Human Immunodeficiency Virus and Breastfeeding

Clinical Considerations and Mechanisms of Transmission in the Modern Era of Combined Antiretroviral Therapy

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KEYWORDS

• HIV • Breastfeeding • Antiretroviral therapy (ART) • Risk reduction

KEY POINTS

- Postnatal human immunodeficiency virus (HIV) transmission through breastfeeding is a rare event when risk reduction strategies are in place.
- Cell-associated HIV in breast milk may be a source of transmission in the setting of sustained undetectable maternal viral load.
- The "gut-breast" axis plays an important role in potential mechanisms of increased transmission in the setting of mixed breast feeding and is a critical area for future studies.

INTRODUCTION

The optimization and widespread use of combined antiretroviral therapy (cART) have significantly transformed the landscape of human immunodeficiency virus (HIV) care during pregnancy and through the postpartum period. Without cART, the risk of HIV transmission through breastfeeding is estimated to be around 15%, depending on several factors including maternal HIV viral load, breastfeeding duration, and feeding practices.[1,2] Consequently, historic guidelines have recommended a zero-risk strategy in high-income settings where infant formula is widely accessible, advising replacement feeding with formula or banked, pasteurized donor human milk for women living with HIV (WLHIV). However, with sustained cART-induced HIV viral

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suppression, transmission of HIV through breastfeeding has become exceedingly rare, dropping to less than 1%.[3–5] Reflecting advancements in cART, the American Academy of Pediatrics (AAP) and the United States Department of Health and Human Services (DHHS) Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission have made pivotal changes in clinical guidance to support breastfeeding for WLHIV with sustained undetectable viral loads throughout pregnancy and postpartum.[6,7] Similarly, the British HIV Association, the European AIDS Clinical Society, and other high-income countries have developed formal guidance to support breastfeeding as an option for WLHIV.[8–11]

This review examines the current state of knowledge on HIV transmission through breast milk in the cART era. The authors explore the risk factors and transmission mechanisms relevant to WLHIV with sustained viral suppression, identify research gaps with direct implications for clinical practice, and highlight risk reduction strategies employed globally.

STATEMENT OF INCLUSION

The authors endorse a broad perspective on gender and acknowledge the challenges posed by gender bias in health care. We also recognize the historic underrepresentation of women in HIV research. Consequently, we will use the term “women” to refer to individuals assigned female sex at birth, which may include people of other gender identities (transgender male individuals and nonbinary individuals). The term “breastfeeding” denotes the act of feeding a child with milk produced from human mammary glands. We acknowledge that some transgender and nonbinary individuals may prefer the term “chest feeding” and that medical providers should consider an individual’s preference of terminology when providing patient care. Our goal is to respect and honor people of diverse gender identities within the scope of this review.

EPIDEMIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS TRANSMISSION THROUGH BREASTFEEDING IN THE COMBINED ANTIRETROVIRAL THERAPY ERA

Without maternal cART, breast milk transmission (BMT) risk is estimated to be around 15% (95% confidence interval [CI] 7, 22%).[12] Clinical risk factors associated with BMT identified in studies from the pre-cART era include elevated maternal plasma and breast milk HIV viral load, low maternal CD4+ T-cell count, and early introduction of formula or solid foods (“mixed feeding”; **Fig. 1**).[13–16] Risk is higher during early lactation (~6% in the first 4–6 weeks), with ongoing risk of transmission risk estimated at 0.9% per month for the duration of breastfeeding.[1,13] Maternal cART initiated during or before pregnancy is associated with lower rates of BMT, but estimates vary by geographic region and timing of maternal cART initiation. A meta-analysis of 6 studies in low-income settings found low rates of BMT among mothers on cART during the first 6 months of breastfeeding (1.1% [95% CI 0.3, 1.9%]); not all mothers had documented sustained viral supression.[5] Maternal cART discontinuation, detectable plasma or breast milk HIV RNA, and lack of sustained plasma viral suppression have been associated with BMT in the context of maternal access to cART.[5,17] A secondary analysis of the Breastfeeding, Antiretrovirals, and Nutrition study in Malawi found that detectable HIV viral load in plasma (>40 copies/mL) was associated with 40-fold increased risk of infant transmission (hazard ratio [HR] 40 [95% CI 15, 107]); detection of HIV in maternal breast milk (>56 copies/mL) was associated with approximately 8-fold higher risk of infant transmission (HR 7.8 [95% CI 3.1, 19.2]). No transmission events occurred in this study when maternal plasma viral load remained below 100 copies/mL.[17] In published studies including over 3000 mother–infant pairs with

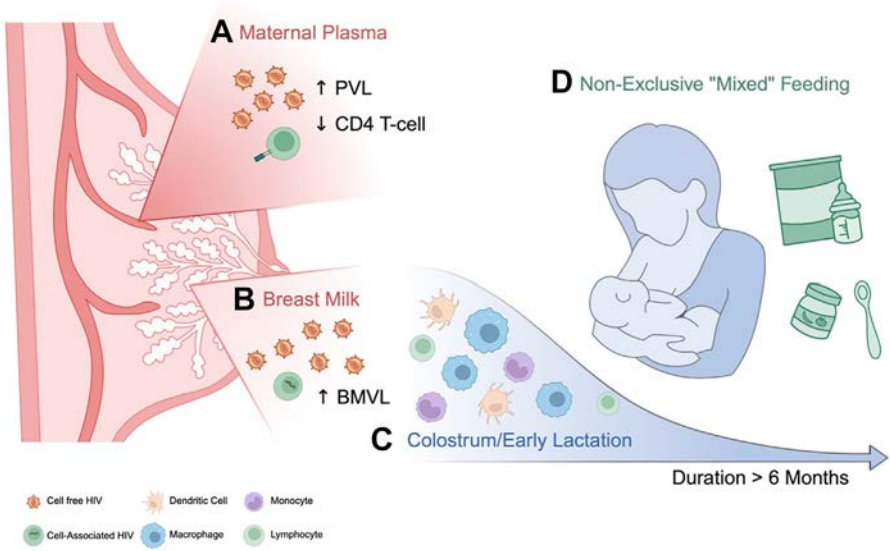

Fig. 1. Risk factors for infant HIV transmission through breastfeeding. (A) Elevated maternal plasma viral load (PVL) and diminished CD4 T-cell counts increase risk of BMT. (B) Breast milk viral load (BMVL) including cell-free and cell-associated HIV is associated with increased risk of BMT.[13–16] (C) Longitudinal analyses have demonstrated higher BMVLs in the first few weeks of breast feeding, possibly related to the increased cellularity of colostrum and early lactation.[53,84] However, cumulative exposure is also an important risk factor.[5,16,68] (D) Mixed breastfeeding (MBF) has been consistently shown to increase transmission risk in the pre-cART era.[58–61] (Created with BioRender.com.)

detailed data on BMT timing and serial maternal viral load monitoring in the era of cART, a total of 19 BMT cases occurred under the following conditions: maternal plasma viral load greater than 50 copies/mL (n = 10), report of poor maternal ART adherence (n = 2), or maternal cART initiation less than 3 months prior to delivery (n = 7) (**Table 1**).[3,18–22] Of note, for 3 BMT transmission cases, mothers had sustained viral suppression (>3 months) prior to the detection of HIV infection of their infants, but maternal cART was started late during the third trimester of pregnancy and mothers had detectable plasma or breast milk viral loads in the early postpartum period. For example, an infant from the DolPHIN-2 trial had confirmed HIV infection at 18 months of age after serial negative HIV PCR tests from delivery through the age of 12 months. While the mother of this infant had documented viral suppression less than 50 copies/mL for 6 months before the infant's HIV was diagnosed, the mother did not achieve viral suppression until 12 weeks postpartum.[22,23] No infant transmission events have been reported among mothers who initiated cART preconception and demonstrated sustained viral suppression throughout pregnancy and breastfeeding[21,24–32] (see **Table 1**).

MECHANISMS OF BREAST MILK TRANSMISSION

For BMT to occur, HIV virions must first bypass the mammary epithelium, remain infectious within the breast milk, traverse infant mucosal barriers, and establish infection in the infant oropharynx or gastrointestinal (GI) tract.[33] This route involves a complex

