Prevention of Mother-to-Child Transmission of HIV-1 through Breast-Feeding: Past, Present, and Future

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(See the articles by The Breastfeeding and HIV International Transmission Study Group [on pages 2154–66 and Ferrantelli et al. [on pages 2167–73].)

In this issue of The Journal of Infectious Diseases, the Breastfeeding and HIV International Transmission Study (BHITS) group presents results from an individual patient data meta-analysis of 4085 HIV-1-exposed, breast-fed children from 9 clinical trials conducted in high-prevalence, resource-limited settings [1]. The risk of late postnatal transmission of HIV-1 (after 4 weeks of age) was 8.9 transmissions/100 child-years of breast-feeding; late postnatal transmission was significantly associated with reduced maternal CD4 cell count and male sex of the child. The transmission rate was generally constant throughout the breast-feeding period, between 1 and 18 months of age. A second article, by Ferrantelli et al. [2], in this same issue of the Journal demonstrates that a triple combination of monoclonal antibodies (MAbs) with potent anti-HIV neutralizing activity protected 4 of 4 neonatal macaques against infection after oral exposure to the virulent virus simian-human immunodeficiency virus (SHIV) 89.6P. This experiment, in which antibodies were administered twice, at 1 h and 8 days after virus exposure, extends and confirms previous pre- and postexposure passive immunization experiments conducted in newborn macaques [3–6].

Taken together, these interesting findings shed light on the risk of late postnatal transmission of HIV-1 in breast-fed children and point to novel biomedical interventions to potentially prevent such transmission in HIV-exposed children.

HIV-1 can be transmitted from an infected mother to her child in utero, during delivery, and postnatally through breast-feeding [7–9]. Prolonged breast-feeding is associated with a near doubling of the risk of mother-to-child transmission of HIV-1 [7, 10–13]. Reduction of transmission of HIV during lactation is one of the most pressing global health dilemmas confronting health policy makers, as well as HIV-infected women, in many areas of the world [14–16]. Breast-feeding ensures that the child receives the best possible nutrition during the important first months of life [17] and protects against infant mortality due to diarrheal and lower respiratory infections [18–20]. This is particularly true in areas where the water supply is unsafe and infant mortality remains exceedingly high. Human milk is also an important natural resource; on the family level, the cost of supplying the extra nutrients for a lactating woman (500 calories and 20 g of protein/day) is universally less expensive than using animal milk or formula [21]. Breast-feeding also helps to delay a return to fertility. In resource-limited settings, the contraceptive value of breast-feeding is perhaps the single most important reason for birth spacing, which is associated with increased child survival [17, 22]. The weight of evidence, thus, strongly favors breast-feeding as being advantageous to infant health and survival in general, but, for children born to HIV-infected women, breast-feeding also carries the risk of transmission of HIV.

In resource-rich settings where replacement feeding is safe, affordable, and culturally accepted, complete avoidance of breast-feeding among HIV-infected women [23] has been one of the pillars of the efforts to prevent mother-to-child transmission of HIV for many years, along with antiretroviral (ARV) drug prophylaxis and, more recently, scheduled cesarean section. In resource-limited settings, the majority of breast-fed children of HIV-infected mothers remain uninfected, even after ≥2 years of breast-feeding, with daily exposure to high amounts of cell-associated and cell-free HIV-1 [13, 24]. The
meta-analysis by the BHITS group [1] shows that a longer duration of breast-feeding is associated with a higher cumulative risk of late postnatal transmission of HIV-1 and that the added risk remains generally constant over time. The very large size of the pooled data set enhanced statistical power. Together with the application of uniform definitions across all trials, this allowed for more-reliable and -precise estimates of the risk and timing of postnatal transmission of HIV-1. Nevertheless, categorization of the exact timing of transmission of HIV-1 was not possible for 454 (46%) of the HIV-infected children in the pooled data set. Thus, some uncertainty about the accuracy of the estimate of late postnatal transmission does remain, despite high statistical precision, as evidenced by the narrow 95% confidence limits. Nevertheless, the meta-analysis provides the best information we have, thus far, on the probability of transmission of HIV-1 through breast-feeding after 4 weeks of age. The results are consistent with those of the only randomized clinical trial of breast-feeding versus formula feeding conducted in Nairobi, Kenya, in which 44% of mother-to-child transmission of HIV-1 was attributable to breast-feeding [7].

