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Women living with HIV in high-income settings and breastfeeding

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Guidelines in high-income settings recommend breastfeeding avoidance amongst women living with HIV (WLWH). Increasingly, WLWH in high-income settings, who are well-treated with fully suppressed viral loads, are choosing to breastfeed their infants, even with these recommendations. The purpose of this article is to review existing research and guidance on infant feeding amongst WLWH in high-income countries and to identify gaps in this evidence that require further investigation. Current evidence on the risk of HIV transmission through breastfeeding in the context of antiretroviral therapy (ART), the significance of cell-associated virus, transmission risk factors, retention in care and adherence postpartum, infant prophylaxis and antiretroviral exposure, and monitoring of the breastfeeding WLWH are summarized. A latent HIV reservoir is persistently present in breast milk, even in the context of ART. Thus, suppressive maternal ART significantly reduces, but does not eliminate, the risk of postnatal transmission of HIV. There are currently limited data to guide the optimal frequency of virologic monitoring and the clinical actions to take in case of maternal detectable viral load whilst breastfeeding. Moreover, retention in care and adherence to ART in the postpartum period may be difficult and more research is needed to understand what clinical and psychosocial support would benefit these mothers so that successful engagement in care can be achieved. The long-term effects of antiretroviral drug exposure in the infants also need further exploration. Thus, there is a need for collecting enhanced surveillance data on WLWH who breastfeed and their infants to augment clinical guidance in high-income settings.

Keywords: breastfeeding, high-income setting, HIV, women.

Introduction

Globally, there were an estimated 17.8 million women living with HIV (WLWH), >15 years of age, in 2016, constituting 52% of all adult people living with HIV (PLWH) [1]. As a result of increased coverage and improved regimens, 80% of the estimated 1.1 million pregnant WLWH received antiretroviral therapy (ART) to prevent transmission to their children, resulting in decreased rates of perinatal HIV transmission worldwide [1]. Despite these improvements, 160 000 children (<15 years old) were newly HIV-infected in 2016 [2].

Perinatal transmission of HIV from mother to child can occur during pregnancy, delivery and breastfeeding [3]. The introduction of different health interventions has markedly reduced perinatal transmission: routine prenatal HIV testing of pregnant women, maternal ART, mode of delivery and infant antiretroviral (ARV) prophylaxis [4]. In high-income settings, WLWH are also advised against breastfeeding; a recommendation that has not changed over time [5–8]. This recommendation of breastfeeding avoidance is based on two fundamental assumptions: there is a risk of breastfeeding-associated transmission, even in the context of ART, and formula feeding is safe in high-income settings [9–11]. The importance of breastfeeding in both low- and high-income settings is well recognized [12], and contrary to the common belief that artificial feeding from birth is without risk in high-income countries, there is a growing body of evidence of increased morbidity associated with formula feeding [13–16]. Furthermore, there is increasing evidence from studies, done in low-income countries, that early and appropriate ART

combined with exclusive breastfeeding results in a low risk of postnatal HIV transmission [10, 11].

Pregnant WLWH receiving lifelong ART may be aware of the new reports of the low HIV transmission rate through breastfeeding and may question the no breastfeeding guidelines [9, 17]. Furthermore, the burden of HIV in many high-income settings disproportionally impacts migrants and immigrants, especially from sub-Saharan Africa [18] where breastfeeding is a cultural norm with important social practices. Formula feeding may therefore be considered unnatural and associated with stigma, as formula feeding may identify them as HIV-infected [9, 19–21]. Some mothers living with HIV may also return to environments where formula feeding may pose a significant risk for the health and well-being of the child [9]. Consequently, stakeholders and researchers have questioned the ethics of maintaining the rigid recommendations about infant feeding in the context of HIV and suggest that it is time to move beyond the hardline counselling against breastfeeding amongst WLWH and into a more open discussion of the risks and benefits of various feeding modalities [9, 17, 22–25].

The purpose of this article is to review existing research and guidance on infant feeding amongst WLWH in high-income countries and to identify gaps in this evidence that require further investigation. A summary of key terms is presented in Table 1.

