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Infant feeding and prevention of mother-to-child transmission of HIV-1

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Abstract

Purpose of review—To review new studies and directions regarding infant feeding and HIV-1 transmission.

Recent findings—With antiretroviral drugs and shortened breastfeeding, breast milk HIV-1 transmission risk can be decreased from 16 to less than 5%. In the context of peripartum antiretroviral drugs/short breastfeeding, replacement feeding provides negligible benefit in decreasing the risk of HIV-1/death in contrast to previous studies of no antiretroviral drugs/unlimited breastfeeding in which it offered benefit. One study noted a high risk of infant HIV-1 or death (17%) after 4 months, with no difference in risk in infants with shortened breastfeeding versus indefinite breastfeeding. This study suggests that shortened breastfeeding needs caution in implementation. Other African studies have noted minimal risk of HIV-1 or death (<2%) after shortened breastfeeding, underscoring the heterogeneity of infant survival in different settings and the potential to improve infant survival.

Summary—Antiretroviral drugs and shortened breastfeeding markedly decrease breastfeeding HIV-1 transmission, shifting the balance to make replacement feeding less beneficial. In some settings shortened breastfeeding poses similar risks as replacement feeding and provides no infant health benefit compared with extended breastfeeding. