Transmission of CMV, HTLV-1 and HIV through breast milk: science, policy and unknowns

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Summary

Breastfeeding is a critical child survival intervention. The potential for transmission of some viral infections from mother-to-child, however, presents the dilemma of how best to interpret the benefits and risks of breastfeeding in different settings. Here, we compare the transmission dynamics, risk factors and outcomes of infection with three chronic viruses transmitted through breast milk: cytomegalovirus (CMV), human T-cell lymphotropic virus type 1 (HTLV-1), and human immunodeficiency virus (HIV). We provide an overview of current intervention approaches and discuss scientific, policy and programming gaps in our understanding of these major global infections.

Key messages:

- Three viruses are known to be transmitted through breastfeeding and to result in chronic infection: CMV, HTLV-1 and HIV.
- CMV transmission through breast milk mostly leads to subclinical infection, except in preterm infants in whom severe clinical disease can occur; the best preventive and treatment approaches in this group remain unclear and more data are needed on long-term sequelae.
- HTLV-1 is restricted to specific geographic foci and can be transmitted from mother-to-child through breastfeeding in 10-25% of cases; the best preventive strategy is avoidance or shortening of breastfeeding where safe alternatives are available.
- The absolute transmission risk of HIV through breastfeeding in the context of suppressive maternal antiretroviral therapy is now low, even over extended periods.
- Guidance for infant feeding for women living with HIV varies by setting: in low- and middle-income countries, breastfeeding with suppressive ART and adherence support is recommended, while in high-income settings formula feeding is advised.

Key words: CMV; HTLV-1; HIV; breastfeeding; virus; infant; survival.

Introduction

Optimal breastfeeding is a critical intervention in the quest to ensure that all children survive and thrive[1, 2]. Early breastfeeding within the first hour of birth and exclusive breastfeeding (meaning no other food or liquids except prescribed medications) for six months, reduce all-cause under-5-year child mortality[1, 2]. However, breastfeeding can also transmit infections. Three viruses are of particular global importance, since they can be transmitted from mother-to-child and lead to chronic infection: cytomegalovirus (CMV), Human T-cell Lymphotropic Virus type 1 (HTLV-1) and Human Immunodeficiency Virus (HIV). Particularly where prolonged breastfeeding for 12-24 months postpartum is usual, this provides a long duration of exposure to a potential source of infection and therefore presents a dilemma: how best to interpret the benefits and risks of breastfeeding in different settings. In this Review, we discuss the basic science, global public health approaches and policy gaps in our understanding of mother-to-child transmission (MTCT) of these three viruses.

Breastfeeding shapes infant development

Breast milk is more than just food: it contains a suite of beneficial components including immunoglobulins, immune cells, stem cells, exosomes, growth factors, cytokines, lactoferrin and oligosaccharides[3]. Breast milk is extraordinarily adaptive, and its composition is governed by multiple factors including mode of delivery[4], time from birth[5], geography[6], sex[7] and infant illness[8]. The mother-infant pair is intimately linked through breastfeeding. The concept of a common maternal-infant mucosal immune system[9] derives from observations that B-cells primed in the mother provide a source of infant immunoglobulins, and maternal immune cells penetrate the infant gut to populate the newborn, providing long-term protection through a process termed maternal micro-chimerism[10, 11]. Breast milk contains a rich microbial community[12], helping to establish the infant intestinal microbiota, which is further shaped by breast milk glycans such as human milk oligosaccharides[13]. Bacterial

colonisation of the infant gut drives immune homeostasis and promotes intestinal maturation, including production of the mucus layer, antimicrobial peptides and gut barrier function[14].

While the mature gut constitutes a remarkable defence system, the young infant gut remains vulnerable to infection during this dynamic period of intestinal adaptation. For example, the newborn has increased intestinal permeability for several weeks after birth to enable the process of maternal micro-chimerism[11], which might facilitate passage of cell-associated viruses in breast milk; there is relative achlorhydria in the stomach, which impairs neutralisation of viruses[15]; and infants have a large population of intestinal CCR5+ memory CD4+ T-cells, which provide a highly susceptible pool of target cells for HIV[16]. Furthermore, exposure to viruses in early life occurs at a time when anti-viral immunity is not well developed due to enhanced tolerogenic responses, reduced Th1 development, and naïve lymphocyte predominance; the capacity to control viral infections only matures over the first few years[17]. However, any potential vulnerability associated with breastfeeding in the context of maternal viral infections must be interpreted against the proven protection of breastfeeding (Figure 1).

Mother-to-child transmission of viruses through breastfeeding

Three viruses are known to be transmitted through breastfeeding and to result in chronic infection, with substantial clinical disease among some infants: CMV, HTLV-1 and HIV. By contrast, despite being found in milk, breastfeeding does not increase the risk of mother-to-child transmission for two other chronic viral infections of global importance, hepatitis B and C[18, 19]. The transmission dynamics and outcomes following MTCT are distinct for CMV, HLTV-1 and HIV (Table 1), and are influenced by maternal, infant, viral and environmental factors.