Maternal antiretroviral therapy

Antiretroviral therapy consists of the combination of ARV drugs to maximally suppress the HIV virus and stop the progression of HIV disease [26]. The goal of ART is to improve the health and lifespan for the person living with HIV, by suppressing the viral load (i.e. the amount of HIV RNA in plasma) to an undetectable level. The viral load is undetectable when the amount of virus in a person's plasma is so low that it cannot be measured by a viral load test [26]. Depending on the country and laboratory, an undetectable viral load may range from <200 to <20 copies per mL. By suppressing the viral load, ART also significantly reduces onward transmission of HIV, for example from mother to child. The results of the ACTG 076 study, published in 1994, showed that maternal treatment with the single ARV drug zidovudine during pregnancy and delivery, as well as postnatal prophylaxis to the infant, could reduce the risk of perinatal transmission of HIV by 68% [27]. Major advances in treatment for pregnant WLWH have been made since then, and current regimens include treatment of HIV infection with a combination of two or more ARV drugs from at least two drug classes [28, 29]. In 2015, the Temprano and START trials showed that early initiation of ART was associated with significant clinical benefits [30, 31], and consequently, the WHO guidelines were updated to recommend immediate initiation of lifelong ART for all persons living with HIV, including pregnant women [26]. The current WHO guidelines recommend initial treatment with tenofovir, lamivudine and dolutegravir (two nucleoside reverse transcriptase inhibitor (NRTI) + one integrase strand transfer inhibitor (INSTI)) as the first-line treatment of HIV amongst adults, including pregnant women [32]. Dolutegravir has recently been associated with an increased risk of neural tube defects amongst infants born to women receiving the drug during the periconception period [33]. Preliminary results from the Tsepamo study in Botswana demonstrated a possible increase in neural tube defects of infants amongst WLWH who conceived whilst on dolutegravir (4/426, 0.9%), compared with infants of women who conceived on nondolutegravir regimens (14/11,300, 0.1%) [33]. Although final study results are pending, the WHO issued a drug safety alert in May 2018 indicating that consideration should be given to avoiding dolutegravir use during the periconception period until more evidence is available [34]. Thus, dolutegravir is not recommended in the first trimester in the USA and Europe, whilst the UK does not recommend dolutegravir in women planning pregnancy and during the first 8 weeks of pregnancy [6–8]. The treatment recommendations for pregnant WLWH in high-income countries is a regimen of two NRTIs, with a nonnucleoside reverse transcriptase Inhibitor (NNRTI), a boosted protease inhibitor (PI) or an INSTI as the preferred third agent [6–8]. Most pregnant WLWH in high-income countries receive ART, due to a high coverage of antenatal HIV screening and the increasing proportion of women already on ART at conception [35, 36]. There is a lack of safety data on most modern ART regimens during breastfeeding, and most studies to date have only examined short-term outcomes [8].

Guidelines on infant feeding in the context of HIV

The WHO guideline on infant feeding in the context of HIV was updated in 2016, recommending that mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding

for up to 24 months or longer whilst being fully supported for ART adherence [37]. This guideline is intended mainly for countries with high HIV prevalence and in settings in which diarrhoea, pneumonia and undernutrition are common causes of infant and child mortality (see guideline for an overview of the current evidence on infant feeding amongst WLWH in low-income countries [37]). However, it may also be relevant to settings with a low prevalence of HIV depending on the background rates and causes of infant and child mortality [37]. In Europe and other high-income settings, WLWH are advised against breastfeeding [5–8]. The contrast between recommendations in low-income and high-income settings has created a challenge for both the WLWH and their healthcare providers [22, 23]. Recently, guidelines from several high-income countries have been updated to recognize this challenge and to acknowledge that WLWH who chose to breastfeed should be supported [5–8]. The European AIDS Clinical Society (EACS) guidelines states that 'We advise against breastfeeding. In case a woman insists on breastfeeding, we recommend follow-up with increased clinical and virological monitoring of both the mother and the infant' [6].

Perceptions of infant feeding amongst women living with HIV

The many benefits of breastfeeding for both the mother and the child are well recognized, and the general public health recommendation in both high- and low-income countries is that 'breast is best' [12]. Qualitative studies, mainly from the UK and Canada, have found that the recommendation not to breastfeed can be a complex recommendation in the context of 'breast is best' and that it may raise unique concerns and challenges for mothers living with HIV [19, 21, 38, 39]. Consequently, some WLWH may choose to breastfeed against medical advice because of social, personal or cultural reasons, or due to stigma, as not breastfeeding may lead to disclosure of their HIV status [19, 21, 24]. For immigrant women breastfeeding may be the cultural norm and formula feeding may be interpreted as a sign of HIV [21].

Moreover, it leads to confusion as to which guideline to follow, because many WLWH in Europe, and other high-income settings, originate from low-income settings, especially from sub-Saharan Africa [18] where breastfeeding is recommended and encouraged. Some women may also follow the discussions in the medical community and social media, such as the Undetectable = Untransmittable (U = U) campaign, launched in early 2016 [40]. A UK study reported that, since 2012, 40 babies born to mothers living with HIV have been breastfed with no transmissions [41]. A recent US study amongst providers caring for WLWH, found that 75% of providers had been asked by a WLWH if she could breastfeed, and 29% reported caring for a patient who breastfed against medical advice [42]. The number of WLWH living in high-income countries who choose to breastfeed is likely to increase over time. Hence, there is a need for collecting enhanced surveillance data on WLWH who breastfeed and their infants, supporting clinical guidance in high-income settings.

