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Pediatric HIV-1 Infection: Advances and Remaining Challenges

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Abstract

HIV-1 infection is one of the leading causes of childhood morbidity and mortality globally and mother-to-child transmission (MTCT) is the major mode of infection. Over the past decade, natural history and interventional studies have improved our understanding of the pathogenesis of MTCT and pediatric HIV-1 infection. This has resulted in the development of effective preventive strategies to reduce new infections and therapeutic strategies to improve outcome following infection. However, successful implementation of these preventive and therapeutic strategies has been limited in resource-poor settings, where the majority of new pediatric infections occur. In addition, toxicities and antiretroviral resistance may limit the long-term utility of currently available strategies. Continued efforts to understand MTCT and pediatric HIV-1 pathogenesis and to refine preventive and therapeutic strategies are of high priority.

Key words

Pediatric AIDS. Mother-to-child HIV-1 transmission. Pediatric HIV-1 pathogenesis.

Introduction

Mother-to-child transmission (MTCT) accounts for the majority of pediatric HIV-1 infections. Over the past decade, improved understanding of the pathogenesis of pediatric HIV-1 infection and the availability of potent antiretroviral agents have led to successful preventive or therapeutic strategies for pediatric HIV-1 infection. Antiretroviral treatment of pregnant women and their infants has reduced the rate of MTCT in many developed countries[1]. Following an increase in the use of combination antiretroviral therapy regimens in HIV-1 infected children, rapid and profound decreases in morbidity and in mortality have been observed[2].

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Despite these successes, HIV-1 remains a major cause of morbidity and mortality in children worldwide (Table 1[3]). In 2001, an estimated 2.7 million children were living with HIV-1/AIDS and approximately 800,000 children under the age of 15 acquired HIV-1 infections. This represents almost 2,200 new infections per day. A steady increase in MTCT has been documented in areas with high incidence and seroprevalence rates among women of childbearing age. Over 90% of new pediatric infections occur in Sub-Saharan Africa, where HIV-1 seroprevalence rates exceeding 30% have been documented in some antenatal clinics. While children account for 7% of individuals living with HIV-1 infection and 16% of all new HIV-1 infections annually, children account for 20% of all HIV-related deaths. This is likely due to the more rapid disease progression observed in infants and children than in adults[4,6]. The increase in pediatric HIV-1 infections has reversed advances in child mortality achieved over the latter decades of the twentieth century through immunization and public health programs. In Southern Africa and some areas of the

Table 1. *Global epidemiology of pediatric HIV-1 infection: 2001*[3]

No. of children living with HIV/AIDS	2.7 million
No. of children born to HIV positive women	2.2 million
No. of children newly infected	800,000
AIDS deaths	580,000
Cumulative no. of children orphaned by AIDS	10.4 million

Caribbean, HIV-1/AIDS has become the leading cause of death in children under the age of 5 years.

This paper will review advances in our understanding of MTCT and pediatric HIV pathogenesis along with their implications for preventing or treating pediatric HIV-1 infection. Critical areas needing further research are also discussed.

Timing of and risk factors for MTCT

In the absence of antiretroviral therapy, approximately 25-30% of HIV-1 infected women transmit the virus to their infants. MTCT can occur during gestation (*in utero*), during delivery (*intra partum*), or *post partum* through breastfeeding. In non-breastfed populations, 25-30% of infected infants have detectable provirus in their peripheral blood lymphocytes at birth, suggesting that they were infected *in utero* (Fig. 1[7]). In the remaining 70-75%, HIV-1 RNA or provirus is not detected at birth, but becomes detectable by a week or two of age, suggesting the *intra partum* transmission of HIV-1. In breastfed populations, approximately 15% of infections are thought to occur *in utero*, 65-70% during delivery, and 15-20% are thought to occur *post partum* through breastfeeding.

Maternal plasma HIV-1 load is one of the strongest predictors of MTCT[8-10]. MTCT can occur at any maternal viral load, but the risk of transmission increases with increasing maternal plasma HIV-1 load. MTCT is rare (<1%) when maternal plasma HIV-1 RNA is <1000 copies/ml. Several studies have also documented increased rates of MTCT with decreased maternal CD4 count.

The precise mechanisms responsible for *in utero* and *intra partum* MTCT remain uncertain. The placenta appears to be a fairly effective barrier to infection, but conditions that compromise the placental unit (e.g., vasoactive drug use or chorioamniontis), and presumably allow the admixture of maternal and fetal blood, have been associated with an increased risk of MTCT[11]. Situations that increase the length of time that the infant is exposed to maternal cervico-vaginal secretions during delivery have also been associated with an increased risk of MTCT, suggesting that exposure to maternal blood and cervico-vaginal fluids, likely through a mucosal (ophthalmic or gastrointestinal) portal of entry, may account for MTCT during delivery. An increased risk of MTCT has been observed in first-born twins[12] and following prolonged rupture of membranes (WITS). In addition, cervico-vaginal ulcers or high maternal cervical or vaginal HIV-1 proviral copy numbers have been significantly associated with MTCT, independent of maternal plasma HIV-1 load[9].