CMV

CMV is a member of the ubiquitous Human Herpes Virus family; humans have been co-existing with these DNA viruses for millennia[20]. Primary CMV infection in the immunocompetent host is usually subclinical and the virus then establishes lifelong latency, with asymptomatic intermittent viral reactivation and excretion via body fluids[21]. Age at CMV acquisition varies geographically: in high-income countries, approximately 5-30% of children are CMV-seropositive by 5-6 years of age, compared with 85-95% in low- and middle-income countries (LMIC)[21]. In some LMIC, infection occurs almost universally during infancy: in a Gambian study, for example, 85% had acquired CMV by the age of 12 months[22]. Worldwide, CMV seropositivity among women of reproductive age therefore ranges from 40-100%, with higher seroprevalence in LMIC[23].

More than 80% of seropositive women excrete CMV in breast milk[24]. Little or no virus is detectable in colostrum, but CMV DNA is increasingly detected in breast milk to a maximum level at 4-8 weeks of lactation, with subsequent decline, often to minimal levels[25]. CMV-seropositive women also excrete virus in the birth canal, saliva and urine; thus the exact route of early CMV transmission can be difficult to ascertain. CMV is excreted by mammary epithelium and is found in both the milk whey and cellular (leukocyte) compartments; cell-free virus in the whey is associated with a higher vertical transmission risk[26]. Mothers with earlier excretion of infectious virus, higher CMV milk viral loads and longer duration of excretion, are more likely to transmit CMV[26-28]. An intriguing recent study from Uganda suggested that infant-to-mother transmission of CMV can also occur, such that infants first acquire primary CMV, either from another child in the house or from their mother through breastfeeding, and then transmit the infection to their mother[29].

Premature infants (<32 weeks' gestation) are at risk of symptomatic postnatal CMV infection[24]. The frequency of transmission and risk of clinical disease in preterm infants is not well established, since most studies have small numbers, lack good control groups, and report variable breast milk exposure durations. However, a meta-analysis of 695 premature infants breastfed by CMV-seropositive mothers (17 studies, median 38 infants per study, range: 7–90), found that CMV transmission ranged from 2-37%; CMV-related symptoms developed in 0-18%, and severe "sepsis-like" symptoms in 0-14% of infants[30]. Among the few studies reporting longer-term follow-up of premature infants (≤1500g birth weight) with postnatal CMV acquisition, some found no significant differences in outcomes compared to controls, while others suggested mild neurocognitive impairments[31-33]. Unlike congenital CMV infection, no sensorineural hearing loss has been found[31, 33].

CMV breast milk transmission is obviated by pasteurisation, but this negatively affects other important breast milk components and is not feasible in many settings[34]. Freezing, ultraviolet-C irradiation and high-power microwave reduce CMV viral load and thus transmission, with less effect on other breast milk components, but more work is required to ascertain the best treatment methodologies, especially in the context of milk banks for preterm infants[35-37]. One study suggested freezing may increase the risk of necrotising enterocolitis, which has to be balanced with the risk of symptomatic CMV[38]. Some national guidelines suggest pasteurisation of breast milk for extreme preterm infants born to CMV-seropositive mothers until around 31 weeks' gestation, aiming to reduce the risk of transmission during the most vulnerable period[39].

Women living with HIV have a higher risk of transmitting CMV than women without HIV, due to longer duration of CMV excretion and higher breast milk, cervical, and salivary CMV viral loads[40, 41]. In the only randomised controlled trial of breastfeeding versus formula feeding,

conducted among mothers living with HIV in Nairobi during the pre-antiretroviral therapy (ART) era, a secondary analysis of CMV transmission was undertaken in 138 breastfed and 134 formula-fed infants[42]. Overall, breastfed infants acquired CMV earlier than formula-fed infants (median age, 4.26 vs 9.87 months; P<0.001) and had a higher 1-year probability of CMV infection (0.89 vs 0.69; P<0.001), although the proportion with symptomatic infection was not reported. The risk of infant CMV acquisition was 1.6-fold greater (95% confidence interval 1.20, 2.16; P=0.002) with breastfeeding, independent of infant HIV status. HIV-infected infants who acquire postnatal CMV can develop severe symptomatic disease, and CMV is a co-factor for HIV disease progression in some studies[43]. There is some evidence that postnatal CMV may affect the immune development, growth and health of HIV-exposed uninfected infants, but more data are needed[44]. The impact of maternal ART on breast milk CMV viral load and postnatal transmission risk is heterogeneous[45-47] and it has been argued that new approaches to reducing postnatal CMV transmission among HIV-exposed infants are needed[44].

Taken together, CMV transmission from mothers to infants occurs at high frequency and very early in life, particularly in LMIC and among women living with HIV. Postnatal infection in very preterm infants can cause clinical disease and strategies to prevent transmission through breast milk are needed. Whether CMV transmission through breastfeeding needs to be reduced in populations other than very preterm infants remains unclear. The available evidence suggests that CMV infection in HIV-unexposed term infants has limited clinical significance. More studies are needed to determine the impact of CMV on HIV-exposed infants.