A few questions remain, however. Previous studies, including the Nairobi clinical trial, have suggested that the first month of life may be a particularly high-risk time for transmission of HIV-1 through breast milk [7, 25]. Unfortunately, this question could not be addressed by the BHITS meta-analysis, since early postnatal transmission (before 4 weeks of age) could not be teased out from intrapartum transmission of HIV-1. Furthermore, the duration of breast-feeding in the mostly urban clinical trial populations included in the meta-analysis (median, 10 months; interquartile range, 5–17 months) was generally shorter than that in most areas of sub-Saharan Africa. Thus, as the authors point out, the risk of mother-to-child transmission of HIV-1 through breast-feeding estimated in the meta-analysis is still an underestimate of the true risk. The potential role of other risk factors on postnatal transmission of HIV-1—such as RNA virus load in milk and plasma [26], mastitis and breast milk stasis, thrush, other infant coinfections, type of infant feeding (exclusive breast-feeding vs. mixed feeding) [27–29], and maternal HIV-1 dual or superinfection [30–33] during lactation—were not able to be evaluated in the meta-analysis.

The study by Ferrantelli et al. [2] demonstrates that intramuscular injection is a feasible route of antibody administration for postexposure prophylaxis against HIV in neonatal macaques. Comparison of the results of this and previous experiments [2–5] suggests that the right combination and sufficient amount of anti-HIV MAbs is the key to success, as relatively minor changes in the combination or their dosage lowered the prophylactic efficacy. These results are very promising and suggest a similar passive-immunization approach to reduce perinatal and postnatal transmission of HIV-1 in human children, and clinical trials in humans are in development. A few caveats should be noted, however. These animal experiments used SHIV89.6P, a virulent virus that is very sensitive to neutralizing antibodies and of which the disease pathogenesis (especially the acute, severe CD4+ T cell depletion) is unlike that of most HIV-1 strains [34, 35]. Thus, it remains to be determined in clinical trials whether this will translate into a similarly high efficacy against transmission of HIV-1 to human children. Other drawbacks of the passive-immunization approach include the need for parenteral administration, necessity to give antibodies shortly after birth, and relatively high cost. Although antibodies have a substantially longer half-life than ARV drugs (allowing less-frequent administration), breast-feeding usually continues for many months, and, thus, regular injections of antibodies (e.g., every 2–4 weeks) would likely be needed to sustain protective antibody levels throughout the whole period of breast-feeding. This seems impractical in most resource-limited settings. Accordingly, a more attractive theoretical strategy (similar to the perinatal hepatitis B model) would be the combination of active/passive immunoprophylaxis regimens early after birth and potentially overlapping with neonatal chemoprophylaxis; in this situation, passively administered antibodies might effectively cover the early breast-feeding period while active immunity is still being developed [36–39]. It will remain to be seen whether this approach could be of additive benefit to maternal postpartum treatment with combination ARV drugs or prolonged ARV prophylaxis to children during breast-feeding.

Short-course peripartum ARV drugs, including nucleoside reverse-transcriptase inhibitors (NRTIs), such as zidovudine (ZDV) and lamivudine (3TC), and nonnucleoside reverse-transcriptase inhibitors (NNRTIs), such as nevirapine (NVP), have been shown to be effective in reducing the transmission of HIV-1 from mother to child in resource-limited settings [40–48]. These ARV regimens reduce the risk of perinatal transmission by decreasing viral replication during pregnancy and the peripartum period, as well as by neonatal prophylaxis during and immediately after exposure to HIV-1. In sub-Saharan Africa, most research, thus far, has focused on short regimens of peripartum ARV drugs in settings of high prevalence of HIV-1, where breast-feeding is usually the norm. The results of HIVNET 012, SAINT, and several other large randomized clinical trials confirm that nearly 50% efficacy in reducing mother-to-child transmission can be achieved with several inexpensive and relatively simple peripartum ARV prophylaxis regimens [49]. Moreover, no serious ARV-related adverse events were observed among >1300 women and children enrolled in the SAINT trial and exposed to single-dose NVP or short-course ZDV/3TC [48]. Recently, transmission rates of 2%–3% (in the absence of breast-feeding) and 4%–5% (in the presence of breast-feeding), at 6–8 weeks of age, have been reported with 2-drug or 3-drug
combination regimens that include third-trimester, intrapartum, and very limited postpartum ARV therapy [46, 50, 51]. For the short-course ZDV and single-dose NVP regimens, long-term relative efficacy (until 18–24 months of age) has been confirmed in breast-feeding populations [47, 52]. It should be noted, however, that long-term relative efficacy is generally reduced in breast-feeding settings, because of postnatal acquisition of pediatric HIV infection [45, 47, 52]. Studies of ARV prophylactic regimens administered to mothers and/or their children during the breast-feeding period are currently underway.