Breast milk transmission can occur at any time, but available data suggest that most breast milk transmission (up to 75%) occurs within the first months of life[13,14]. In a meta-analysis of multiple cohort studies, the risk of breast milk transmission

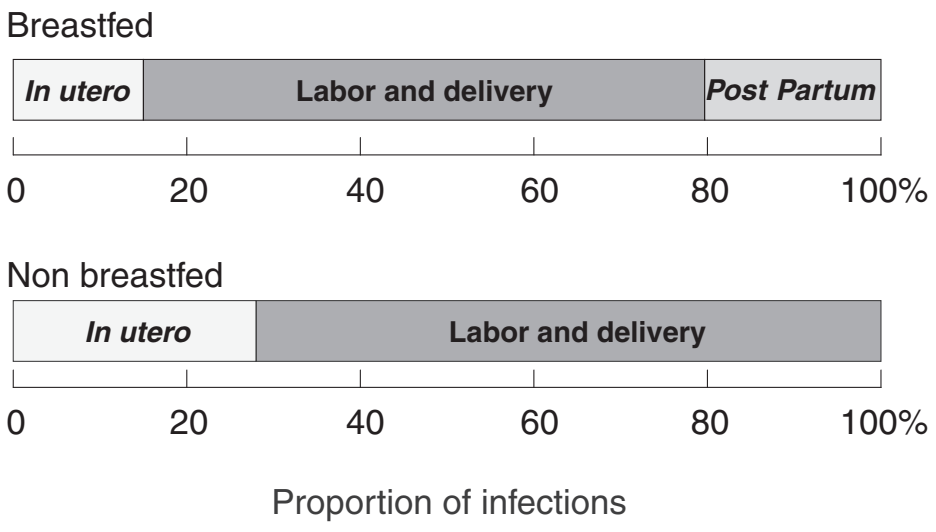

Figure 1. *Vertical HIV-1 transmission: timing.*

was approximately 3.2% per year of breastfeeding after 4 months of age[15]. High breast milk viral loads and maternal mastitis or nipple lesions have been associated with an increased risk of breast milk transmission.

While SIV transmission has been documented following the application of cell-free virus to macaque tonsillar tissues[16], infants have sparse tonsillar tissue. The small intestine is the more likely portal of entry for intrapartum or breast milk transmission. Decreased gastric acidity and/or a relative increase in the permeability of the gastrointestinal tract may increase the susceptibility of young infants to the acquisition of HIV-1 infection.

Prevention strategies for MTCT

In 1994, an empiric trial (PACTG 076) demonstrated that the administration of zidovudine (ZDV) to pregnant women and their infants markedly decreased the risk of MTCT[17]. Further analyses of data from that[18] and similar trials revealed that ZDV decreased transmission across all viral load and CD4 strata; the magnitude of reduction in plasma HIV-1 load did not correlate with the degree of protection. Interestingly, the administration of ZDV to the infant alone within 48 h of delivery resulted in MTCT rates comparable to the original regimen[19]. These latter data suggested that the majority of infections in this non-breastfed population were occurring at delivery and that prophylaxis of the infant was important.

Subsequent antiretroviral intervention trials focused on evaluating the efficacy of short-course therapies given in late pregnancy or the peri-partum period. The efficacy of ZDV monotherapy and ZDV/3TC have been demonstrated in this setting[20,21]. Particularly notable were the results of a study from Uganda (HIVNET 012[22]) that demonstrated that a simple and relatively inexpensive (ca US $5) regimen of a single dose of nevirapine to the mother at birth, followed by a single dose of nevirapine to the infant at 48-72 h, resulted in a 47% reduction in transmission compared with ZDV. In the SAINT trial conducted in South Africa, a peripartum nevirapine regimen was comparable in efficacy to peri-partum ZDV/3TC[23]. Of interest, is that the SAINT trial also demonstrated that maternal receipt of nevirapine dosing less than 2 h prior to delivery was associated with a higher risk of early *post partum* (0-4 weeks) MTCT. Again, these data suggest that the achievement of sufficient inhibitory concentrations of antiretroviral agents in the infant at birth (i.e. infant prophylaxis) is a key component for the success of perinatal antiretroviral regimens. Unfortunately, while successes in reducing MTCT have been demonstrated in these clinical trials, these simple and less expensive regimens have been difficult to implement widely in resource-poor settings.

