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Review Article

Breastfeeding and women living with HIV: Is it possible to move beyond the avoidance?

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Abstract

The risk of mother-to-infant transmission of HIV 1 during breastfeeding ranges from 10% to 15% in the absence of maternal Antiretroviral Therapy (ART) and infant Antiretroviral (ARV) prophylaxis. WHO guidelines 2016 recommend women living with HIV and fully supported for ART adherence should breastfeed for at least 12 months and up to 24 months or longer. Anyway, in high-income settings, women living with HIV are suggested to avoid breastfeeding, regardless of maternal viral load or antiretroviral therapy status. The advantages of breastfeeding in low and middle-income settings are well recognized. This brief narrative review aims to summarize existing evidence on mechanisms and risk factors for HIV transmission during breastfeeding and the possible prevention strategies in the context of ART adherence.

Introduction

Perinatal HIV transmission may occur during pregnancy, delivery, and breastfeeding [1]. The risk of mother-to-infant transmission of HIV 1 during breastfeeding ranges from 10 to 15% in the absence of maternal Antiretroviral Therapy (ART) and infant Antiretroviral (ARV) prophylaxis.

Newborn ARV regimens should be started preferably within 6 hours of delivery. 4-week Zidovudine (ZDV) prophylaxis regimen can be used in low-risk newborns whose mothers received ART during pregnancy and had viral suppression within 4 weeks prior to delivery. High-risk newborns should receive a presumptive HIV therapy based on ZDV, lamivudine (3TC) and Nevirapine (NVP) (treatment dose) or ZDV, 3TC, and Raltegravir (RAL) administered from birth up to 6 weeks [2].

However, the overall risk of perinatal transmission decreases to 1% thanks to ART and other prophylactic interventions [3]. Among these, the United States Department of Health and Human Services (DHHS) strongly recommends women living

with HIV avoid breastfeeding, regardless of maternal viral load or antiretroviral therapy status [4], due to the safety of formula feeding in high-income settings.

On the other hand, the importance of breastfeeding in low- and middle-income countries is well recognized not only because it provides optimal nutrition but also because it reduces the risk of malnutrition, diarrhea, and respiratory illness [5].

According to WHO guidelines 2016 women living with HIV and fully supported for ART adherence should breastfeed for at least 12 months and for up to 24 months or longer [6].

Breastfeeding can be considered a total nutritional and emotional bond between mother and newborn and represents a powerful source of health benefits for children and mothers [7]. Concerning the newborns, some authors described short-term effects such as the reduction of mortality and morbidity (diarrhea, respiratory infections, and otitis media) [8-10] and long-term effects (an increase of intelligence quotient, reduction of overweight or obesity, type 2 diabetes and of

childhood leukemia) [11-13]. Data concerning the protection against allergic disorders are unclear [14]. Among the mother's advantages, breastfeeding seems to have a protective effect on breast and ovarian cancer (due to prolonged amenorrhea) [15].

Considering the importance to avoid breastfeeding only if there is a real risk for the newborns, with this brief review we aimed to summarize existing evidence on mechanisms and risk factors for HIV transmission during breastfeeding and the possible prevention strategies in the context of ART adherence.

Methods

This is a narrative review. A literature search was conducted in Medline, EMBASE, and PubMed as electronic databases, using a combination of the following keywords and text words "HIV", "Transmission", "Breastfeeding", "lactation duration", "antiretroviral therapy", "ART".

We included only articles published from 2012 to 2022 and written in the English language. A review of articles also included the abstracts of all references retrieved from the search.

Mechanisms of transmission

Cell-free (RNA) and cell-associated (DNA) shedding of HIV-1 virus in breast milk are both involved in postnatal transmission. Ndirangu, et al. [16] conducted a case-control study involving thirty-six HIV-positive mothers who transmitted HIV-1 by breastfeeding and thirty-six non-transmitting HIV-1 infected mothers and demonstrated that cell-associated virus level (per ml) is more important than cell-free virus during the early post-partum period (6 weeks). Actually, the antiretroviral therapy suppresses the release of cell-free HIV virus (RNA) and inhibits ongoing cycles of replication, but a cell-associated (CD 4+ T lymphocytes) reservoir of HIV (DNA) remains in the mammary gland and may be activated after extravasation or transepithelial migration. These cells may release viral particles which are considered 17 times more effective in producing HIV antigens than plasma ones [17].

Other cell types, such as macrophages, CD4-positive progenitor T cells, and dendritic cells can be infected in the breast and may play a role in transmission [18].

The effect of long-term ART on these latent cells is still unclear; moreover, a viral threshold in breast milk associated with an increased risk of transmission has not been defined yet.

Risk factors of transmission

A detectable maternal viral load in plasma and advanced maternal disease are strongly associated with HIV transmission through breastfeeding [19,20].

Poor adherence to maternal ART has been described in studies from both low- and high-income settings, in particular among women starting ART during pregnancy. It may lead to a viral rebound up to six months after delivery [21]. There is also a nearly ten-fold higher risk of HIV transmission when

the mother starts ART after childbirth due to a delay in the diagnosis [22].