Risk of HIV transmission through breastfeeding in the context of antiretroviral therapy

In the absence of maternal ART and infant ARV prophylaxis, the risk of perinatal transmission of HIV ranges from 25% to 40% (from conception to cessation of breastfeeding), when infants are breastfed for up to two years. The risk is 10–15% during the breastfeeding period only [43]. The overall risk of perinatal HIV transmission in the context of ART and other effective prophylactic interventions is reduced to below 1% [4]. To our knowledge, no study has examined the risk of postnatal HIV transmission through breastfeeding in high-income countries. A meta-analysis published in 2017 in relation to the update of the WHO infant feeding guidelines, found six studies in low-income settings in which mothers started ART before or during their most recent pregnancy [11]. The estimated postnatal transmission risk (excluding perinatal transmissions) up to 6 months of age was 1.08% (95% CI 0.32–1.82%), with higher rates from mothers who started ART in the later stages of pregnancy [11]. Two studies reported postnatal transmission up to 12 months of age, and the pooled estimate of postnatal HIV transmission in this analysis was 2.93% (95% CI 0.68–5.18%) [11]. The Promoting Maternal Infant Survival Everywhere (PROMISE) trial, which randomized WLWH with a high CD4 count in Africa and India to either postpartum maternal ART or prolonged infant ARV prophylaxis (until 18 months postdelivery or until cessation of breastfeeding), reported a postnatal HIV transmission risk of 0.3% (95% CI 0.1–0.8%) at 6 months and 0.7% (95% CI 0.3–1.4%) at 12 months, with no difference found in the two arms [10]. A study from Tanzania amongst infants born to mothers on ART and in which maternal

viral load was monitored up to 11 months postdelivery, found no postpartum HIV transmission in virally suppressed mothers [44]. However, 18% of the children died were transferred to another clinic or were lost to follow-up prior to the exclusion of HIV infection.

Thus, successful treatment with ART throughout pregnancy and breastfeeding can significantly reduce, but not eliminate, the risk of HIV transmission through breast milk. However, most studies reported HIV transmission events after discontinuation of maternal ART, so the findings may not be generalizable to mothers who remain on treatment for life. HIV transmission during breastfeeding, despite undetectable HIV RNA in plasma and breast milk, has been reported from a perinatal transmission study amongst 560 women in Botswana. Following a negative HIV-1 test at age 1 month, two infants had a positive HIV-1 result during the breastfeeding period. These transmissions were not associated with a detectable HIV-1 RNA in either maternal plasma or breast milk. However, transmission during the perinatal period cannot be excluded with certainty as both infants received post exposure prophylaxis, which could result in a false negative test result as it suppresses viral expansion and detection in the blood [45].

The significance of cell-associated HIV in breast milk

Both cell-free (RNA) and cell-associated (DNA) virus in breast milk have been associated with transmission of HIV [46, 47] (see Fig. 1). In a case–control study amongst WLWH receiving single dose nevirapine for prophylaxis of HIV perinatal transmission, cell-associated virus load in breast milk was a stronger predictor of the risk of early postnatal HIV transmission, whilst cell-free virus load was a stronger predictor of later postnatal HIV transmission [46]. The effect of ARV drugs seems to be different on cell-free and cell-associated virus in breast milk. Studies comparing HIV cell-free and cell-associated virus in breast milk suggest that ART during pregnancy and after delivery suppresses cell-free but not cell-associated HIV loads

