Journal of Virus Eradication 2016; **2**: 112–113

Human breast milk: is it the best milk to prevent HIV transmission?

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Abstract

A significant proportion of mother-to-child transmission (MTCT) of HIV still occurs during breastfeeding in settings where replacement feeding is unsafe and impractical. However, very few babies born to HIV-infected women and breastfed during the first 6 months of life become infected postnatally. The fact that the majority of babies who are breastfed by HIV-infected mothers remain uninfected even after several months of breastfeeding constitutes one of the major enigmas of HIV transmission via breast milk.

Ziegler and colleagues reported the first case of HIV transmission through breastfeeding in 1985 in Australia [1]. Since then, in settings where replacement feeding is unsafe and impractical, a significant proportion of mother-to-child transmission (MTCT) of HIV still occurs during breastfeeding. In an individual patient data meta-analysis of over 3,000 mother–infant pairs in sub-Saharan Africa, up to 42% of MTCT of HIV was attributable to breastfeeding [2]. However, less than 10% of babies born to HIV-infected women and breastfed during the first 6 months of life become infected postnatally [3]. The fact that the majority of babies who are breastfed by HIV-infected mothers remain uninfected even after several months of breastfeeding constitutes one of the major enigmas of HIV transmission via breast milk [4]. Indeed, an infant's daily exposure via oral and gastrointestinal mucosae to HIV has been calculated to be at least 700,000 viral particles per day [5] whereas the overall probability of transmission via breastfeeding was estimated to range from 0.050% [6] to 0.064% [7] per litre of breast milk ingested. Such low frequency of breastfeeding acquisition suggests that anti-infective factors in the breast milk of HIV-infected mothers as well as in HIV-exposed breastfed children may be involved [5,8,9].

The daily efficacy of human milk to prevent HIV infection has been tested in a set of experiments led by Wahl *et al.* who developed a novel humanised mouse model of oral HIV transmission utilising bone marrow/liver/thymus humanised mice. In this study, human milk from HIV-infected transmitter and non-transmitter mothers from Zambia was shown to prevent HIV infection in 75% of orally exposed mices, whereas the entire control group was infected [9]. Interestingly, human milk was also tested as a potential microbicidal agent. When the HIV challenge was performed by the vaginal and intravenous routes in the presence of breast milk from HIV-infected mothers, a significant protective effect was seen. Surprisingly however, a similar rate of protection was obtained using milk from HIV-negative mothers, thus excluding a direct role of HIV-specific immunity in conferring this ability. Such antiviral activity was not found in milk from cow, camel, goat or monkey, supporting the idea that the *in vivo* HIV-inhibitory activity of milk is restricted only to humans Noteworthy, this property of human milk was not hampered by pasteurisation or by manipulations designed to selectively remove or destroy the different components of human milk such as protein, sugars or fats. This suggests that multiple factors in breast milk may act in concert to inhibit mucosal HIV transmission. The authors also hypothesised that in HIV-infected breastfeeding mothers, a transient change in breast-milk composition, such as an increase of specific anti-HIV factors might occur, which can play a major role in reducing HIV transmission. Indeed, breast-milk proteins with a well-characterised *in vitro* anti-HIV activity, such as tenascin C[10] and purified lactoferrin [11], were unable to inhibit HIV transmission when tested at physiological concentrations in this *in vivo* model. A limitation of the *in vivo* model proposed in this study is the lack of tonsils in mice, a potential site of HIV transmission after oral exposure. Furthermore a change in faecal microbiota that occurs during different phases of lactation cannot be recapitulated in this model. Recent data show that composition changes in both breast milk and faecal microbiota in mothers and infants might play a major role in HIV transmission through breastfeeding [12]. These limitations can partially explain some of the diversity from data produced in humans.

The degree to which breast milk anti-HIV factors contribute to reducing postnatal transmission rates is most likely to be affected by whether each distinct transmission event involves cell-free or cell-associated virus. Experiments in the animal models proposed thus far have been unable to discriminate between the two types of events. Previous studies in HIV-infected mothers have shown that increases in the level of cell-associated HIV in breast milk are predictive of postnal transmission during early lactation [4,13].

Co-infections in breast milk with cytomegalovirus (CMV) and Epstein–Barr virus (EBV) have also been associated with increased HIV-1 shedding in this compartment and a higher incidence of HIV transmission [14]. In addition, microbial translocation occurring in infants with gastrointestinal infections as a result of damage to mucosal integrity has been associated with a higher acquisition rate of HIV infection through breastfeeding [15]. Recent data support the hypothesis that the HIV-inhibitory activity of breast milk from HIV-infected mothers may be further enhanced by the presence of HIV-specific antibodies and immune cells. With this view, Pollara and colleagues have reported that the presence of secretory IgA responses in human milk against a consensus HIV-1 envelope (B.con env03 gp140) may play a protective role for breastfeeding against HIV transmission [16]. This finding, in contrast to Wahl's results, highlights the importance of the specificity and functionality of milk antibodies in terms of neutralisation and antibody-dependent cell-mediated cytotoxicity in infant protection.

Finally, a breakthrough reported at the Conference on Retroviruses and Opportunistic Infections 2016 has revealed, through the analysis of 647 viral envelopes from 22 Zambian maternal–infant pairs, unique genotypic and phenotypic signatures that depend upon transmission route [17]. Specifically, breast-milk transmission selects infant viral isolates with fewer potential gp41 N-glycosylation sites than their maternal counterparts (P=0.017) and that are more sensitive to the glycan-dependent broadly neutralising

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antibodies PG9 and PG16 ($P \leq 0.014$) [17]. Additional data are thus necessary to define all the different mechanisms by which breast milk inhibits HIV infection *in vivo*. Given the importance of breastfeeding and the global impact of HIV infection, more research is needed to clarify the nature of antiviral factors present in human milk and to design novel approaches to prevent HIV transmission through breastfeeding so that infants in resource-limited settings are not denied the health benefits of breast milk.

Acknowledgements

I thank Prof Paolo Rossi and Dr Nicola Cotugno for their helpful suggestions and kind revision of the manuscript.

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