els of HIV-1–Infected Breast Milk Cells and Risk of Mother-to-Child Transmission

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Abstract:

Understanding how the level of human immunodeficiency virus type 1 (HIV-1)ï infected breast milk cells (BMCs) affects HIV transmission via breast-feeding can shed light on the mechanism of infection and aid in establishing effective interventions. The proportion of infected cells to total cells was measured in serial breast milk samples collected from 291 HIV-1ï infected women in Nairobi, Kenya, by use of real-time DNA polymerase chain reaction amplification of BMCs. The number of infected BMCs per million cells was associated with levels of cell-free viral RNA in breast milk (R = .144; P = .032), levels of cell-free virus in blood plasma (R = .365; P < .001), and the detection of proviral DNA in cervical and vaginal secretions (P < .001 and P = .030, respectively). The number of infected BMCs per million cells was lower in colostrum or early milk than in mature milk (P < .001). Previous studies demonstrated that the concentration of BMCs varies throughout lactation, and we used these data to transform infected BMCs per million cells to infected BMCs per milliliter. The estimated concentration of infected BMCs per milliliter was higher in colostrum or early milk than in mature milk (P < .001). Each log10 increase in infected BMCs per milliliter was associated with a 3.19-foldï increased risk of transmission (P = 002), after adjustment for cell-free virus in plasma (hazard ratio [HR], 2.09; P = 03) and breast milk (HR, 1.01; P = 1.00). This suggests that infected BMCs may play a more important role in transmission of HIV via breast-feeding than does cell-free virus. More than one-third of all mother-to-child transmission of HIV-1 in breast-feeding populations is estimated to occur via breast milk [1]. The exact mechanisms of this transmission are unknown. Although both cell-free virus and infected cells have been identified in breast milk [2ï 6], their respective roles in infant infection remain undefined. In vitro, studies suggest that infection of gastrointestinal cells and mucosal cells can be initiated by both cell-free virus and infected cells (reviewed in [7]). For example, several reports indicate that epithelial cells from the upper gastrointestinal tract mucosa can selectively take up and transfer both cell-free virus and cell-associated virus to target cells in vitro [8ï 12]. In rhesus macaque models, it has been demonstrated that both cell-free and cell-associated virus can be transmitted via both oral and genital mucosa [13ï 16]. It is difficult to know how well these model systems mimic the transmission process in humans and whether the results are applicable to transmission of HIV-1 in humans via breast-feeding. Breast milk contains many inhibitors to viral replication, such as secretory leukocyte protease inhibitor, chemokines, and lactoferrin [17ï 19]. Secretory leukocyte protease inhibitor has been shown to inhibit infection of lymphocytes by cell-free virus in culture but not to inhibit cell-associated transcytosis of HIV-1 [20]. Chemokines and lactoferrin have been postulated to prevent viral infection by blocking virus-to-cell binding (reviewed in [21, 22]). These data suggest that these factors may inactivate some of the cell-free virions present in

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er, to date there have been few published data reporting
the levels of HIV-1 infected breast milk cells (BMCs) and their association with HIV-1 transmission relative to the levels of cell-free virus in breast milk. To develop effective interventions to prevent transmission of HIV-1 via breast-feeding, the relationship of the level of virus in breast milk to transmission needs to be clearly defined. Studies of cell-free virus in breast milk have demonstrated that the concentration of cell-free virus is associated with HIV-1 transmission, the level of virus in maternal plasma, cell-associated virus in genital secretions, and breast disease [3, 5, 23]. Also, cell-free HIV-1 RNA concentrations in breast milk have been found to be highest early after delivery, a time when transmission via breast milk may be high [1, 3, 24ï 27]. Understanding how the level of cell-associated virus in breast milk correlates with the level of cell-free virus in breast milk, with virus levels throughout the body, and with mother-to-child transmission may shed light on the mechanism of transmission via breast-feeding and the relationship between virus levels in different body compartments. To address the above questions, infected BMCs and total cells in breast milk were quantified in women enrolled in a randomized clinical trial of transmission of HIV-1 via breast-feeding in Nairobi, Kenya, by means of real-time polymerase chain reaction (PCR) amplification methods. The relationship between these measurements and the risk of mother-to-child transmission, concentrations of cell-free virus in breast milk, virus levels in blood and genital secretions, and CD4 T cell count was assessed