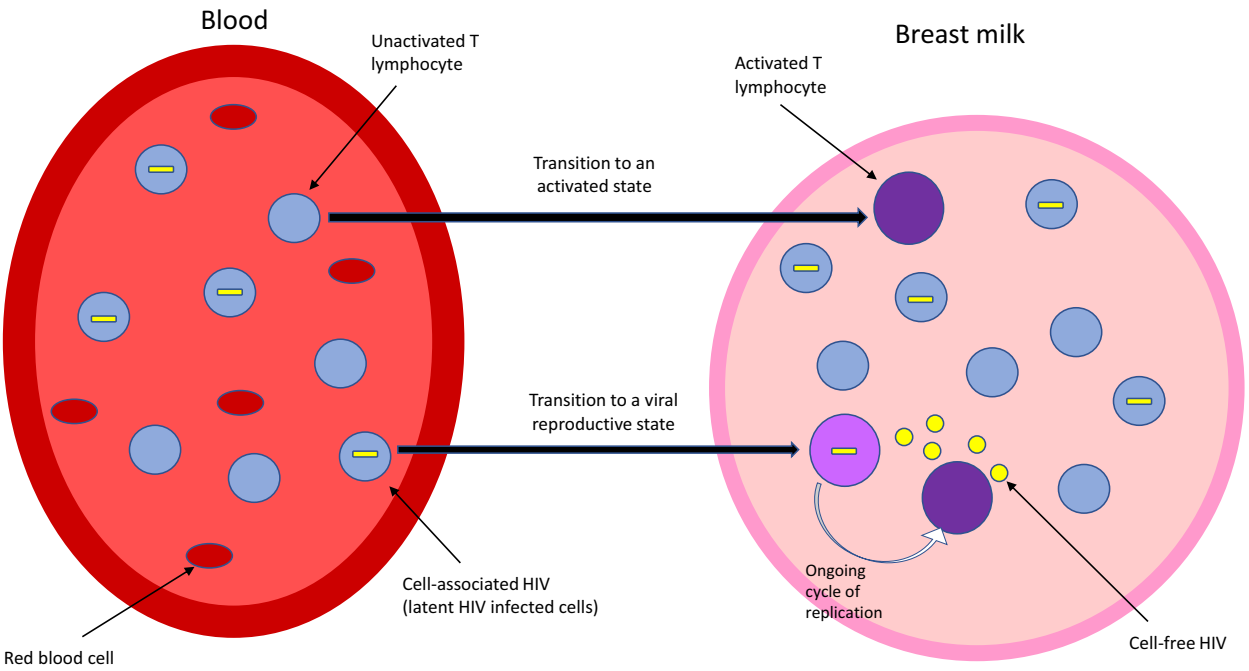

Fig. 1 *Transmission of HIV through breastfeeding in successfully treated women living with HIV. In the blood, combination ART suppress the release of cell free HIV virus (RNA) and inhibit ongoing cycles of replication. However, a cell associated reservoir of HIV (DNA) is persistently present, and in the mammary gland, these cells become activated through extravasation or transepithelial migration. After activation, virus from these stable reservoirs is released into breastmilk. Figure inspired by Van Perre et al. [51].*

in breast milk [48–50]. Thus, a residual CD4+ T cell-associated reservoir of HIV is persistently present in breast milk [49]. These latently infected CD4+ T cells in breast milk of WLWH can transcribe HIV DNA and generate viral particles, and are potentially 17 times more effective than their plasma counterparts in producing HIV antigens [51, 52]. Other cell types in breast milk may also be susceptible to HIV infection, such as macrophages, CD4-positive progenitor T cells and dendritic cells, which could also be involved in transmission [51]. Hence, even in the face of ART, latent reservoirs in breast milk can still replicate and plasma viral suppression does not equate to breast milk viral suppression [49, 51]. However, it is unknown if this holds for women on long-term ART or whether any newer drugs influence these latent T-cells. As ART is being implemented globally to all WLWH, there is an increasing need to better define the viral reservoir in women receiving ARV drugs, to clarify the potential of these cells to produce infectious virus and to define a viral threshold in breast milk for increased transmission risk [53].

Other risk factors for postnatal HIV transmission in women

Factors that increase the risk of HIV transmission via breast milk have mainly been studied in women not on ART and relate to the virus, the mother and the infant. These risk factors are probably also

Table 1. *Summary of key terms*

Antiretroviral (ARV) drugs	Medications for the treatment of infection by retroviruses, primarily HIV. Different classes of antiretroviral drugs act at different stages of the HIV life cycle
Antiretroviral therapy (ART)	The treatment for HIV with a combination of two or more antiretroviral drugs that target different stages of the HIV life cycle
Cell-associated virus	Refers to HIV which lives inside the cell, measured as HIV DNA
Cell-free virus	Refers to parts of the virus (virions) not associated with a cell, measured as HIV RNA
Exclusive breastfeeding	The infant receives no other food or drink, not even water, other than breast milk (which can include expressed breast milk), with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines
Integrase strand transfer inhibitor (INSTI)	Antiretroviral drug that binds to and blocks integrase, an HIV enzyme. Antiretroviral drugs from this class include dolutegravir and raltegravir
Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI)	Antiretroviral drug that binds to and blocks reverse transcriptase, an HIV enzyme. Antiretroviral drugs from this class include nevirapine and efavirenz
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Antiretroviral drug that binds to and blocks reverse transcriptase, an HIV enzyme. Antiretroviral drugs from this class include abacavir, emtricitabine, lamivudine, tenofovir and zidovudine
Perinatal transmission	Transmission of HIV virus from mother to child during pregnancy, delivery or through breastfeeding. Also referred to as vertical transmission
Postnatal transmission	Transmission of HIV to an infant or child after delivery, during the breastfeeding period
Protease Inhibitor (PI)	Antiretroviral drug that blocks protease, an HIV enzyme. Antiretroviral drugs from this class include atazanavir, darunavir and lopinavir
Undetectable viral load/virally suppressed	A person living with HIV is considered to have an 'undetectable' viral load – or to be virally suppressed – when antiretroviral treatment has brought the level of virus in their body to such low levels that blood tests cannot detect it. For most tests used clinically today, this means fewer than 50 copies of HIV per millilitre of blood (<50 copies per mL). Reaching an undetectable viral load is a key goal of ART
Viral load	The amount of HIV RNA in plasma. It indicates how well a person's antiretroviral treatment is working