The results of the BHITS meta-analysis in this issue of the Journal indicate that, since the risk of late postnatal transmission of HIV is strongly associated with lower CD4 cell count (adjusted hazard ratio, 8.0 of HIV is strongly associated with lower CD4 cell count (adjusted hazard ratio, 8.0 for maternal CD4 cell count <200 vs. ≥500 cells/mm³), the use of highly active antiretroviral therapy (HAART) should be actively pursued among severely immunosuppressed women. Providing HAART to HIV-infected pregnant women during the last weeks of their pregnancy and to breast-feeding mothers during the crucial first 4–6 months of lactation with early weaning, with the women continuing HAART for their own health if they meet World Health Organization criteria for ongoing ARV treatment, would provide a crucial link between prevention and care [53, 54]. Most likely, this would greatly accelerate uptake of prevention programs of mother-to-child transmission of HIV, in resource-limited settings. Through various initiatives, many organizations are working to greatly expand access to ARV drugs in resource-limited settings [54–56].

Transient resistance to NVP is seen 6–8 weeks postpartum in ~1 in 5 women given single-dose NVP at the start of labor [57–59]. Data on whether exposure to single-dose NVP during a prior pregnancy could adversely affect the efficacy of single-dose NVP for prevention of perinatal HIV in a subsequent pregnancy are not currently available. It is also not known whether transient detection of maternal NVP-resistant virus could lead to more-rapid treatment failure and thus limit later HAART options using NNRTI-based regimens for the mother. Preliminary data from Thailand suggest that mothers exposed to single-dose NVP may be less likely to experience maximal virological success of NNRTI-based therapy initiated within 6 months of delivery and that initiation of NNRTI-based therapy after 6 months may be associated with an improved virological response [60]. Definitive studies on these issues are urgently needed to inform and guide public health policy decisions, and these studies are underway [57, 61]. New NNRTIs that have the promise of being active against HIV-1 even when resistance mutations are present are currently under development, and initial clinical tests with one such agent (TMC 125) suggested potent antiviral efficacy even in the presence of mutations conferring phenotypic resistance to efavirenz and NVP [62]. Tenofovir, a potent nucleotide analogue reverse-transcriptase inhibitor, is another investigational drug for prevention of mother-to-child transmission of HIV-1 and could potentially be useful in such situations [63, 64]. Two perinatal protocols looking at the safety of perinatal use are currently in development.

Future studies of postnatal transmission of HIV-1 will enable us to gain information on the risk of transmission through breast-feeding during the first 4 weeks after birth and plan efficacious interventions to reduce early postnatal transmission. Use of neutralizing antibodies [2], in addition to a short peripartum/postnatal ARV prophylactic regimen [65], may be an attractive approach. Planned research on active immunization of infants to prevent postnatal transmission of HIV-1 through breast milk also holds promise, and studies of infants to evaluate the safety and immunogenicity of HIV-1 vaccines are underway [26, 36]. Although still theoretical and not yet tested in human infants, a combined approach of active and passive immune strategies that would integrate humoral and cellular immunity, to prevent mother-to-child transmission of HIV-1 through breast-feeding during the first 2 years of life, would be appealing [36, 66]. If successful, such an approach might allow for all the benefits that breast-feeding provides for child health, development, and promotion of birth spacing and avoid toxicities associated with chronic exposure to ARV drugs for women and their children. In theory, it might also provide a primary immunization that could be boosted during early adolescence to protect against sexual transmission of HIV.

References

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