Table 1
Breast milk transmission

Maternal cART Initiation	Study	Population *(N, Location)*	Timing and Type of cART *[Duration Median (IQR)]*	Breastfeeding Practices *(Duration Median [IQR])*	Infant BMT *(Overall rate, transmission details)*
Postpartum	PROMISE Flynn et al,[3] 2018	N = 1220 Sub-Saharan Africa India	7–14 d PP (N = 527) 2nd/3rd Trimester (N = 648) • 26 w GA (IQR 21, 31) LPV/r + (AZT/3 TC) or (TDF/FTC)	EBF/MBF not specified	7/1219 (0.6%) • 1 infant HIV+ at 3 m; MPVL <40 c/mL Prior MPVL >200 c/mL at delivery, PVL>50 c/mL 6 w PP • 1 infant HIV+ at 9m; MPVL <40 c/mL; Prior MPVL <40c/mL at 14 w, 26 w PP, MPVL >200 c/mL at delivery, 6 w PP • 5 infants HIV+, MPVL >200 c/mL (median 13,479 c/mL)
Pregnancy	Mma Bna Shapiro et al,[19] 2010	N = 527 Botswana	2nd/3rd Trimester • 26–34 w GA LPV/r or ABC + (AZT/3 TC)	EBF (93%)/MBF	2/517(0.4%); 10 LTFU • 1 infant HIV+ at 3 m, MPVL and BM VL <50 c/mL Prior MPVL at delivery 257 c/mL, MPVL and BMVL <50 c/mL at 1 m PP • 1 infant HIV+ at 3 m, MPVL and BMVL <50 c/mL Prior MPVL at delivery <50, PVL and BMVL at 1 m PP <50 c/mL. Mother reported cART adherence challenges
	Safe Milk for African Children (SMAC) Giuliano et al,[20] 2013	N = 288 Malawi	2nd/3rd Trimester • 26w GA (IQR 24, 30) • 83 d (IQR 62, 87) AP among BMT NVP+ (AZT/3 TC) or (d4T/3 TC)	EBF 26w (IQR 25, 26)	6/278 (2.1%) • 1 infant HIV+ at 3 m, MPVL <40 c/mL, BMVL 90 c/mL Prior MPVL and BMVL <40 c/mL at 1 m PP • 1 infant HIV+ at 12 m, MPVL <40 c/mL, BMVL unknown Prior MPVL<40 c/mL at 1 m, 3 m, 6 m PP; BMVL 293 c/mL at 1 m PP, BMVL <40 c/mL at 3 m, 6 m PP • 4 infants HIV+, maternal PVL >200 c/mL
	Tshilo Dikotla Study Volpe et al,[85] 2022	N = 247 Bostwana	2nd/3rd Trimester • 16–36 w GA DTG or EFV + (TDF/FTC)	EBF/MBF All: 24.7 w (range .1, 86) EBF: 18 w (range 0, 41)	0/247 (0.0%)
	DOLPHIN-2 Malaba et al,[22] 2022	N = 268 South Africa, Uganda	3rd Trimester • 55 d (IQR 33, 77) AP EFV or DTG + (TDF/FTC) or (TDF/3TC)	EBF/MBF	1/242 (0.4%) • 1 infant HIV+ at 18 m, MPVL <50 c/mL Prior MPVL 69 c/mL at 6 w PP, 126 c/mL at delivery and 24 w PP

Preconception	KIULARCO Luoga et al,[18] 2018	N = 228 Tanzania	3rd Trimester/preconception • 23 m (IQR 4, 52) AP EFV+ (TDF/FTC) or (TDF/3 TC)	EBF/MBF 52 w (IQR 41, 54)	2/186 (1%); 19 LTFU; 18 Died • 1 infant HIV+, MPVL 144,111 copies/mL at 5 wk PP • 1 infant HIV+, mother discontinued cART
	Crisinel et al,[24] 2021	N = 20 Switzerland	Preconception (18), 1st trimester (2)	EBF/MBF 6.3 m (IQR 2.5, 11.1)	0/20 (0%)
	Nashid et al,[25] 2020	N = 3 Canada	Preconception	EBF/MBF	0/3 (0%)
	ISOSS[28] 2022	N = 150 England	Preconception/Pregnancy	EBF/MBF 56 d (IQR 23 d, 140 d)	0/106 (0%)
	Yusuf et al,[27] 2021	N = 10 US	Preconception	EBF 4.4 m (1.0, 8.5)	0/10 (0%)
	Koay et al,[31] 2022	N = 7 US	Preconception/Pregnancy	EBF/MBF 2 w–6 m	0/7 (0%)
	Prestileo et al,[29] 2022	N = 13 Italy	Preconception (9), 1st trimester (4) LPV/r or RAL + (TDF/FTC)	EBF/MBF not specified 5.4 m	0/13 (0%)
	Weiss et al,[30] 2022	N = 30 Germany	Preconception INSTI, NNRTI, or PI-based cART	EBF/MBF 2 w–12 m	0/22 (0%); 8 LTFU
	Levison et al,[26] 2023	N = 72[a] US and Canada	Preconception (62)/Pregnancy INSTI, NNRTI, or PI-based cART	EBF/MBF 24 w (range 1 d, 72 w)	0/68 (0%); 4 LTFU
	Abuogi et al,[32] 2023	N = 13 US	Preconception (11)/Pregnancy • 39 w (37, 40) AP	EBF/MBF 62 d (16, 188)	0/10 (0%)
	Boyce et al,[21] 2024	N = 7 US	Preconception/pregnancy	EBF/MBF 2 m–20 m	1/7 (14%) • 1 Infant HIV+ at 17 m, MPVL 5.9 million c/mL, LTFU after 4 w

