Transmission of Human Immunodeficiency Virus Type 1 through Breast-Feeding: How Can It Be Prevented?

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One-third to two-thirds of maternal transmission of human immunodeficiency virus type 1 (HIV-1) infection to breast-fed infants can be attributed to ingestion of breast milk. The presence of HIV-1 as cell-free and as cell-associated virus in milk has been documented. Several substances in breast milk may be protective against transmission, including maternal anti-HIV antibodies, vitamin A, lactoferrin, and secretory leukocyte protease inhibitor. The portal of virus entry in the infant's gastrointestinal tract is unknown but may involve breaches in mucosal surfaces, transport across M cells, or direct infection of other epithelial cells, such as enterocytes. Timing of transmission of HIV-1 during lactation should be further clarified. An early rebound of plasma viremia after withdrawal of antiretrovirals was recently detected. This rebound may reduce the benefit of antiretroviral prophylaxis when women breast-feed their infants. Interventions should be viewed from the public health perspective of risks of infant morbidity and mortality associated with breast-feeding versus risks from formula-feeding.

Pediatric human immunodeficiency virus type 1 (HIV-1) infection is an issue of dramatic magnitude in developing countries where, in some places, it has already erased the decrease in child mortality rates that was achieved over several decades of public health work. More than 90% of the HIV-infected children worldwide live in sub-Saharan Africa. It is estimated that there are three times more children who acquire HIV-1 infection in the city of Bobo-Dioulasso, Burkina Faso (400,000 inhabitants), than in the whole country of France (58 million inhabitants).

Maternal HIV-1 infection is the primary source of pediatric infections; thus, the burden of pediatric HIV-1 infection is reflecting the high prevalence of HIV-1 infection among pregnant women. Rates of mother-to-child transmission of HIV-1, which are estimated from observational studies, are consistently higher in developing countries than in industrialized countries [1]. It has been hypothesized that this difference is attributable, at least in part, to transmission of the virus during breastfeeding. Indeed, in breast-fed infants, the timing of mother-to-child transmission of HIV-1 is substantially different than it is in non-breast-fed infants born to HIV-infected mothers. In non-breast-fed infants, HIV-1 transmission appears to occur mainly in late gestation and during labor and delivery [2]. In contrast, one-third to two-thirds of overall transmission occurs as a result of postnatal transmission by breast milk [3]. The additional risk of mother-to-child transmission has been estimated by meta-analysis at 14% (95% confidence interval [CI], 7%–22%) from prevalent maternal infections [4] and at 26% (95% CI, 13%–39%) in incident cases [5].

Which Breast Milk Compartment(s) Is Replicating or Harboring HIV-1?

In other models of retroviral transmission by breast milk (human T cell leukemia virus type 1 and visna-maedi or caprine arthritis-encephalitis virus in animals), cell-associated (primarily macrophage) virus has been shown to play a central role as the source of infection in breast milk [6]. However, macrophages may or may not be the source of transmitted HIV-1 because virus has been identified in both cell-associated [7, 8] and, more recently, in cell-free compartments of breast milk [9]. In addition, in vitro experiments suggest that ductal and alveolar mammary epithelial cells may also replicate HIV-1 [10]. The physiologic relevance of these observations remains to be clarified, but they may be particularly important for late, postnatal virus transmission, since mammary epithelial cell shedding of HIV-1 into breast milk is found almost exclusively at later stages of lactation [11].

Studies from Nairobi, Kenya, showed that the proportion of HIV-1–infected cells in the total cell content seems to remain constant or increase slightly over successive lactation stages [8]. In the same report, shedding of HIV-1–infected cells was associated in a dose-dependent manner with maternal vitamin A deficiency. These data can be linked with the results of another observational study conducted in Malawi, where the rate of mother-to-child transmission of HIV-1 increased with increasing vitamin A deficiency [12]. The biologic plausibility for an impact of vitamin A deficiency on HIV-1 transmission is...
found on well-known effects of vitamin A on host immune defenses and its influence on the integrity of mucosal surfaces.

Other substances in breast milk may also be protective, such as lactoferrin [13], lysozyme, mucins, immunocompetent T cells, complement, and secretory leukocyte protease inhibitor (SLPI). SLPI, a serine protease inhibitor, is present at potentially active concentrations (>100 ng/mL) in colostrum and transition milk, and it can inhibit HIV-1 entry into host cells in vitro [14, 15].

**What Is the Portal of Entry of HIV-1 on Infant Mucosal Surfaces?**

The precise portal of entry for HIV-1 across mucosal surfaces in infants is unknown. HIV-1 conceivably could be introduced into the submucosa by a breach in the integrity of an epithelial cell layer, by minor defects in tight junctions between epithelial cells as a consequence of a nutritional defect, or by concomitant pathogenic viruses or other infectious agents. Other candidates for the portals of entry include epithelial cells, such as enterocytes, and M cells, which are highly differentiated follicle-associated epithelium specialized in the transport of foreign antigens or infectious agents to the underlying mucosa-associated lymphoid tissue (MALT) for priming of an immune response. MALT containing T and B cells in addition to macrophages and dendritic cells is located along the gastrointestinal tract. The specific role of oral mucosa, including tonsils, as a portal of entry for HIV-1 remains to be studied.

**What Is the Timing of Postnatal Transmission of HIV-1 by Breast-Feeding?**

It is not known what time during lactation is of highest risk for HIV-1 transmission. There have been data presented to make a case for higher risk during early lactation (colostrum and transition milk) as well as later during lactation. Advocates of transmission during long periods of lactation have suggested that under certain conditions breast-feeding for the initial 6 months after birth would be preferable to breast-feeding beyond this age. Table 1 shows the arguments for and against the hypothesis that colostrum and transition milk can transmit HIV-1 more effectively than mature milk. It is exceedingly difficult to determine what the net effect of these competing or diverging factors is on the final outcome. Determining the relative weight of the different factors is of critical importance for the design of interventions aimed at reducing the risk of mother-to-child transmission of HIV-1 in the context of breast-feeding.