relevant if the woman is on ART, although to a lesser degree and depending on adherence and viral load suppression.

It is well established that detectable maternal viral load in plasma and advanced maternal disease are significantly associated with HIV transmission through breast milk [54–56]. Longer duration of breastfeeding also increases the risk of transmission [54, 55]. A study amongst WLWH, not on postpartum ART in West and South Africa, found that each additional month of breastfeeding beyond six months of age was associated with a 1% risk of HIV acquisition (95% CI 0.5–1.7) for the infant [57].

Breast health has been associated with postnatal transmission, with breast pathologies such as clinical and subclinical mastitis, and nipple lesions increasing the risk [55, 58, 59]. Infant oral thrush has also been associated with increased transmission risk, but the direction of causality is difficult to establish since early HIV infection may be associated with thrush [55, 58].

Exclusive breastfeeding reduces HIV transmission risk [60], whilst the introduction of solid food increases the risk of HIV transmission significantly. This seems to be especially associated with food given to infants less than 2 months of age [57, 61]. Amongst WLWH not on ART whilst breastfeeding, the estimated risk of HIV transmission through breast milk is 9.0/100 child-years of exclusive breastfeeding and 41.2/100 child-years of breastfeeding plus solid foods [57]. This is most likely because introducing solid foods to the infant alongside the breast milk may damage the already delicate and permeable gut wall of the small infant and allow the virus to be transmitted more easily [62, 63].

Retention in care and adherence to postpartum antiretroviral therapy

Retention in care and poor adherence to maternal ART, particularly in the postpartum period, has been documented in studies from both low- and high-income settings [64]. Postdelivery physical and emotional stresses, including the stresses and demands of caring for a new baby, depression and stigma, might make adherence more difficult [64]. Data from the Swiss HIV cohort study found that amongst 695 pregnancies in which two-thirds of the women were on ART at the time of conception, 34% had delayed clinical visits and 12% were lost to follow-up, that is no clinical visit in the year following delivery [65]. The proportion of women being lost to follow-up was lower amongst women conceiving on ART compared with women initiating ART during pregnancy [65]. A French cohort study including 169 women delivering in 2001 found that 14% of the women had irregular visits and 11% had no clinical visit in the two years following delivery [66]. Decreased adherence can lead to viremia, and consequently, increased risk of postpartum transmission through breastfeeding. A study from South Africa examined patterns of viremia after initial suppression in women starting ART during pregnancy [67]. The study found that up to one-third of women who achieved initial viral suppression experienced detectable viral loads within 1 year postpartum, often with repeated episodes over time [67]. Similar results are reported from European cohorts. In a UK study amongst 321 women initiating ART during pregnancy, who were virally suppressed at delivery, 35% had evidence of viral rebound (>200 copies per mL) up to six months postpartum [68]. Similarly, in a cohort of 700 women in the United States, 56% of women who were suppressed at delivery had a viral load >1000 copies per mL at 12 months postpartum [69]. The parallels across countries in findings for high levels of viremia in WLWH with access to ART during the postpartum period points to intersecting behavioural, social and/or psychological drivers of ART nonadherence during this phase of women´s lives [67]. Hence, postpartum strategies, reminding women that the health and well-being of their child remain connected to their own health, even after delivery, are important to achieve successful engagement into HIV care [70].