Abbreviations: 3 TC, lamivudine; AP, antepartum; AZT, zidovudine; BMT, breast milk transmission; BMVL, breast milk viral load; cART, combination antiretroviral therapy; d, days; DTG, dolutegravir; EBF, exclusive breastfeeding; EFV, efavirenz; FTC, emtricitabine; GA, gestational age; LPV/r, lopinavir/ritonavir; m, months; MBF, mixed breastfeeding; MPVL, maternal plasma viral load; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NSTI, integrase strand transfer inhibitor; NVP, nevirapine; PI, protease inhibitor; PP, postpartum; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; w, weeks; y, years.

[a] N, 51 unique cases not reported by Yusuf, Koay or Abuogii.

interplay of HIV viral dynamics with maternal and infant immunologic and microbiologic factors that shape transmission risk (**Fig. 2**).

Human Immunodeficiency Virus Viral Dynamics in Breast Milk

Breast milk of WLHIV contains both cell-free and cell-associated viruses. Cell-free HIV RNA is detected in over half of WLHIV in the absence of cART and is strongly positively associated with concurrent plasma RNA levels.[34] Documented temporal correlation of intermittent HIV RNA in plasma and breast milk suggests that cell-free virus in breast milk arises from plasma transport, though local replication and/or virion production may also occur.[34,35] HIV infects several types of cells in breast milk, including CD4+ T-cells, macrophages, and mammary epithelial cells.[33] The cellular composition of breast milk is dynamic overtime; overall cellularity is higher in colostrum and early breast milk, but frequencies of T lymphocytes and macrophages can fluctuate in response to pathogen exposure and hormonal changes.[33] The CD4+ T-cell reservoir is thought to be primarily responsible for cell-associated BMT, but HIV-infected macrophages and epithelial cells may facilitate cell-to-cell T lymphocyte infection and contribute to HIV viral persistence in breast milk.[33] Cell-associated HIV DNA in breast milk independently predicts transmission after adjusting for plasma and breast milk cell-free viral load from pre-cART studies.[36] Sequence analysis of viral envelope fragments in maternal breast milk and plasma of infants who acquired HIV postnatally suggested that transmission from cell-associated HIV DNA in breast milk occurs throughout early and late breastfeeding periods, whereas cell-free HIV RNA was associated only with infant transmissions that occurred after 9 months of breastfeeding.[36]

Treatment with cART suppresses cell-free RNA in both plasma and breast milk, but cell-associated DNA can persist in latent memory CD4+ T-cells or macrophages after cART initiation and is a potential source for BMT.[33–35,37] Studies characterizing cell-associated HIV reservoirs in breast milk among women with long-term viral suppression are lacking; proviral DNA levels in breast milk after cART initiation have been followed for less than 6 months.[33–35,37] In addition, latent CD4+ T-cell reservoirs in breast milk may have a lower activation threshold for latency reversal and more robust production of replication-competent HIV virions. In vitro activation resulted in a higher number of HIV Gag-secreting cells in breast milk compared to peripheral blood (500 vs 45), even when the quantity of HIV DNA was comparable between compartments.[38]

Mastitis, or breast inflammation, is known to influence breast milk HIV viral dynamics. Mastitis is characterized by compromised epithelial barriers, enhanced recruitment and translocation of neutrophils, macrophages, lymphocytes, and elevated levels of cell-free HIV RNA in breast milk in pre-cART studies.[15,35,39,40] Subclinical mastitis, as measured by the ratio of sodium to potassium (Na:K) and/or neutrophil count, was associated with higher levels of cell-free HIV RNA but not cell-associated HIV DNA among mothers not taking cART.[41] Clinical circumstances leading to mastitis, such as infrequent breast emptying or rapid weaning, should be avoided among WLHIV as a precaution, although it is unknown if mastitis induces virus production from breast milk cellular reservoirs and/or an influx of virus-containing cells into the milk in the setting of cART.[42–44]