While the mono and dual antiretroviral prevention strategies have been remarkably successful to date, there is some concern regarding their long-term feasibility and success. Studies have documented the selection of viruses with antiretroviral resistance mutations following the addition of one or two agents in the setting of incomplete control of viral replication[24,25]. The longevity and implications of these resistance mutations are unclear, but are under evaluation[25]. In addition, a sizeable number of children acquire infection through breastfeeding beyond the perinatal period.

Several studies have demonstrated a decreased risk of MTCT with formula feeding (e.g.[14]). However, malnutrition and gastrointestinal infections are common sequelae of formula feeding in settings with limited resources. Of interest, is that two studies have reported an increased risk of MTCT with mixed (formula plus breastfeeding) feedings compared with exclusive formula feeding or breastfeeding[26,27]. It has been proposed that mixed feeding may provide continued exposure to HIV-1 in the context of compromised integrity of the gastrointestinal tract mucosa due to intestinal infections introduced by contaminated formula. Inflammation due to infection could also have increased the numbers or activation state of dendritic cells, macrophages, and T-cells within the gastrointestinal tract, increasing the substrate for early replication or dissemination of the virus. Also of concern is a report of increased mortality associated with breastfeeding among HIV-1 positive women[28]. Further work is needed to clarify the impact of feeding practices on the risk of MTCT and overall maternal-child health.

Again, while perinatal antiretroviral therapies can markedly reduce vertical HIV-1 transmission, their implementation in resource-poor settings has been difficult and they do not reliably protect against breast milk transmission beyond the newborn period. An active/passive vaccine regimen, begun at birth, could protect against MTCT and provide the basis for lifetime immunity to HIV-1.

Early viremia

As outlined above, HIV-1 nucleic acids can be detected in peripheral blood specimens of infected infants at birth (*in utero* infection) or within a couple of weeks of acquisition of infection (*intra partum* and breast milk transmission). Similar to other modes of HIV-1 transmission, viruses obtained in early vertical infection most commonly use the CCR5 co-receptor, although occasional use of other receptors has been reported[29]. While some investigators have reported limited diversity of HIV-1 envelope third variable region gene sequences of viruses obtained in early vertical HIV-1 infection (suggesting the transmission or post-transmission selection of single viral strains[30]), others have reported more variability in other envelope regions[31,32]. Plasma HIV-1 RNA levels of 10^5 to 10^7 copies per milliliter have been documented in vertically-infected infants over the first 1-2 months of life[33]. In infected infants, plasma HIV-1 RNA levels decrease gradually over the first 1-2 years of life, reaching a median of 34,000 copies/ml by the age of 2 years[33]. Continued declines in plasma HIV-1 RNA levels (mean 0.2 to -0.3 log decline per year) have been documented

through 6 years of age. The persistently high plasma viral load over the first 2 years of life contrasts with the 100- to 1000-fold reduction in plasma HIV-1 RNA levels reported in adults within 1-2 months following presentation with symptoms and the subsequent steady state plasma HIV-1 RNA levels documented within 6-12 months of primary infection.

Several factors likely contribute to the prolonged elevation of plasma HIV-1 RNA levels over the first 2 years of life. Persistently high plasma HIV-1 RNA levels in infancy and early childhood may be due to a larger pool of substrate cells. Relative lymphocytosis and a large CD4 T-cell pool size are the norm in early life due to active thymopoiesis. Of interest, however, is that most circulating CD4 T-cells in early childhood are of the *naïve* phenotype[34]; *naïve* CD4 T-cells reportedly have lower cell surface levels of CCR5 and are less permissive for HIV-1 replication than memory CD4 T-cells. Further work is necessary to better delineate cellular substrates for HIV-1 replication in early vertical HIV-1 infection.

Infection at a time of reduced ability to generate effective virus-specific immune responses might also account for the persistently high levels of viral replication in infancy and early childhood. Lower, direct antibody-dependent, cell-medicated cytotolysis (ADCC) of HIV-1 infected cells by neonatal natural killer cells has been documented[35]. Following the decline of passively-acquired maternal ADCC antibodies, the active generation of HIV-1 specific ADCC antibodies by infected infants is delayed[36]. HIV-1 specific CD8+ T-cell responses in vertically-infected infants are less vigorous and appear later in primary infection than in adults[37-39]. These deficiencies in HIV-1 specific cellular immunity may preclude the effective containment of viral replication in early infection and thus contribute to the relatively rapid disease progression often observed in children.