HTLV-1

HTLV-1, the first human retrovirus to be discovered in the early 1980s[48], infects at least 5-10 million people worldwide, mainly in highly focal endemic areas such as southern Japan, West/Central Africa, the Caribbean and parts of South America and Australo-Melanesia[49]. Typically, adult prevalence in these endemic foci is around 1-2%, although up to 20-40% of people aged over 50 years are living with HTLV-1 in some areas[49]. HTLV-1 preferentially infects CD4+ T-cells, but CD8+ T-cells may also be important reservoirs; to a lesser extent, monocytes, B-cells, dendritic cells, and endothelial cells can be infected. Infection occurs by transmission of HTLV-1-infected cells between individuals, through semen, blood, and breast milk[49]. HTLV-1 infection is associated with two distinct diseases: a lymphoproliferative disorder termed Adult T-cell Leukaemia/Lymphoma (ATL), and an inflammatory neurological disease called tropical spastic paraparesis or HTLV-1-associated myelopathy (TSP/HAM). Acquisition of HTLV-1 during childhood is a major risk factor for the development of ATL[50], which has a median age at diagnosis of around 50 years and usually runs a very aggressive course: the median survival in a case series from Jamaica was only 20 weeks[51]. Despite improvement in treatment approaches, the acute and lymphoma types of ATL still have a poor prognosis, with a 4-year survival of 11-16% in Japan between 2000-2009[52]. TSP/HAM typically has an insidious onset in adulthood, with sensory and bladder disturbance, together with slowly progressive pyramidal signs; however, a case series of children with early-onset disease in Bahia, Brazil was recently reported[53]. HTLV-1 is also associated with other inflammatory diseases such as infective dermatitis (mainly in children), uveitis and myositis.

MTCT of HTLV-1 occurs in 10-25% of breastfed infants[49]. Based on epidemiological, virological and experimental data, risk factors for MTCT have now been established. First, transmission of HTLV-1 increases with longer duration of breastfeeding: for example, in a prospective birth cohort in Jamaica, followed to at least 2 years of age, 19/60 (32%) children

who breastfed for longer than 12 months acquired HTLV-1, compared to 8/86 (9%) children who breastfed for less than 12 months[54]. Second, higher HTLV-1 proviral load in maternal blood and breast milk increases MTCT[55, 56]. The proviral load is a proxy for the number of infected cells, and reflects the fact that HTLV-1 transmission is cell-associated, and not due to cell-free virus. A recent longitudinal study showed that the proviral load is stable during pregnancy but elevated after delivery[57]. Finally, higher HTLV-1 antibody titres in maternal blood are associated with increased MTCT risk, which may partly reflect the correlation between antibody titres and maternal proviral load[56]. The processes underlying MTCT of HTLV-1 remain largely unknown, although potential mechanisms have recently been reviewed in detail[58].

As there is no vaccine, and no antiretroviral regimen has been evaluated for PMTCT (or adult-to-adult transmission), the only preventive strategy is for mothers living with HTLV-1 to avoid breastfeeding. This approach has led to huge reductions in HTLV-1 MTCT in Japan. For example, in the Nagasaki Prefecture, the introduction of exclusive formula feeding was associated with a reduction of MTCT from 20.3% to 2.5%[59]. However, universal antenatal screening is currently only undertaken in Japan. In a recent open letter to the WHO[60], experts have argued strongly for more action to prevent HLTV-1, including routine antenatal testing and avoidance or shortening of breastfeeding among mothers living with HTLV-1 where safe, alternative methods of infant feeding are available. Further research is needed to inform alternative approaches, including the role of maternal and/or infant antiretroviral prophylaxis in reducing HTLV-1 MTCT.

HIV

In 2017, 36.9 million people globally were living with HIV, of whom 1.8 million were children[61]. Despite the enormous impact of PMTCT interventions, which have averted an

estimated 1.4 million new paediatric infections since 2010, around 180,000 children acquired HIV in 2017[61]. In the absence of any preventive interventions, transmission of HIV by breastfeeding is estimated to be 0.74% per month of breastfeeding[62] and contributes around one-third of the overall MTCT risk[63]; the relative contribution of postnatal transmission has increased in most breastfeeding countries following the increased coverage of antenatal PMTCT interventions[64].

Cell-free and cell-associated viral loads in milk are major determinants of transmission[65]; other risk factors include the duration of breastfeeding[62], severity of maternal immunodeficiency[62], maternal immune response to HIV[66], presence of an inflammatory process in the mammary gland (engorgement, mastitis, breast abscess)[67], and early introduction of non-breast milk feeds (mixed feeding)[68]. With effective maternal HIV suppression on ART, the absolute transmission risk, even over extended periods, is less than 1% in trial settings[69, 70]. However, the risk of postnatal transmission is extremely high (approximately 30%) if the mother acquires HIV while breastfeeding[71], particularly among young infants, in whom the combination of high maternal HIV viral load and immature intestinal integrity may increase susceptibility to transmission[71].

