HIV-1 infection is a significant global source of childhood morbidity and mortality, and mother-to-child transmission (MTCT) is the major mode of infection. Research over the past two decades has improved our understanding of the pathogenesis of MTCT and pediatric HIV-1 infection, lending to the development of effective preventive and therapeutic strategies. However, successful implementation of these strategies has been limited in resource-constrained settings, where the majority of new pediatric HIV infections now occur. Continued efforts are necessary to better understand MTCT and to refine preventive and therapeutic strategies to allow their successful implementation in the most needed places.

Introduction
Mother-to-child transmission (MTCT) accounts for the majority of pediatric HIV-1 infections. According to the World Health Organization, half the approximately 4 million new HIV infections that occur annually around the world occur in women, most of whom are of childbearing age (www.who.int/hiv/en/). Approximately 3 million infants are born to HIV-infected women per year and are at risk for acquiring HIV infection. Each year, 530,000 infants are infected through MTCT (1500 new infections per day). The majority (95%) of new pediatric infections occur in sub-Saharan Africa or South/South East Asia, settings in which maternal and infant HIV infection are associated with particularly high morbidity and mortality. Several studies have demonstrated increased morbidity and mortality among infants born to HIV-positive women in sub-Saharan Africa [1]; high infant morbidity and mortality are associated with maternal CD4 depletion, high maternal viral loads, advanced disease, or death. Excess mortality has also been documented in HIV-infected infants compared with HIV-uninfected infants born to HIV-positive mothers [2,3]. In a recent meta-analysis, mortality among HIV-infected infants was 35% compared with 4.9% in HIV-negative infants at 1 year and 52% (vs 7.6% in HIV-negative infants) at 2 years [4]. Thus, HIV contributes significantly to overall child mortality, particularly in areas of high seroprevalence. HIV accounts for an estimated 10% of all child mortality in Africa, but it contributes to almost 50% of all child mortality in Southern Africa [5].

Over the past two decades, natural history and/or interventional studies have improved our understanding of MTCT and have guided the development of successful preventive or therapeutic strategies for pediatric HIV-1 infection. In high- or medium-resource settings, these interventions have markedly reduced MTCT and improved the outcome of HIV infection in children. For many reasons, however, the successful translation of these strategies has been much more difficult to achieve in limited-resource settings. This paper reviews recent advances and the remaining global challenges in preventing MTCT or treating pediatric HIV infection.

Timing and Pathogenesis of MTCT
In the absence of antiretroviral therapy (ART), 15% to 45% of women will transmit HIV to their infants. MTCT can occur during gestation (in utero), during delivery (intrapartum), or post-partum through breast milk. In nonbreastfed cohorts, 25% to 30% of infected infants have detectable HIV nucleic acids in their peripheral blood at birth, suggesting in utero infection [6]. In the remaining 70% to 75% of infected infants, HIV nucleic acids are not detected at birth, but are detected by 1 week of age, suggesting intrapartum HIV transmission. In breastfed populations, an estimated 15% of MTCT occurs in utero, 40% to 50% occurs during delivery, and 30% to 40% occurs through breastfeeding.

Maternal plasma HIV load is one of the strongest predictors of MTCT [7]. Although MTCT can occur at any maternal viral load, 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 [8], particularly when mothers are receiving ART [9]. Advanced disease and decreased maternal CD4 count are also associated with increased risk of MTCT.

The precise mechanism and timing of in utero MTCT remain unknown. For the most part, the placenta seems to be an effective barrier to infection; conditions that compromise placental integrity (e.g., chorioamnionitis) have been associated with an increased risk of MTCT [10]. Several lines of evidence suggest that a high proportion of in utero infections occur over the last 1 to 2 months of pregnancy [11]. ART administered during the last trimester of pregnancy can reduce in utero MTCT [12].