The Influence of Breast Milk Immunity on Human Immunodeficiency Virus Transmission

Studies from the pre-cART era demonstrate that innate and adaptive immune responses in the breast milk compartment influence HIV replication and the risk for BMT. Innate immune factors in human milk such as mucins, lactoferrin, and bile salt stimulating lipase inhibit cell-free HIV replication but are less protective against cell-

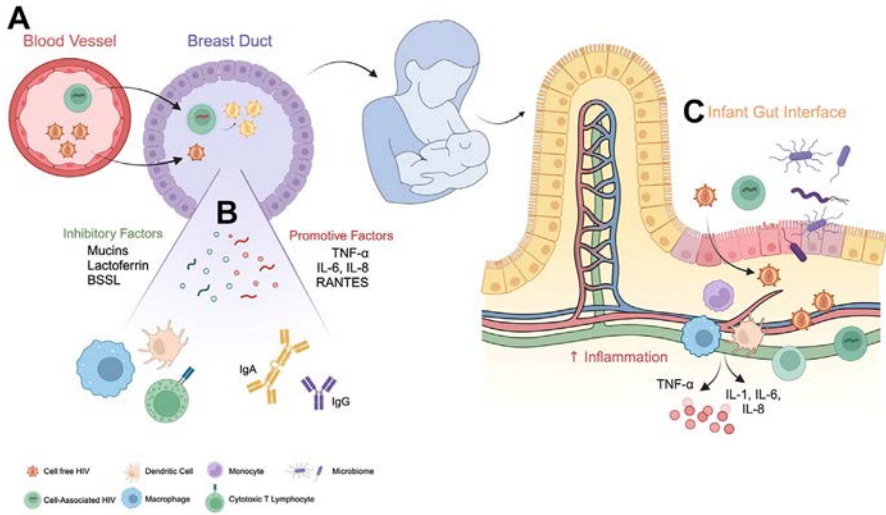

Fig. 2. Maternal and infant immune factors that impact postnatal HIV transmission through breast milk. (A) The mammary epithelium prevents HIV entry, maintaining at least a 100 fold lower HIV RNA level compared to plasma.[48] (B) Breast milk contains inhibitory factors, including innate components (lactoferrins, homeostatic cytokines, and mucins) that may protect against cell-free HIV replication.[45–47] Pro-inflammatory cytokine profiles (TNF, IL-6, IL-8 and RANTES) are associated with increased risk for BMT.[49,50] HIV-specific cytotoxic T lymphocytes (CTL), IgA, and IgG antibodies affect BMT. (C) Disruption of the infant gut interface enables HIV to traverse the epithelial layer, leading to microbiota disturbance and allowing the virus to establish infection in CD4+ CCR5+ T cells.[54] (Created with BioRender.com.)

associated virus.[45–49] Pro-inflammatory cytokines, such as TNF, IL-6, IL-8, and RANTES, in breast milk are associated with elevated breast milk viral loads and increased transmission risk.[49,50] Breast milk HIV-specific cellular IFN-γ responses lowered transmission risk by 70% (adjusted odds ratio [aOR] 0.29 [95% CI 0.092, 0.91]) in a Kenyan cohort.[51] In addition, passively transferred maternal IgA and immunoglobulin G (IgG) in breast milk may exert virologic control through direct neutralization and other Fc-mediated functions. Pollara and colleagues[52] found that HIV-1 envelope-specific breast milk IgA levels were associated with reduced risk of BMT, but no such association was found for HIV-specific IgG in breast milk.

The Infant Gastrointestinal Tract Immune Interface

The link between breast milk and the infant GI tract (also called the "gut-breast axis") is essential for both GI tract and systemic infant immune development. The infant GI tract is relatively permeable or "leaky," allowing low-dose systemic exposure to dietary antigens or pathogens while sustaining a tolerant immune environment characterized by increased regulatory T-cells (Tregs), Th17, and Th2 cells.[53] However, these conditions may inadvertently be conducive to HIV transmission. The infant gut is populated with high levels of CD4+ CCR5+ T-cells that are the targets for initial HIV infection (see **Fig. 2**B).[54] Cell-free HIV may also bypass the permeable GI tract epithelium by transcytosis or breaks in the epithelial barrier.[55,56] Epithelial barrier integrity is heavily influenced by the gut microbiome, and breastfeeding plays a vital role in its development by promoting structural integrity, functionality, and maintenance of mucosal barrier properties. Conditions that dysregulate infant GI

microbiome, increase epithelial permeability, or also increase mucosal immune cell trafficking, such as infant oral thrush and GI illness, have the potential to increase risk of HIV transmission.[57]