Moreover, some authors investigated the importance of the duration of breastfeeding and reported that infants breastfed for more than 6 months by women living with HIV in West and South Africa, not undergoing ART, have more than 1% of risk being infected [23].

On the other side, the introduction of solid food before 2 months of age, is associated with a significant increase in the risk of transmission because of the potential damage to the gut wall which makes easy the passage of the virus [24]. In the same way, an infant oral thrush is meant to be a risk factor for transmission, but, unfortunately, also one of the first clinical signs of early HIV infection [25].

Moreover, breast health is necessary for safe breastfeeding. Unfortunately, the concept of subclinical mastitis (SCM) in humans is still poorly understood [26].

Some authors describe this condition as a local inflammation without symptoms, which leads to an increased membrane permeability. Moreover, these inflammatory processes of the mammary gland lead to considerable changes in the breast milk immune factors [27]. Rutagwera, et al. [28] conducted a longitudinal sub-study (nested in the ANRS12174 randomized trial (NCT00640263)) including 270 breastfeeding mothers in Lusaka, Zambia, and reported that SCM is common among breastfeeding HIV-1 positive mothers later during the breastfeeding period (beyond 14 weeks) and characterized by a Na⁺/K⁺ ratio of 1. Then, severe SCM, characterized by a Na⁺/K⁺ ratio > 1, is commonly associated with an increase of pro-inflammatory cytokines in the mammary gland and a higher risk of HIV transmission due to the virus shedding in breast milk. Anyway, the impact of HIV on milk immune factors remains still unclear. Schaub, et al. conducted a cross-sectional study involving 40 HIV-infected women. They reported a higher concentration of IP-10 (inflammatory protein 10) and MIG (monokine induced by gamma interferon), which provide antiviral defense, associated with a lower and impaired capacity to face SCM, and this condition is meant to contribute to facilitating HIV transmission by breastfeeding [29].

Possible prevention strategies

The most useful tool to promote breastfeeding and prevent HIV mother-to-child transmission is antiretroviral therapy. Pregnant women living with HIV are recommended to use a regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase Inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI) as the preferred third agent. [30]. Dolutegravir is reported to be associated with neural tube defects [31,32], so it is not recommended during the first trimester in the US, Europe, and the UK [33,34]. Even if data concerning the safety of ART during breastfeeding are limited (1;27), nowadays it is considered safe for both mother and children, since they are exposed to a lower ARV dose than pediatric established one [22]. A possible consequence of the



ingestion of low concentrations of ARV drugs consists in drug resistance mutations, which may lead to a failure of therapy in adulthood [35,36].

Moreover, WHO also suggests extending the prophylaxis with Zidovudina and Nevirapina in high-risk infants for 12 weeks after delivery (instead of 4-6 weeks after delivery) [37].

However, the PROMISE trial found that infant prophylaxis was equally effective as maternal ART in preventing HIV transmission via breast milk [38].

According to the PROMISE trial results, no clinically relevant differences concerning the growth (length, weight, and head circumference measures) have been observed between the group exposed to mother ART and the group exposed to Nevirapine prophylaxis.

Nevertheless, Stranix-Chibanda, et al. evaluated the effect of the exposure during breastfeeding to tenofovir-containing ART on maternal bone mineral density in comparison with infants treated with nevirapine prophylaxis and they reported a decrease in bone mineral density 74 weeks after the delivery in women belonging the tenofovir- ART arm [39].

Data concerning a safe duration of breastfeeding are not still available. However, according to a recent update of WHO, based on the success of the Option B plus strategy introduced in 2016 [40], HIV+ women should continue to breastfeed for at least 12 months, but ideally for up to 24 months or longer while remaining fully ART adherent [35]. Breastfeeding should be promptly stopped in case of mastitis [34].

The best way to perform postnatal monitoring during breastfeeding is still not well defined [41]. The British HIV Association (BHIVA) recommends testing monthly for both the mother and the infant [34], while the US guidelines recommend a maternal viral load 1-2 times per month and infant monitoring at standard timepoints, following every 3 months and after cessation of breastfeeding [42]. This strict monitoring may lead to improving the patient-doctor/clinician relationship and adherence to therapy. Data regarding the better sample (plasma alone or both plasma and milk) for monitoring HIV viral load are still not available [43].

Limitations of the study

This is a narrative brief review. A comprehensive search was conducted but the majority of the studies deal with low- and middle-income countries. The heterogeneous nature of the interventions and variability in outcomes reported make it difficult to combine studies statistically.

Conclusion

According to our findings, in presence of a suppressed viral load and strong adherence to ART, the risk of HIV transmission through breastfeeding is extremely rare. A more supportive and open approach should be introduced to move beyond the avoidance of breastfeeding both in high-income and low/middle-income settings. Tailored counseling, regarding

the risks and benefits of breastfeeding, taking into account the patient's cultural background, should be recommended. Anyway, in the case of breastfeeding, close viral load monitoring is mandatory.

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