HIV actively replicates and produces viral particles during the whole duration of infection in adults, particularly in sub-mucosal compartments, which are rich in lymphoid cells[72]. HIV transmission can therefore arise from both cell-free and cell-associated reservoirs in breast milk[73]. Compared with lymphoid cells from blood, breast milk cells are more frequently activated memory cells, which express homing markers indicating their mucosal origin[74]. Quiescent CD4+ T-cells infected with HIV are also present in breast milk; if activated *ex vivo*, these cells are much more capable of producing infectious particles than corresponding blood cells[74]. *In vivo,* the activators of these quiescently infected cells may be co-infections,

since CMV and Epstein Barr virus DNA in milk are associated with shedding of HIV virions[75]. In addition, activated CD4+ T-cells with actively replicating HIV can be identified in breast milk of mothers on ART despite an undetectable plasma HIV viral load[74]. This activated reservoir may be particularly prone to cell-to-cell transfer of HIV in the infant, providing a residual source of postnatal transmission risk despite suppressive maternal ART[64]. Other cell types, such as macrophages and dendritic cells, may also be involved in the establishment of HIV reservoirs in the mammary gland and breast milk. Maternal micro-chimerism through breastfeeding, which seeds long-lived maternal cells into infant tissues, may include cells infected with HIV such as CD4+ progenitor T-cells, and may therefore represent an additional source of HIV transmission[10, 11].

Preventing breast milk HIV transmission in LMIC settings

Prior to availability of ART in LMIC settings, WHO recommended counselling of individual mothers living with HIV to choose between replacement feeding or breastfeeding, considering their living conditions and what method of feeding would most likely result in their infants surviving while remaining HIV-uninfected[76, 77]. Recommendations changed in 2010 following studies showing that ART significantly reduced HIV transmission risk, together with reports of increased mortality, morbidity and growth failure due to gastroenteritis and malnutrition among infants given replacement feeds as an HIV prevention strategy[78, 79]. There was increasing recognition that improving HIV-free survival, rather than preventing vertical HIV transmission alone, was the ultimate goal of PMTCT programmes. Consequently, the 2010 WHO recommendations introduced infant post-exposure prophylaxis throughout breastfeeding (PMTCT Option A) or maternal triple ART (PMTCT Option B) for HIV-exposed breastfeeding infants whose mothers were not receiving ART for their own health[80]. Within two years, these recommendations were rapidly adopted into policy in the vast majority of high HIV prevalence LMIC. Ministries of Health and local

communities had been grappling with the dilemma of preventing postnatal transmission without undermining breastfeeding as a child survival strategy; a public health approach of providing ART to all pregnant and lactating mothers living with HIV and recommending breastfeeding addressed these competing demands. Yet, even in these settings, it was noted that the 2010 WHO recommendations were not always "…translated into action by… front-line workers because of a variety of structural and ideological barriers"[81].

In 2012, WHO guidelines recommended lifelong ART (referred to as Option B+) for all pregnant and breastfeeding women to simplify interventions and to amplify the gains beyond PMTCT, including preventing horizontal HIV transmission and protecting future pregnancies[82]. ART is now recommended for adults and children from the time of diagnosis[83]. As a result of these changes, multiparous mothers are now more likely to conceive on ART, nulliparous pregnant women more likely to initiate ART earlier in pregnancy, and breastfeeding mothers are more likely to be on ART. This earlier and increased antiretroviral use provides a platform for maternal viral load suppression and for eliminating mother-to-child HIV transmission (EMTCT), defined as <5% MTCT and ≤50 new paediatric HIV infections per 100,000 live births[84]. Although these updated policies have set the scene for EMTCT, data from LMIC indicate poor retention in care and ART adherence (73-76% antenatal adherence, falling to 55-65% postnatally)[85-87]. Although viral load monitoring during pregnancy, delivery and breastfeeding is gaining momentum, it is not yet fully integrated into routine care. Furthermore, although there is a correlation between plasma and breast milk viral loads, an undetectable plasma HIV viral load does not indicate lack of HIV infectivity, due to activated latent CD4+ T-cells in breast milk, even in the presence of antiretroviral drugs. Whilst ART for mothers living with HIV or extended prophylaxis for their infants in a clinical trial setting can reduce MTCT to <1% at 1-2 years of age[69, 70], these results are not easily reproducible in real-life LMIC settings. The challenges

posed by inadequate maternal adherence, irregular virological monitoring, uncertain implications of low-level viraemia for MTCT, and residual breast milk infectivity, question the feasibility of eliminating breastfeeding MTCT in LMIC using present antiretroviral regimens. Thus, the evaluation of combination strategies, including maternal ART with support for adherence and maternal and/or infant passive immunoprophylaxis or active vaccination is a research priority.

Breastfeeding and HIV in high-income settings

Avoidance of breastfeeding was the first effective PMTCT intervention for HIV in high-income countries. Based on a single case of transmission following transfusion-acquired postpartum HIV infection[88] and detection of HIV-1 in breast milk[89], the first United States Centers for Disease Control and Prevention recommendation to undertake exclusive formula feeding was published in 1985[90], and has been a core component of PMTCT guidelines in high-income countries ever since. Consequently, postpartum HIV MTCT in high-income countries is rare, and placing an infant at risk of HIV infection through breastfeeding has been considered a child protection issue in some settings[91].