The Effect of Mixed Feeding on Mucosal Immunity

Coadministration of breast milk with formula or solid foods before the age of 6 months, or "mixed breastfeeding" (MBF) is a well-defined clinical risk factor for BMT from the pre-cART era.[58–60,61] While the precise mechanism is undefined, MBF is associated with increased intestinal permeability, alterations in intestinal microbiome composition, and differences in mucosal and systemic immune profiles.[62–65] Two notable studies provide evidence that MBF is associated with mucosal recruitment of HIV target cells. McFarland and colleagues[66] found a higher proportion of peripheral blood CD4+ CCR5+ T-cells expressing an intestinal homing profile (β7hi) among Ugandan infants born to WLHIV who were MBF compared to exclusive breastfeeding (EBF). Wood and colleagues[67] observed higher expression of chemokines and chemokine receptors implicated in recruiting HIV target cells in the oral mucosa of South African infants who experienced MBF compared to EBF. In this study, MBF was also associated with greater diversity of bacterial species in the infant's intestinal microbiome and higher levels of peripheral CD4+ T-cell activation. Additional studies are needed to understand how the type of mixed feeding (nonhuman milk vs solid food) influences the intestinal microbiome, mucosal, and systemic immune maturation and BMT risk. A pooled analysis of West and South African mother–infant pairs in the pre-cART era found similar rates of postnatal HIV transmission among infants whose mothers practiced MBF with nonhuman milk compared to EBF infants, while introduction of solid foods before 2 months of life was associated with a 3 fold higher risk of BMT.[68] It is unknown whether mixed feeding is associated with BMT among infants born to mothers on sustained cART. Njom Nlend and colleagues[69] demonstrated higher BMT for MBF versus EBF infants (3 out of 14 [21%] vs 25 out of 658 [3.8%]) in a cohort of mother–infant pairs from Cameroon, of whom 52% of mothers were taking cART, but the risk of MBF on BMT was not stratified by maternal cART use. In a recent systematic review and meta-analysis of breast milk HIV transmission in the cART era, no studies provided data on mixed feeding.[5] Investigating the mechanism of increased BMT risk in mixed feeding will inform future studies needed to define the actual risk with long-term ART suppression. Similarly, understanding relative BMT risk related to infant gut mucosal inflammation induced by liquid formula and solid food introduction in the context of maternal cART will be important to strengthen evidence-driven and patient-centered counseling.

CLINICAL MANAGEMENT OF BREASTFEEDING MOTHERS WITH HUMAN IMMUNODEFICIENCY VIRUS AND THEIR INFANTS TO REDUCE BREAST MILK TRANSMISSION

The clinical care of WLHIV who choose to breastfeed and their infants involves multidisciplinary care by obstetricians, pediatricians, lactation specialists, and infectious disease specialists. Interventions to reduce BMT extend from preconception through pregnancy, infant delivery, and postpartum follow-up.

Maternal Antiretroviral Therapy

Initiation of maternal cART as early as possible, ideally preconception, and maintenance of viral suppression through pregnancy and breastfeeding are critical to avoid BMT. The postpartum period, often called "the fourth trimester," introduces unique

individual and structural barriers for WLHIV to maintain cART adherence, including sleep deprivation while caring for a newborn, hormonal changes associated with mood disturbance, and increased financial burden. Studies have consistently demonstrated increased rates of viral rebound, poorer adherence to ART, and poor retention in care during the postpartum period.[70–72] Frequent maternal virologic monitoring (every 1–2 months) while breastfeeding is recommended, alongside endorsement of behavioral health strategies to optimize adherence, including use of mobile phone alarm reminders, pill boxes or prepackaged medications, and identification of an adherence support partner.[73,74] In the future, long-acting antiretroviral agents could be of particular benefit to ensure optimal drug levels while breastfeeding, and pharmacokinetic studies are underway.[75,76]