Infant prophylaxis with antiretroviral therapy

In most high-income countries, prophylaxis with ARVs is provided to the infant from birth until 4–6 weeks of age if the mother is virally suppressed. If the mother has detectable viral load in plasma prolonged prophylaxis may be provided to the infant [5–8]. Prolonged infant prophylaxis with ARV drugs during breastfeeding has also been suggested as a prevention strategy, both in virally suppressed WLWH in relation to the uncertainty in transmission risk and if the mother has a viral rebound. Two systematic reviews including cohorts from high- and low-income countries found limited, but supportive evidence that prolonged prophylaxis in high-risk infants reduces breastfeeding transmissions, that is in situations where the

mother did not receive any ART, received insufficient treatment or had a detectable viral load prior to delivery [71, 72]. The PROMISE trial found that infant prophylaxis was equally effective as maternal ART in preventing HIV transmission via breast milk [10]. Maternal ART therefore seems to provide sufficient prophylaxis for breastfed infants, however; there is at present no clinical trial of maternal ART plus infant prophylaxis in the context of breastfeeding. Prolonged infant ARV prophylaxis is not recommended in the guidelines from several high-income countries [5, 7, 8]. As lifelong maternal ART is now recommended by WHO, infant prophylaxis regimens are less likely to be used on a large scale [7]. However, infant prophylaxis plus maternal ART could be a feasible approach in situations, where women may not have fully suppressed viral loads or in the event of a detectable maternal viral load [73].

Infant toxicity due to antiretroviral therapy

Breastfed infants born to WLWH on ART may be exposed to long-term low-dose ARVs through breast milk. Exposures to ARVs through breastfeeding seem to result in much lower exposure than established paediatric dosing, and PI concentrations in breast milk are generally lower compared to NRTIs and NNRTIs. However, the clinical relevance of ART concentrations in breast milk is not fully understood [74]. Serious adverse events in infants, due to maternal ART, appear to be relatively uncommon. Two perinatal HIV transmission studies from low-income countries describe no significant difference in serious adverse events observed in infants where the mother was on ART vs infants who received prolonged ARV prophylaxis [10, 75].

There is a lack of safety data on the use of integrase inhibitors in pregnancy and breastfeeding. Individual patient data from the Netherlands has shown transfer of dolutegravir into breast milk, resulting in significant plasma concentrations in the infant [76]. Although several ongoing studies conducted in sub-Saharan Africa, North America and Europe are currently exploring the question of safety of dolutegravir in pregnant WLWH and their infants [77–80], the safety aspect of dolutegravir in breastfeeding women also needs further exploration.

Overall, there is a lack of lactation studies for most ARVs. The pharmacokinetic properties of ART in breast milk and the potential effects of exposure to ARV drugs in the breast milk in infants who do not acquire HIV are therefore poorly understood [17]. Moreover, most studies to date have examined short-term adverse events, and there are little data on whether there might be long-term consequences of these ARV drug exposures.

Infant resistance to antiretroviral therapy

Another concern is the development of HIV resistance in infants should transmission of HIV occur, either from prophylactic treatment or through breast milk exposure. A recent meta-analysis documented increasingly high rates of ARV resistance over the past decade amongst HIV-infected infants and young children exposed to ARVs through prophylactic interventions [81]. The highest proportion of resistance was to NNRTIs followed by NRTIs [81]. The HTPN 046 trial performed in four sub-Saharan countries compared the safety and efficacy of extended infant nevirapine from 6 weeks to 6 months with placebo for the prevention of perinatal HIV transmission. Nevirapine resistance was detected in 75% (6 out of 8) of the infected infants in the nevirapine arm compared with 6% (1 out of 17) in the placebo arm [82]. A secondary analysis from The Kisumu Breastfeeding Study (KiBS) found that 67% of the 24 infants who were HIV-infected by 6 months developed resistance to one or more ARVs, most likely because of exposure through breast milk [83]. Most of the mothers of HIV-infected infants had no HIV drug resistance mutations, and only one mother–infant pair had an overlapping pattern of HIV drug resistance mutations [83]. This suggests that infant ingestion of low concentrations of ARV drugs through breast milk can promote the development of drug-resistant mutations in the infant should transmission occur. Persistence of resistant mutations at low levels has been associated with increased risk of treatment failure in adult European studies [84]. Thus, maternal ART regimen should be considered when choosing treatment regimen for infants who are found to be HIV-infected. Almost all data on drug exposure to breastfed infants come from populations in low- and middle-income settings, prior to the recommendation of treatment for all. More research on infant resistance is needed related to new ARVs and when breastfeeding is occurring in high-income countries.