In 2009-2010, findings from several observational studies[92-94] and two randomised trials[95, 96] highlighted the low rates of HIV transmission associated with breastfeeding in the context of either maternal combination ART or infant prophylaxis with nevirapine or other antiretroviral drugs. Guidelines in high-income countries have continued to recommend exclusive formula feeding regardless of maternal HIV viral load or therapy, since even with a consistently undetectable maternal viral load, the MTCT risk is low but not negligible. However, there has been a subtle but important shift in advice in high-income settings since these trial findings; for example, British HIV Association (BHIVA) guidelines in 2010 stated that "…if a woman is on effective HAART and has compelling reasons to breastfeed, she

should be supported to do so as safely, and for as short a period as possible". Current BHIVA guidelines[97] continue to recommend formula feeding, but provide advice regarding clinical and laboratory monitoring for women who decide to breastfeed after evidence-based counselling, similar to European[98] and US[99] guidelines.

In the context of sexual transmission, an undetectable viral load is now considered to indicate that HIV is untransmittable (so-called "U=U"). However, a similar confidence has not permeated the PMTCT context, for several possible reasons. There is a lack of data on transmission risk to provide accurate information to mothers; concerns regarding maternal adherence to ART; the potential for local HIV replication in the breast during episodes of mastitis; uncertainty regarding the impact of low-dose exposure to ART through breast milk; and intense monitoring is required during breastfeeding. High-quality evidence is therefore still needed to inform these issues and to guide recommendations on infant feeding by mothers living with HIV.

Exposure to antiretroviral drugs through breastfeeding

Since current guidelines recommend that mothers living with HIV in LMIC undertake prolonged breastfeeding on ART[83], it is essential to quantify the clinical importance of any adverse effects of infant ART exposure through breast milk. Factors influencing drug exposure in breastfed infants are shown in Figure 2. The peak concentrations of ART in breast milk lag behind those for plasma, and the elimination phase may be prolonged; such kinetics are seen for the nucleoside reverse transcriptase inhibitors (NRTIs)[100]. Exclusively breastfed infants receive up to 10% of the weight-adjusted infant dose of NRTIs and non-NRTIs (NNRTIs) whereas protease inhibitors have little transfer to the infant[101]. Genetic differences, such as CYP2B6 polymorphisms in the case of efavirenz, result in higher infant drug exposure[102].

The major potential risk to the infant from exposure to maternal ART through breastfeeding is toxicity. However, it can be difficult to distinguish the effects of *in utero* and breast milk exposure to a drug. There has been considerable debate about the effects of infant exposure to tenofovir, although a recent systematic review suggests changes in bone mineral density have no clinical relevance[103]. Dolutegravir is the first integrase strand-transfer inhibitor to be studied in breastfeeding mother-infant pairs, and is measurable in both breast milk and the plasma of the breastfed infant[104], but the clinical consequences are currently uncertain. Pharmacovigilance among infants exposed to drugs through breastfeeding is not well established, with under-reporting of adverse drug reactions, and a likely skew towards the most serious events[105]. Whilst few studies have systematically collected infant safety data, the recent PROMISE trial showed no increase in toxicities among infants exposed to ART through breast milk, compared to extended infant nevirapine prophylaxis[69]. Whilst the Antiretroviral Pregnancy Registry is well established, no parallel system exists to systematically collect data on clinical outcomes, growth and development in breastfed infants. Furthermore, the clinical tools needed to identify subtle toxicities have not been established.

Breast milk ART exposure may increase the risk of drug resistance among infants who acquire HIV. Secondary analysis of two large PMTCT trials indicated that, although MTCT rates were very low, infants who acquired HIV during breastfeeding while their mother was receiving ART had high rates (75-100%) of multi-class drug resistance, defined as resistance to both NRTIs and NNRTIs[106, 107]. Analysis of mother-infant pairs indicated that resistance arose in the infant as a result of selective drug pressure[108]. This risk likely remains in breastfeeding mothers who have poor adherence to therapy and is a potential challenge for future first-line treatment options among infants and young children.

An emerging clinical challenge is the impact of infant exposure to maternal ART, including during breastfeeding, on the accuracy of current early infant diagnosis protocols. Analysis of more than 13,000 HIV-exposed South African infants indicates an increase in equivocal results since 2015 among infants who are later confirmed as HIV-infected, in parallel with the change in guidelines to lifelong maternal ART and increased duration of breastfeeding. Maternal ART may reduce levels of infant viraemia and hence impair detection of HIV by PCR[109]. This warrants further evaluation programmatically.

Breast milk transmission of HIV: unknowns and future directions

The ultimate goal of policies and programmes to prevent postnatal HIV transmission is for mothers to breastfeed their infants without consideration of their HIV status; three areas of research therefore remain essential. First, there is a need to improve the efficacy, flexibility and safety of ART regimens. Currently available interventions have transformed the landscape for infant and young child feeding in the context of HIV but they could be improved. Determining the most effective maternal and/or infant ART regimens during breastfeeding, while decreasing their adverse effects, will help increase coverage and bring transmission rates closer to zero. Second, learning how to identify all mothers living with HIV (especially those infected postpartum) and evaluating pre-exposure prophylaxis strategies to reduce incident infection during breastfeeding remains pivotal. Third, facility- and community-based interventions are needed to increase rates of retention-in-care of mothers, regardless of feeding practice. In Malawi, effective peer support increased postnatal retention in care and associated ART adherence to over 80% at 24 months with improved viral suppression and reduced resistance[110].