Infant Antiretroviral Prophylaxis

Infant antiretroviral prophylaxis serves as an added layer of protection against BMT, but the selection of optimal agents and duration of prophylaxis for breastfeeding infants vary considerably among published guidelines. The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial compared infant prophylaxis with nevirapine to maternal cART and found no difference in transmission rates at 6 months or 12 months.[3] Some experts recommend single-drug prophylaxis (zidovudine or nevirapine) through 4 to 6 weeks after breastfeeding cessation, while others endorse prophylaxis for only 2 to 4 weeks, similar to non-breastfeeding populations.[30,32] A more conservative approach includes 3 drug prophylaxis (nevirapine or raltegravir with zidovudine and lamivudine) for 4 to 6 weeks, followed by nevirapine or zidovudine through 4 to 6 weeks after breastfeeding cessation.[27] More studies are needed to provide insight into the duration of infant prophylaxis and whether or not triple ART infant prophylaxis could be beneficial in the early stages of breastfeeding when there may be a higher theoretic risk for HIV transmission informed by pre-cART studies. Infants taking prolonged antiretroviral prophylaxis should have periodic screening for antiretroviral drug toxicities including neutropenia or hepatic dysfunction at baseline and after 2 to 4 weeks, with additional follow-up testing for abnormal results or clinical symptoms. Virologic monitoring of infants who are breastfeeding should include HIV DNA or RNA PCR at 14 to 21 days of life, 1 to 2 months of life, 4 to 6 months of life, and every 2 months thereafter if breastfeeding continues. Infants should receive additional HIV DNA or RNA PCR 6 weeks, 3 months, and 6 months after breastfeeding cessation.[7]

In the future, use of broadly neutralizing antibodies (bNAbs) targeting the HIV envelope for infant prophylaxis could lessen the burden of ART toxicity and decrease frequency of administration. Phase 1 clinical trials in infants exposed to HIV have shown a positive safety profile.[77,78] The Tatelo study, a 1 out of 2 clinical trial in Botswana, demonstrated sustained viral suppression for 24 weeks among 11 out of 25 infants with HIV who received bNAb-only treatment, pointing to the potential for bNAbs as infant prophylaxis.[79] Use of long-acting injectable antiretroviral agents is being evaluated for pre-exposure prophylaxis in adults; age-de-escalation pharmacokinetic studies could also inform infant use in the setting of breastfeeding.

Establishing Exclusive Breastfeeding and Addressing Clinical Complications

Less than 25% of the general US population practices EBF for the first 6 months, and proactive involvement of a lactation specialist is beneficial to support WLHIV to establish and maintain EBF.[80] Prenatal consultation to provide education and ensure access to lactation pump supplies in advance of delivery, in-hospital assistance with optimal positioning and infant latch and outpatient follow-up to address challenges with milk supply enhance the potential for successful EBF.

Close collaboration between a lactation specialist and a pediatrician is essential for management of breastfeeding complications. Short-term supplementation with pasteurized human donor milk, flash-heated breast milk, or infant formula may be needed in particular circumstances, such as delayed milk production, mastitis, severe infant thrush or GI illness, and detectable maternal viremia.[7] In the case of mastitis, or cracked/bleeding nipples, a mother can feed from the non-affected breast while pumping and disposing breast milk from the affected breast until resolution. Management of maternal viremia should involve temporary cessation of breastfeeding while obtaining a repeat HIV viral load. If maternal viremia persists, breastfeeding cessation should be strongly considered and some experts recommend initiation of 3 drug infant prophylaxis for 4 to 6 weeks.[32] If maternal viremia resolves on repeat testing and any adherence challenges have been addressed, breastfeeding may continue. Guidance on the duration of breastfeeding varies; some experts advise mothers to wean after 6 months, while others defer to maternal preference. Parents should be counseled to introduce a bottle before the of age 1 month to prepare for eventual weaning. Slow weaning over 2 to 4 weeks is recommended, replacing one feed with formula every 2 to 3 days.[32]