Situations that increase the intensity or duration of the infant’s exposure to maternal cervicovaginal secretions during delivery are associated with an increased risk of intrapartum MTCT, presumably through a mucosal (ophthalmic, skin, or gastrointestinal) portal of entry. For example, an increased risk of MTCT has been observed in first-born twins [13] and following prolonged rupture of membranes. In addition, cervicovaginal 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. Elective cesarean section prior to labor onset and rupture of membranes protects against MTCT [14]. In a recent study, elective cesarean section effectively reduced MTCT even in women with undetectable blood HIV load [15]. However, increased morbidity has been associated with cesarean section in HIV-positive women in some settings, and the potential risks of the procedure must be balanced with its potential benefits. In the United States, current guidelines recommend elective cesarean section only in cases in which maternal blood viral load exceeds 1000 copies/mL, particularly when mothers are receiving ART [12].

Data from several studies have suggested that breast milk transmission most commonly occurs within the first months of life [17,18]. However, a recent meta-analysis indicated a constant risk of transmission (8–9 transmissions/100 child-years of breastfeeding) between 1 month and 18 months old [19]. The probability of transmission has been estimated at 0.00064/L of ingested breast milk or 0.00028/day of breastfeeding; the latter is roughly equivalent to the probability of HIV transmission per unprotected sex act(s) between adults [20]. Again, low CD4+ T-cell counts and high plasma HIV RNA levels are associated with a high risk of breast milk transmission [19,21]. High breast milk viral loads, maternal mastitis, and nipple lesions are also associated with increased risk of breast milk transmission [22].

The Challenge of Reducing MTCT in Low-resource Settings

In 1994, a randomized, placebo-controlled trial (Pediatric AIDS Clinical Trials Group Protocol 076 [23]) demonstrated that zidovudine (ZDV) therapy of women throughout pregnancy and delivery along with postpartum ZDV treatment of their infants resulted in a transmission rate of 8.3% compared with a transmission rate of 25.5% in the placebo group (67% reduction in MTCT). Data from that and subsequent trials revealed that ZDV decreased transmission across all viral loads and CD4+ T-cell count strata; further, the magnitude of reduction in plasma HIV-1 load did not correlate with the degree of protection. Finally, the administration of ZDV to the infant alone within 24 to 48 hours of delivery resulted in MTCT rates comparable to the original regimen [24], suggesting that prophylaxis of the infant played an important role in protecting infants from infection. Over the years, the use of highly active ART to optimize maternal health and the avoidance of breastfeeding have further reduced overall MTCT rates in high- and middle-resource countries to under 2% [25].

Many of the antiretroviral (ARV) regimens and practices that successfully reduced MTCT in high- or middle-resource countries were initially considered impractical for implementation in limited-resource settings. With the realization that many cases of MTCT occur at delivery, efforts in the past decade have focused on developing perinatal ARV regimens to prevent intrapartum MTCT. Several perinatal regimens have been demonstrated as effective in reducing MTCT (Table 1) [26]. Of these, the simplest and least expensive is the administration of a single dose of the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (NVP) to a woman during labor, followed by a single dose of NVP (SD-NVP) to the baby at 48 to 72 hours [27]. However, even SD-NVP has been difficult to implement widely; 8 years following the demonstration of the efficacy of SD-NVP, it is estimated that fewer than 10% of HIV-positive women in limited-resource settings around the world have actually received prophylactic ARV despite the fact that the manufacturer (Boehringer-Ingelheim, Ingelheim, Germany) has provided NVP free of charge to MTCT prevention programs [28]. Although the number of women receiving ARV to prevent MTCT is steadily increasing, delivery of ARV to prevent MTCT has lagged behind efforts to more generally deliver ART [28]. Key impediments to the successful implementation of regimens to prevent MTCT appear to be lack of access to routine prenatal care and the infrequency of infant delivery in healthcare facilities [29]. Intensified efforts to integrate HIV counseling, testing, and provision of ART to HIV-positive mother–infant pairs into prenatal and peripartum care have met with some success.

Mutations in reverse transcriptase associated with high-level resistance to NVP and other NNRTIs have been detected in 20% to 70% of HIV-positive women and 30% to 50% of infected infants who have received SD-NVP [26], raising concerns that resistance might eventually limit the utility of this and other NNRTIs in preventing MTCT. In addition, because NNRTIs are commonly used as first-line agents for primary therapy...