As women living with HIV in high-income settings question their eligibility to breastfeed, and women in LMIC are currently advised to breastfeed without effective counselling on risks, the ethics of policies that argue for or against breastfeeding and the rights of women to choose an infant feeding practice need examination. Breastfeeding in the context of HIV has been a highly contested and divisive issue, often splitting the HIV and maternal-child health (MCH) communities. The integration of HIV-specific interventions into facility- and community-based MCH services is now a realistic policy and programme option; it is also an imperative as funding streams call for greater efficiencies.

Conclusions

Breastfeeding remains critical to child survival globally. Recent insights into the science of breastfeeding, including the complex and adaptive properties of breast milk and the long-term benefits from its diverse range of constituents, demonstrate the importance of continuing to apply modern tools to an ancient and highly evolved practice. However, the risk of transmission through breastfeeding of three chronic viral infections of global health importance (CMV, HTLV-1 and HIV) has implications for public health policy. CMV transmission through breast milk is mostly of concern for preterm infants (<32 weeks or $\underline{<}$1500g birth weight) in whom severe clinical disease can occur. However, the best prevention and treatment approaches are currently uncertain, meaning practice varies across settings, and further data are needed on long-term sequelae. MTCT of HTLV-1, which is restricted to specific geographic foci, can be prevented by avoiding or shortening breastfeeding, provided safe alternatives are available. Guidelines for infant feeding by mothers living with HIV vary by setting: in LMICs, breastfeeding with maternal ART and adherence support is the recommended approach, while in high-income countries, exclusive formula feeding is advised, although some women on suppressive ART are now choosing to breastfeed.

There are some remaining gaps in our understanding of the transmission dynamics and potential interventions to reduce MTCT for these viruses (Panel). However, HIV is an excellent example of how our knowledge of viral kinetics and interventions has advanced since the virus was first identified in breast milk in 1985[89], and how this understanding has impacted public health interventions for children. Research remains an essential mechanism for informing global guidelines and national policies and identifying viable options for intervention to maximize the benefits of breastfeeding while minimising the risks of viral transmission, to promote child health, development and long-term human capital.

Search strategy and selection criteria

References for this Review were initially identified by each author based on their knowledge of the field. In addition, we searched PubMed using the search terms "CMV", "HTLV-1", "HIV", "infant" and "breastfeeding" to identify additional studies, published in English, from inception up to 6th November 2018. The final reference list was generated based on inclusion of historical landmark studies, originality and relevance to the broad scope of this Review.

Declaration of interests

EJA has participated in Viiv pharmaceuticals and Merck pharmaceuticals paediatric advisory committees. The other authors declared no conflicts of interest. The views expressed in this review are those of the individual authors and do not necessarily reflect the positions or recommendations of their institutions or organisations.

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Author contributions

AJP and EHL drafted the section on CMV; AG and PVP drafted the section on HTLV-1; AJP, AEG, GPT and NR drafted the section on HIV; and CW and EJA drafted the section on antiretroviral exposure through breastfeeding. AJP integrated all author contributions and

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Figure legends

Figure 1: Balancing the benefits and risks of breastfeeding in the context of breast milk viral transmission.

Figure 2: Factors influencing drug exposure in the breastfed infant.