Approach to Shared Decision-making and Infant Feeding Counseling

Shared decision-making between WLHIV and medical providers regarding infant feeding choices is endorsed by updated clinical guidelines, and health care providers should initiate early conversations about feeding options for WLHIV who are pregnant or considering pregnancy. Prior to changes in AAP and DHHS guidance, many WLHIV opted to breastfeed without communicating their choice to their health care provider due to fear of stigma and lack of perceived support.[5] Feeding choices among WLHIV are influenced by many individual, cultural, and health care system factors.[81] Providers should explore an individual's motivations for breastfeeding and discuss all feeding options with patients in a nonjudgmental manner. Replacement feeding with certified donor human milk or formula is the only option to ensure 0% risk of HIV transmission after delivery; however, even in high-income settings, social inequities that disproportionally affect WLHIV may limit access to replacement feeding options. The well-established benefits of breastfeeding for maternal and child health should also be acknowledged. Breastfeeding is associated with lower risk of metabolic syndrome, obstetric complications, and cancer among mothers.[82] Breastfeeding lowers rates of infant sudden infant death syndrome, necrotizing enterocolitis, and sepsis and has longer term benefits, including reduced incidence of obesity, asthma, diabetes, and autoimmunity during childhood.[82,83] As health care providers discuss feeding options with WLHIV, a variety of clinical and social factors should be considered for an individualized risk assessment, including history of cART adherence, duration of viral suppression, mental health and substance use history, and the social, emotional, and financial support systems available to the patient during the breastfeeding period. Preemptive discussions should include the planned clinical schedule for maternal and infant viral load monitoring, potential side effects of infant antiretroviral prophylaxis, potential complications that may warrant temporary or permanent breastfeeding cessation, and parental coping strategies if the infant were to acquire HIV.

KNOWLEDGE GAPS AND RESEARCH PRIORITIES

Addressing knowledge gaps and setting research priorities is essential to support collaborative efforts between patients and providers, ensuring optimal outcomes in

the context of breastfeeding and HIV transmission during the modern cART era. Basic science studies employing advanced technology for reservoir cell detection in breast milk of long-term ART-suppressed individuals would be beneficial to assess persistence of cell-associated HIV from longitudinal clinical samples. Epidemiology studies on the risk of HIV transmission from MBF among mothers on cART should distinguish between formula supplementation and solid food introduction and include precise exposure time measures. Development and evaluation of point-of-care laboratory tests to evaluate qualitative and/or quantitative cell-free RNA in breast milk could guide clinical management decisions. Additionally, clinical risk-assessment tools to aid in decision-making for both providers and WLHIV would be beneficial.

SUMMARY

Postnatal HIV transmission through breastfeeding is a rare event when risk reduction strategies are in place, including maternal cART, infant prophylaxis, and close maternal and infant virologic monitoring. Early conversations about feeding options between patients and health care providers are important to review current evidence on transmission risk in the cART era and consider an individual's preferences, clinical history, and social support. Future research to evaluate HIV viral dynamics in breast milk among women with sustained viral suppression will be important to inform evidence-driven clinical guidance.

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Best Practices

What is the current practice for WLHIV who desire to breastfeed?

- Health care providers should provide education to WLHIV regarding infant feeding options, communicating that (1) replacement feeding with formula or certified donor human milk is the only way to ensure 0% risk of HIV transmission after birth; and (2) breastfeeding is associated with less than 1% risk of HIV transmission to the infant if maternal viral suppression is maintained throughout pregnancy and breastfeeding.
- If a WLHIV with sustained viral suppression during pregnancy chooses to breastfeed, health care providers should support this decision, and clinical care of the mother and infant should include the following:
  - Prenatal and postnatal lactation support to establish and maintain EBF.
  - Continuation of maternal cART with virologic monitoring every 1 to 2 months through the breastfeeding period.
  - Provision of infant antiretroviral prophylaxis according to guidance from a pediatric HIV specialist, with serial infant virologic monitoring (at 14–21 days, 1–2 months and 4–6 months of life, followed by every 2 months thereafter if breastfeeding continues, and 4–6 weeks, 3 months, and 6 months after breastfeeding cessation).
  - Gradual weaning over 2 to 4 weeks.

Pearls/pitfalls at the point-of-care:

- Early education and open communication about feeding choices are crucial for shared decision-making between health care providers and WLHIV.

- Prenatal referral to a lactation specialist and pediatric HIV provider is optimal to ensure that WLHIV who choose to breastfeed are prepared for EBF and outpatient follow-up for infant antiviral prophylaxis and virologic monitoring.
- Risk reduction interventions involve coordination among multidisciplinary health care providers, including obstetricians, pediatricians, lactation consultants, and adult and pediatric HIV specialists.
- Management of complications that arise during breastfeeding including maternal mastitis, infant thrush or GI illness, maternal viremia, or maternal cART adherence challenges can include temporary supplementation with certified human donor milk, flash-heated breast milk, or formula, followed by continuation of breastfeeding if the complication resolves. In the United States, guidance for nuanced clinical decisions is available through the National Perinatal HIV Hotline (1–888–448–8765).

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DISCLOSURE

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