Counselling and shared decision-making regarding breastfeeding

For WLWH in high-income countries, there are several factors that may impact infant feeding

decisions, including internal, family and societal pressures, and some women may choose to breastfeed with or without the knowledge of healthcare providers [22]. The unique circumstances of mothers living with HIV regarding infant feeding have recently been acknowledged in the guidelines, moving beyond the simple categorical breastfeeding recommended/breastfeeding not recommended to a more supportive and open approach [5–8]. Several experts have also called for a patient-centred, harm reduction approach of counselling WLWH on infant feeding options in high-income countries [23, 24]. Shared decision-making has been proposed in the literature as an ideal process by which infant feeding options should be discussed in the clinic [23, 25]. In this model, the physician and patient exchange and share preferences, considering treatment options in relation to the patient´s beliefs and values. Both parties agree upon what should be the ideal result as it combines the recommendations from the care provider with the unique values and circumstances of the individual woman [85]. However, it is important to recognize that a full discussion about the risks and benefits of breastfeeding may not be relevant for every mother and that information and counselling about breastfeeding should be individualised to each woman´s needs and preferences. [23].

Monitoring of breastfeeding amongst women living with HIV and their infants

Postnatal monitoring if a woman decides to breastfeed is not clear. The EACS guidelines recommend increased clinical and virologic monitoring of both the mother and the infant [6]. The British HIV Association (BHIVA) is more specific, recommending monthly testing of both the mother and the infant if breastfeeding takes place [7]. The US guidelines recommend maternal viral load 1-2 times per month and infant monitoring at standard time-points, following every 3 months, plus after cessation of breastfeeding (exact time-points are not mentioned) [8]. Increased monitoring might improve patient–doctor/clinician relationship and adherence, but it may also lead to an increased perception of being under surveillance, which consequently could affect the psychological and emotional well-being of WLWH who choose to breastfeed [17, 86].

There is no specific data to guide whether HIV viral load should be monitored in plasma alone or in plasma and in breast milk [17]. Important elements are the testing time, the rapid return of test results, and prompt clinical intervention in response to elevated HIV viral load. Ideally, an initial raised viral load in a breastfeeding woman should be detected and followed up within days [87]. There is little guidance in the literature on the clinical action to be taken if a breastfeeding mother has a detectable viral load in plasma or breast milk. Similarly, there is little guidance on what to do in case of maternal breast infection/mastitis. Data from the pre-ART era indicate an increased risk of transmission if the woman has subclinical or clinical mastitis [55, 58, 59]. There are no data on the association between mastitis and transmission amongst women on treatment with a fully suppressed viral load. BHIVA recommends cessation of breastfeeding if the woman has a breast infection/mastitis [7]. However, stopping breastfeeding abruptly is difficult and there may be a production of breast milk for a long time, which could lead to intermittent breastfeeding against medical advice [17]. It is therefore important to counsel the women on how to stop breastfeeding and inform her that she should not initiate breastfeeding once she has introduced formula milk, and of the risks of mixed feeding, especially in case of a detectable viral load [17].

Emerging research questions about women living with HIV and breastfeeding

This review has revealed important gaps in the evidence on infant feeding in the context of HIV in high-income settings with access to reimbursed ART, ARVs and safe formula feeding (see Box 1 for summary). It has been established that postnatal transmission risk is most likely very low, but there is no evidence that it is nil. Cell-associated transmission through breast milk with or without viral suppression does occur [51]. What is less clear, is if the significance of cell-associated virus still holds for women on long-term ART or if any newer ART influences cell-associated virus. The long-term adverse effects of infant ARV drug exposure through breast milk and/or prophylaxis are also not well understood.

It is increasingly being recognized that women´s responses to the recommendation to not breastfeed may be complicated and that WLWH might choose to breastfeed against medical advice because of social-, personal- or cultural-reasons or due to stigma. However, there is limited guidance on optimal frequency of virologic monitoring and the clinical actions to take in case of maternal detectable HIV RNA whilst breastfeeding. Moreover, the

Box 1. Summary of key issues in breastfeeding among women living with HIV in high-income settings

Perceptions of infant feeding among WLWH

- The recommendation to not breastfeed may raise unique concerns and challenges for mothers living with HIV
- An increasing number of WLWH in high-income countries are choosing to breastfeed
- WLWH may choose to breastfeed because of social, personal or cultural reasons, or because of stigma
- Collection of enhanced surveillance data on WLWH who breastfeed, and their infants is essential for the provision of evidence-based clinical guidance in high-income settings

Risk of HIV transmission through breastfeeding in the context of ART

- No study has examined the risk of transmission through breastfeeding in high-income countries
- Studies from low-income countries report low postnatal transmissions rates in the context of ART
- Successful treatment with ART significantly reduces the risk of postnatal transmission, but does not eliminate the risk
- Current research findings may not be generalizable to WLWH on lifelong treatment

