent studies reflect overall rates of approximately 35%, depending on the duration of breast feeding, which is nearly universal in the area [26].
Breast feeding seems to be the major factor causing regional variability [27]. Delivery methods and obstetrical practices also could alter transmission rates. Additionally, nutritional deficiencies, inadequate prenatal care, and high rates of other infections, particularly sexually transmitted diseases, may increase the incidence of premature deliveries, which are associated with higher transmission rates. Other methodologic differences could play a role, such as the background infant mortality rates, and the relative number of mothers with newly acquired or advanced disease [28,29].

Timing of Perinatal Transmission of HIV-1

Vertical transmission of HIV-1 occurs via three different routes including in utero, intrapartum, and through breast milk (Table 1). Understanding the timing and routes of transmission of HIV are critical factors for assessment of maternal and infant risk factors for both transmission and disease progression in the infant, since these may differ based on whether the child is a fetus, a premature or full-term infant, or young child at the time of infection. In addition, the intervention strategies will depend on the time of initiation and the effectiveness of the intervention. Perinatal HIV transmission is a multifactorial process, and many factors are probably interrelated. There have been repeated observations that pregnant women who have more clinically advanced disease (AIDS) and lower CD4 counts (which are in turn associated with higher levels of HIV plasma viremia and poorer levels of immune control), have a higher risk of transmission [18,30,31,32•,33,34]. It has been shown that timing of infant infection has a significant prognostic value for long-term outcome. Dickover et al. [35] has shown that both the time of infection in fetus/infants and the pattern and magnitude of HIV-1 virus load during early primary infection have a significant prognostic value for long-term outcome. Children who have HIV-1 detected at birth generally have a higher number of copies of viral RNA, clinical progression, and mortality. Rapid progressors showed a continued rise in plasma viremia that did not reach a maximum peak until 12 weeks of age and was associated with a profound drop in CD4+ cell count (Fig. 1) [35]. Infants who were infected intrapartum generally had a lower rate of early disease progression and a higher chance of becoming long-term nonprogressors. Other studies have also shown a correlation between viral load during primary infection and infant disease progression [36].

There has been greatly expanded knowledge over the past 5 years about the relative contributions of the different routes of transmission and factors affecting them. Technologic advances have led to more sensitive techniques for polymerase chain reaction (PCR), allowing a more precise estimate of the timing of transmission and detection of virus in the infant by DNA and RNA PCR-based assays. Early arguments questioned whether the techniques were sensitive enough to pick up infected infants at birth, or whether some of the infants identified in the first few weeks of life were truly infected before birth. Although we are continually refining our detection techniques, there have not been dramatic differences in the ability to detect HIV at birth using RNA versus DNA PCR-based analysis. Although we now generally accept that in utero transmission occurs, the relative timing of this transmission is unknown, but believed to be greatest in the third trimester.

### Table 1. Evidence for in utero, intrapartum, and breast feeding transmission of HIV-1

<table>
<thead>
<tr>
<th>In utero</th>
<th>Intrapartum</th>
<th>Breast feeding</th>
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<tbody>
<tr>
<td>Positive DNA PCR in first 24–48 hours of life</td>
<td>Negative DNA PCR at birth, with subsequent positive results</td>
<td>Isolation of HIV-1 from cell-free breast milk</td>
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<tr>
<td>Maternofetal transfusion (proposed) Identification of HIV-1 in fetal tissue from 10 weeks of gestation</td>
<td>Increased risk in first-born twin Isolation of HIV-1 in neonatal gastric aspirates Increased transmission risk with prolonged rupture of membranes Decreased transmission with elective cesarean section</td>
<td>HIV DNA detected in colostrum Increased risk of transmission when compared with exclusively bottle-fed infants Breast feeding was only exposure of HIV-1-infected children</td>
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<td>Placental membrane inflammation</td>
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</tbody>
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Figure 1. Correlation between peak HIV RNA in infants and progression of clinical disease. Rapid progressors were seen most frequently in in utero-infected infants, whereas slow progressors were invariably infected intrapartum. (Adapted from Dickover et al. [35].)