Recently, Scott, et al.[39] have reported the detection of cytomegalovirus (CMV)-specific CD8+ T-cells in young HIV-1 and CMV-co-infected infants in whom HIV-1 specific CD8+ T-cells could not be detected. The detection of CMV-specific CD8+ T-cells in these infants suggests that young infants are capable of generating virus-specific CD8+ T-cell responses and that the paucity of detectable HIV-1-specific CD8+ T-cell responses represents a selective defect in the generation or maintenance of HIV-1-specific CD8+ T-cells. Possible mechanisms that could account for this include the acquisition of HIV-1 infection in the presence of high titers of passively-acquired maternal antibodies or early depletion of HIV-1-specific CD4 T-cell help for the generation and maintenance of HIV-1 specific CD8+ T-cell responses.

Goulder, et al.[40] have proposed HLA haplotype sharing between mother and infant as another potential explanation for the decreased detection of HIV-1 specific CD8+ T-cells in the peripheral blood of young infants. CD8+ T-cell responses are restricted by HLA Class I molecules, of which the infant shares at least 3 with his or her mother. Maternal-infant HLA Class I concordance increases the risk of MTCT[41] and HIV-1 infected infants may share more than three HLA Class I alleles with their mothers. The significance of this is that HIV-1 "escape" variants that are poorly recognized by maternal CD8+ T-cells might predominate in the replicating virus pool and be more commonly transmitted to her infant. The infant would be less able to mount effective CD8+ T-cell responses restricted by shared HLA alleles and thus less able to control viral replication. Further evaluation of this hypothesis is in progress.

Early combination therapy successfully controls viral replication and preserves immune function

In the mid-1990's, potent antiretroviral agents in forms suitable for administration to young infants became available and several studies evaluated the virologic and immunologic consequences of early therapy for vertical HIV-1 infection. Long-term control of plasma viremia and preservation of immune function has been observed in the majority of infants who began combination antiretroviral therapy prior to 3 months of age[42]. Of interest, however, is that while total CD4 counts and general immune function appeared intact in children who received early therapy, persistent HIV-1 specific immune responses (antibodies, CD4+ lymphoproliferative responses, and CD8+ T-cell responses) were not detected in the majority of infants. The lack of persistent HIV-1 specific immune responses contrasted with the development of antibody and lymphoproliferative responses to routine infant vaccines (e.g. tetanus) and CD8+ T-cell responses to other viral infections, suggesting that the defect was HIV-1 specific. The lack of persistent HIV-1 specific immune responses in infants contrasts with the persistent HIV-1 specific immune responses reported in adults who receive combination antiviral therapy within 3-4 months of acquisition of infection. Future trials are planned to provide an HIV-1 specific vaccine following early combination therapy, in an attempt to boost HIV-1 specific immune responses.

Recently, there has been a great deal of discussion over when to begin antiretroviral therapy in infected children (Reviewed in[43,44]). In situations where antiretroviral therapies are available and adherence is likely, the initiation of antiretroviral therapy within the first year of life has been recommended[43]. There are several compelling reasons to begin antiretroviral therapy within the first few months of life, whenever possible. First, currently available molecular techniques allow the majority of infected children to be identified within weeks of infection. Second, there are no reliable indicators that distinguish rapid progressors from slow progressors within the first year of life. Finally, several different combination antiretroviral regimens have been shown to be safe, effective, and well tolerated over years of administration in infants and children. Given the promise of early therapy for vertically-infected children, efforts to develop and make available simple and relatively inexpensive combination

therapy regimens for children in developing countries is of high priority.

Treatment of established pediatric HIV-1 infection and immune reconstitution

As in adults, several combination regimens have proven effective in suppressing viral replication in older children with established disease (Reviewed in[43,45]). Early suppressive therapy was not available to many children currently living with HIV-1 infection. Unfortunately, response rates to newer regimens may decrease with prior antiretroviral exposure[46] and may be compromised by antiretroviral resistance. Evidence suggestive of ongoing viral replication has been documented even in children with plasma HIV-1 RNA levels under the limits of conventional assay systems[47] but the long-term implications of this are unclear. Of interest, however, is that the evolution of antiretroviral resistance mutations has not been detected over time in children with plasma HIV-1 RNA < 50 copies/ml and ongoing viral replication[48]. Better understanding of the extent and the location of ongoing viral replication are needed in order to improve therapeutic strategies for pediatric HIV-1 infection.

The potential for CD4+ T-cell reconstitution (and *naïve* CD4 T-cells, in particular) appears to be greater in children than in adults[49,50]. This is thought to be due to greater thymic activity in early life[51]. At present, however, the functional ramifications of the increase in CD4 T-cell numbers following therapy are poorly understood. Research to better understand this is currently underway.

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