The significant of cell-associated HIV in breast milk

- Both cell-free (RNA) and cell-associated (DNA) virus in breast milk have been associated with transmission of HIV
- ART during pregnancy and delivery suppresses cell-free but not cell-associated HIV virus in breast milk
- A reservoir of latent CD4+ T cells persist in breast milk, even if the WLWH has an undetectable viral load in plasma
- There is a need to better define the viral reservoir in WLWH on lifelong ART
- There is also a need to examine how newer ARV drugs influence these latent T cells

Risk factors for postnatal transmission of HIV

- Mainly studied in WLWH not receiving lifelong ART
- Detectable maternal viral load, advanced maternal disease, breast pathologies and longer duration of breastfeeding are associated with an increased risk of transmission in WLWH not on lifelong ART
- Mixed feeding, that is the introduction of other fluids or solid foods increases the risk of postnatal HIV transmission, especially when food is given to infants less than two months of age.
- More research is needed on the risk factors for postnatal transmission in WLWH on lifelong ART.

Retention in care and adherence to postpartum treatment

- Retention in care and adherence to ART in the postpartum period may be difficult
- More research is needed to identify the optimal postpartum strategy for supporting WLWH in engagement into HIV care, including qualitative research elucidating the perspective of the mothers.

Prolonged infant prophylaxis with ARV

- Maternal ART seems to provide adequate prophylaxis for breastfed infants
- Prolonged infant prophylaxis with ARV during breastfeeding may be a feasible approach in situations, where the woman is not virally suppressed or in the event of a detectable viral load
- There is limited data to define optimal prophylaxis for the breastfed infant whose mother has an undetectable viral load
- There is also limited data to define the optimal infant prophylaxis to be given in the event of maternal detectable viral load

Box 1 (*Continued*)

Infant toxicity due to antiretroviral therapy

- Infants born to WLWH on ART may be exposed to long-term low-dose exposure ARVs through breast milk
- The clinical relevance of the specific ARV drug concentrations is not well understood
- Serious adverse events in infants exposed to ARVs through breast milk appear to be relative uncommon
- The potential effects of exposure to newer ARV drugs in breast milk are not well understood
- More research is needed on the long-term consequences of ARV exposure through breast milk

Infant resistance to ARV

- Exposure to low concentrations of ARV drugs through breast milk may lead to the development of drug-resistant mutations in the infant should transmission occur
- Persistence of resistant mutations at low levels may be associated with increased risk of treatment failure
- Maternal ART regime should be considered when choosing treatment regime for infants who are infected with HIV
- More research related to infant resistance is needed to new ARVs and also when breastfeeding is occurring in high-income countries

Counseling and shared decision-making regarding breastfeeding

- Several factors may impact infant feeding decisions among WLWH, including internal, family and societal pressures
- Shared decision-making has been proposed as the ideal process by which infant feeding options should discussed in the clinic
- A full discussion about the risks and benefits of breastfeeding may not be relevant for every mother
- More research is needed to determine if there are different subpopulations of women who wish to breastfeed (or who choose to breastfeed) that may require different models of care

Monitoring of breastfeeding among WLWH and their infants

- There is limited guidance on the optimal postnatal monitoring for WLWH who decide to breastfeed
- The frequency of virologic monitoring and the clinical action to take in case of maternal detectable viral load while breastfeeding is not clear
- There are no data to guide the clinical response to maternal breast infection /mastitis
- Qualitative research could elucidate maternal practices and attitudes with breastfeeding in the context of HIV

ART, antiretroviral therapy; ARV, antiretroviral; WLWH, women living with HIV.

significance of mastitis and breast health, when the mother is virally suppressed, is not known.

Postnatal retention in care and adherence can be difficult for some women, and more research is needed to understand the motivations for breastfeeding and issues related to ART adherence, so that the optimal clinical and psychosocial support to these mothers can be identified. It is likely that there are different subpopulations of women who wish to breastfeed, including women who have migrated from low-income countries where breastfeeding is the cultural norm, and those born in high-income countries, and they may require different models of care [17].

Conclusion

At present, breastfeeding is not actively recommended to women living with HIV in high-income settings with access to safe formula feeding. Suppressive maternal ART significantly reduces, but does not eliminate, the risk of postnatal transmission of HIV through breastfeeding. However, it is

important to recognize and acknowledge that some women living with HIV may wish to breastfeed their infant, in which both the healthcare providers and the women need evidence-based information about the risks and benefits to enable an informed decision. Currently, there is insufficient evidence to guide the clinical and virologic monitoring of the breastfeeding woman living with HIV and her infant, and for the action to be taken in case of mastitis or if the woman has detectable viral load.

Authorship contribution

Both authors have substantially contributed to the conception and design, analysis and interpretation of data. EM has drafted the manuscript, which has been critically revised by NW. Both authors have approved the final version.

Conflict of interest

The authors have no conflicts of interest to declare.

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