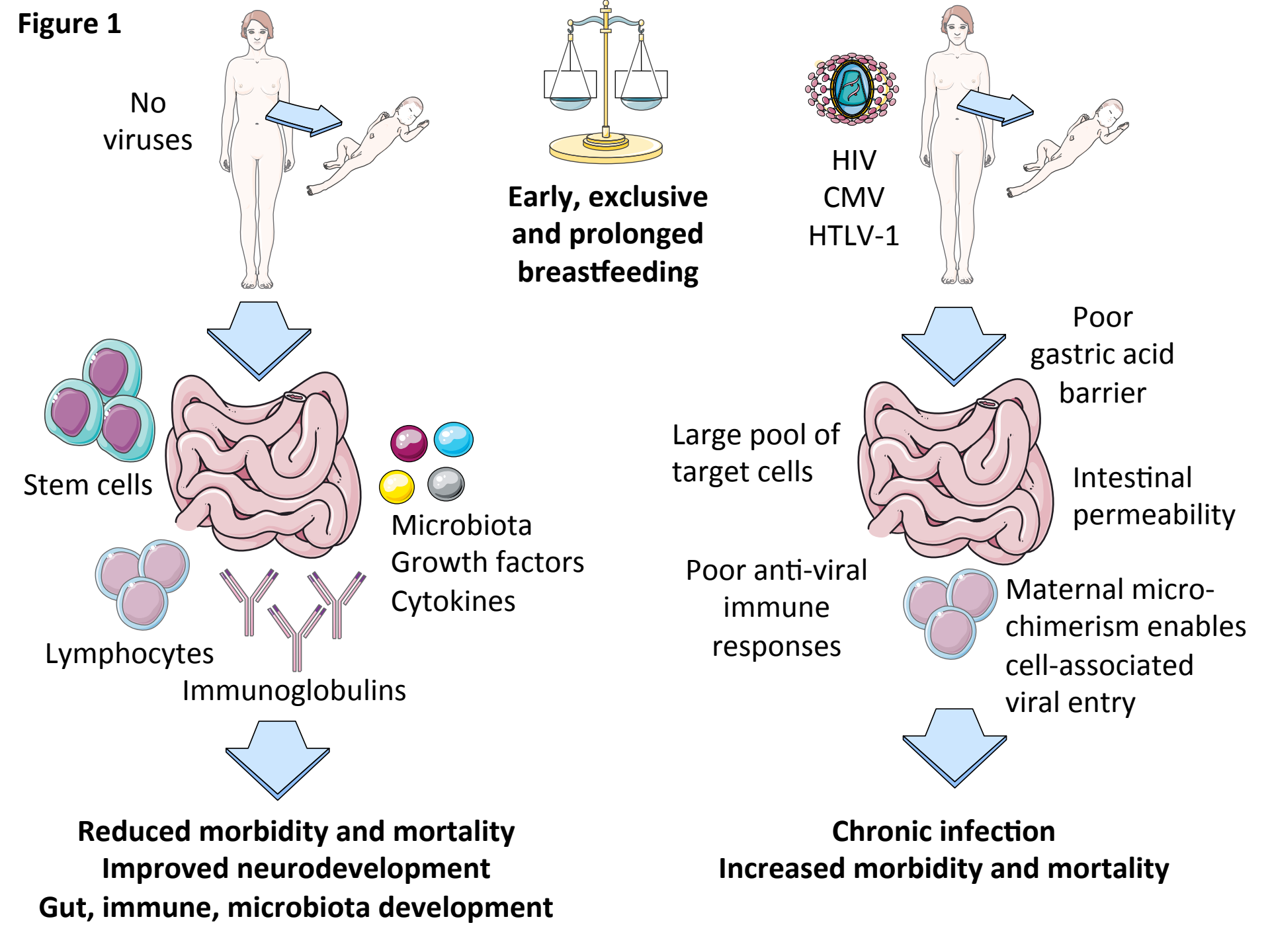
Table 1. Biological and epidemiological characteristics of human viruses transmitted by breastfeeding

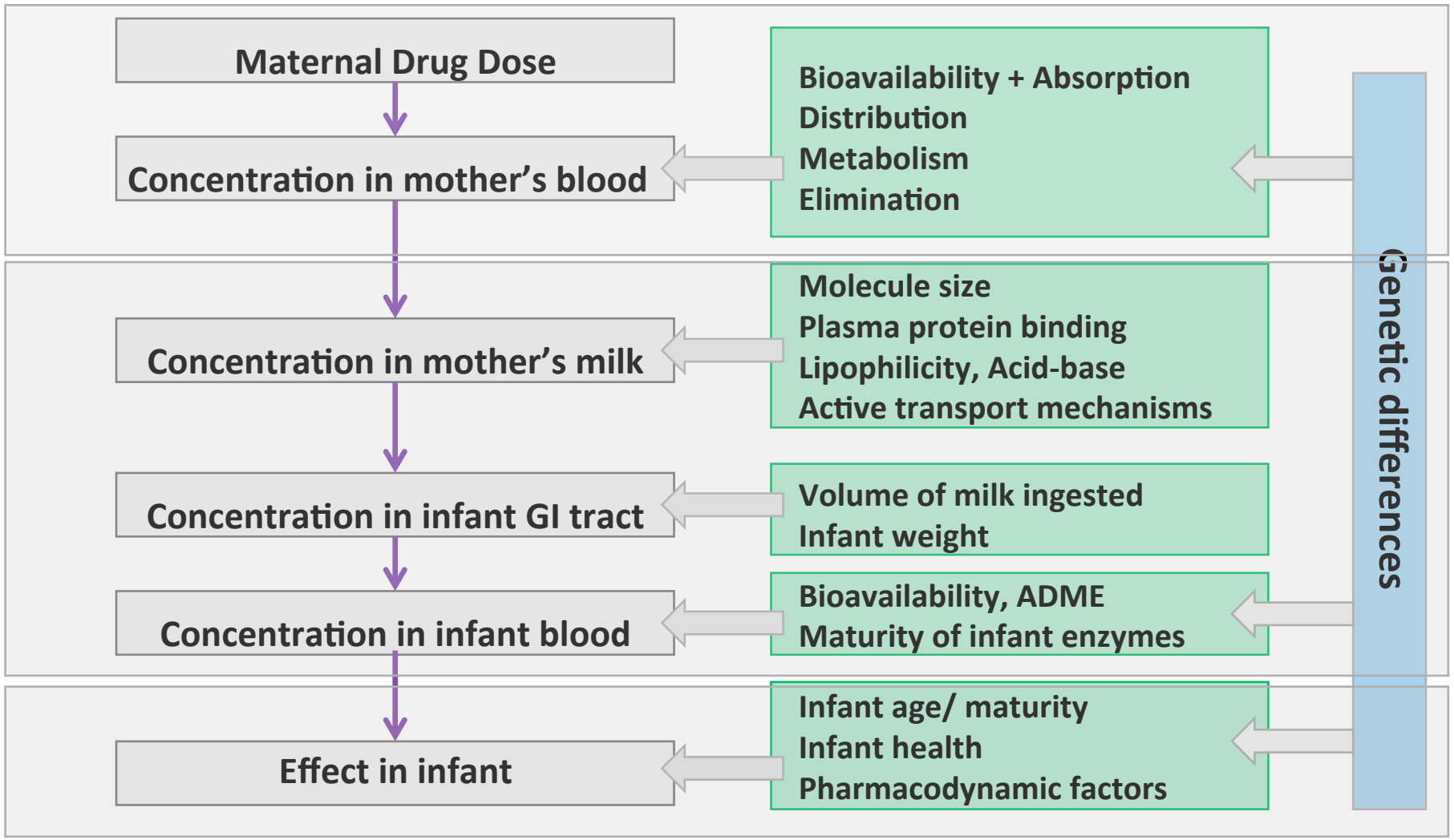
Characteristic	HTLV-1	HIV-1	CMV
Rate of shedding in breast milk (PCR)	>80% (HTLV-1 DNA)	20-60% (HIV RNA and/or DNA)	>80% seropositive mothers (CMV DNA)
Mode of excretion in breast milk	Cell-associated	Cell-free and cell-associated	Cell-free and cell-associated
Transmission rate by breastfeeding in the absence of prevention	Transmission occurs in 10-25% of breastfed infants	0.74% transmission per month of breastfeeding	80 to 90% infants infected by 12 months in LMIC; 20-40% in high-income settings
Risk factors for breastfeeding transmission	Duration of breastfeeding Proviral load in breast milk and blood High titres of maternal anti-HTLV-1 antibodies	HIV RNA viral load in blood and/or in breast milk Duration of breastfeeding Early (before 6 months of life) addition of a replacement feed (mixed feeding) Severity of maternal immunodéficiency Absence of anti-HIV IgM and/or sIgA in breast milk Absence of HIV-specific cytotoxic T-cells in breast milk Mastitis and other inflammatory process in breast and breast milk	Duration of breastfeeding Earlier CMV excretion in milk Higher CMV viral load Trans-placental maternal anti-CMV IgG may be protective High-avidity anti-CMV IgG in breast milk may be protective