**Designing Interventions to Reduce the Risk of Postnatal Transmission of HIV-1 by Breast-Feeding**

While maternal virus load is not a perfect predictor for the risk of mother-to-child transmission of HIV-1, several studies have shown that infants born to mothers with higher virus loads are at higher risk of infection. Many interventions now under scrutiny with the aim to reduce mother-to-child transmission of HIV-1 are based on this principle. The most widely publicized and used intervention is the administration of zidovudine according to the AIDS Clinical Trial Group protocol 076. This regimen consists of zidovudine treatment of HIV-1-infected pregnant women from their second trimester of pregnancy, intravenous delivery of drug during labor, and treatment of newborns during their first 6 weeks of life. This strategy has been shown to reduce the rate of mother-to-child transmission of HIV-1 by nearly two-thirds in non-breast-feeding populations of women in the United States and France. This protocol is now the standard of care, together with strict artificial feeding, in most industrialized countries. More recently, a modified regimen, with treatment of the pregnant woman late in gestation and no treatment of the infant, was evaluated in Thailand with substantial reduction in transmission. However, the regimen still relied on strict artificial feeding of the infants born to the HIV-1-infected mothers.

Concerns have been raised about the applicability of even the modified strategy in developing countries because of costs, logistics, limited access to prenatal care, and the very real concerns that breast-feeding is essential for the health of infants in areas of the world with endemic diarrheal diseases and where alternative sources of nutrition for young infants are not available. In this setting, one of the uncertainties is the potential efficacy of antiretroviral agents given only during gestation and delivery when subsequent breast-feeding is common practice.

The eventuality of a rebound effect on virus load after discontinuation of the antiretroviral compound [16] is of particular concern. The presence of an “overshoot” of HIV-1 viremia after antiretroviral withdrawal has been detected recently in 4 of 5 patients shortly after treatment with antiretrovirals was discontinued [17]. The increase in virus load occurred within the very first days following discontinuation of treatment and was

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<td>Low proportion of infected cells in colostrum</td>
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<td>Pro</td>
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<td>Achlorhydria in neonates</td>
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<td>Higher virus load in colostrum*</td>
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<td>Immune system in neonates</td>
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<td>High mammary epithelial cell content in mature milk</td>
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<td>Higher concentration of IgA and IgM in colostrum</td>
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<td>High colostrum concentrations of anti-infectious substances</td>
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<td>(e.g., secretory leukocyte protease inhibitor and lactoferrin)</td>
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<td>Presence of maternally derived HIV antibodies in neonate and infant</td>
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<td>Aggravation of maternal vitamin A deficiency with duration of lactation*</td>
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* Not yet demonstrated.
of unexpectedly high magnitude, ranging from 0.6 to 1.5 logs of plasma viral RNA above pretreatment levels. In 2 of the 4 patients, this viral burst was comparable to the average virus loads measured during acute, primary infection. A few days after this viral burst, HIV-1 virus load declined and reached levels that approximated pretreatment levels. The most likely explanation for this observation is the increased availability of target cells as a consequence of treatment. Indeed, virus load in the 4 patients was consistent with CD4 cell counts.

A study is underway in Bobo-Dioulasso to measure the evolution of HIV-1 virus load in breast-milk samples collected repeatedly in the first few days after discontinuation of oral zidovudine. Preliminary results suggest that the rebound of virus load may also be observed in the breast milk of some mothers after discontinuation of oral zidovudine (unpublished data). Although this viral burst appears to be of short duration and have minimal effect on the clinical course of HIV-1 disease progression in the mother, it may not be so benign in terms of enhanced transmissibility of the virus via breast milk. Although suggested by studies in lactating mothers with primary infection [5], it is currently not established that the risk of transmission of HIV-1 by breast-feeding is directly related to virus load in milk. It is also not established that transmission of HIV-1 by breast-feeding more closely parallels the plasma virus load measurements. It can be noted, however, that the highest risk of mother-to-child transmission of HIV-1 by breast-feeding occurs when acute primary infection develops in the mother while she is breast-feeding her infant. Obviously, interventions to prevent transmission of HIV-1 to uninfected women while they are breast-feeding are also warranted to reduced the risk of mother-to-child transmission of HIV-1.

Intervention using antiretroviral treatment during pregnancy and delivery, which must be interrupted after delivery at the same time that lactation is initiated, may expose newborns to an unacceptable risk of transmission due to a viral burst occurring in their mothers [16]. Mother-to-child transmission of HIV-1 occurs preferentially late during gestation, and it is highly unlikely that any intervention using antiretrovirals for interruption of peripartum transmission could be withdrawn with a sufficient time span to both maintain efficacy and prevent consequences of transient overshoot in virus load on breast-feeding transmission.

Perspectives and Conclusions

If the viral burst after withdrawal of antiretrovirals increases HIV-1 transmission during breast-feeding, it is conceivable that interventions would need to be redesigned for continued administration in these settings. This would considerably hamper the applicability of these interventions in developing countries, where most women have no feeding alternative to breast-feeding. Issues about transmission of HIV-1 in breast milk with and without antiretroviral therapy need to be explored with utmost urgency to design and implement efficient and applicable interventions to prevent up to 30% of the newly acquired pediatric HIV-1 infections that are occurring via breast-feeding.

References