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Virologic and host determinants of breastfeeding transmission of human retroviruses

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Breastfeeding (BF) transmission is responsible for approximately 300,000 new paediatric HIV infections each year. Mechanisms of transmission of HIV by BF are difficult to decipher due to the progressive maturation of the neonate/infant defences and to the evolving content of human milk over different stages of lactation. HIV is distributed and diversifies according to the constraints of anatomic sites. This is particularly true for the mammary gland and breast milk. The portal of entry of HIV on infant's mucosal surface remains largely mysterious. A rabbit model suggests that M cells may transport HIV particles by transcytosis to the lamina propria of Peyer's patches. In an ex vivo human model, HIV enters human enterocyte from HIV-infected cells through an agrin-dependent viral synapse, is transported by transcytosis across the enterocyte's cytoplasm and delivered in the vicinity of lamina propria. A macaque model suggests that tonsils crypts may behave as portal of entry for SIV. Cell-associated HIV in milk is the source of infection in most of the early transmission events and that free virus in milk is more frequently involved later on. Latently HIV infected T cells in breast milk are considerably more prone to enter viral cycle after ex vivo activation and to produce viral particles than their blood counterparts. This strongly suggests that local microenvironment in milk may favour transcription of integrated viral DNA from latently infected cells and its translation into proteins and new virions. Human milk contains also DCSIGN-expressing monocytes and dendritic cells that are able to transport and propagate R5 viruses in breast milk. It contains also HIV-specific MHC class I-restricted CD8+ Cytotoxic T lymphocytes that may play a role in the clearance of HIV-infected cells in breast milk. Human milk is extraordinary rich in soluble factors, some of them with immunomodulating or antiinfectious properties. Lactoferrin, Lewis X factor, SLPI, Interleukin-7 and αdefensins have all been suggested either in vitro or in vivo to modulate transmission. Breast milk of HIV infected women contains high concentration of HIV antibodies. HIV-specific secretory IGA and IgM have been associated with an absence of breast milk transmission in some but not all studies. Transmission of HIV by BF is a clearly multifactorial. The exact picture remains unclear but certainly involves a complex intercompartment cell trafficking, fuelled with complex viral populations, and modulated by a richly diversified microenvironment. Knowledge of the mechanisms of mucosal transmission of retroviruses should help designing new preventive interventions.