Public health impact of breastfeeding transmission	Restricted to highly endemic regions Severe but infrequent clinical disease, mostly in adults (ATL, TSP/HAM)	Global pandemic, approximately 100,000 new pediatric infections attributed to breastfeeding transmission annually Frequent and severe disease if infant ART is not initiated early	Mostly asymptomatic Clinical disease in immunocompromised or very preterm infants, including sepsis-like illness Impact of breast milk transmission on growth and neurodevelopment uncertain
Prevention	In highly endemic areas: antenatal HTLV-1 testing and exclusive formula feeding Administration of freezed-thawed expressed breast milk Feeding by wet nurse or milk from healthy donors	High-income settings: Formula feeding recommended LMIC: Breastfeeding with maternal ART Infant post-exposure prophylaxis (currently recommended by WHO for six weeks or longer if risk of MTCT is high) Infant pre-exposure prophylaxis (currently not recommended by WHO) Pasteurisation of breast milk (currently not included in WHO guidelines) Potentially, passive immunoprophylaxis (under evaluation)	Uncertain Pasteurisation reduces transmission, but negative effects on other breast milk components Potentially freezing, ultraviolet-C irradiation and high-power microwave Role of antiviral interventions uncertain (toxicity, cost, efficacy)

PCR: Polymerase chain reaction; LMIC: Low- and middle-income countries; IgM: immunoglobulin M; sIgA: secretory immunoglobulin A; IgG: Immunoglobulin G; ATL: Adult T-cell leukaemia/lymphoma; TSP/HAM: Tropical spastic paraperesis / HTLV-1 associated myelopathy; ART: antiretroviral therapy; WHO: World Health Organziation; MTCT: Mother-to-child transmission.

Figure 1


No viruses
Early, exclusive and prolonged breastfeeding
HIV
CMV
HTLV-1
Stem cells
Microbiota
Growth factors
Cytokines
Lymphocytes
Immunoglobulins
Poor gastric acid barrier
Large pool of target cells
Intestinal permeability
Poor anti-viral immune responses
Maternal micro-chimerism enables cell-associated viral entry
Reduced morbidity and mortality
Improved neurodevelopment
Gut, immune, microbiota development
Chronic infection
Increased morbidity and mortality


Maternal Drug Dose
Concentration in mother's blood
Concentration in mother's milk
Concentration in infant GI tract
Concentration in infant blood
Effect in infant
Bioavailability + Absorption
Distribution
Metabolism
Elimination
Molecule size
Plasma protein binding
Lipophilicity, Acid-base
Active transport mechanisms
Volume of milk ingested
Infant weight
Bioavailability, ADME
Maturity of infant enzymes
Infant age/ maturity
Infant health
Pharmacodynamic factors
Genetic differences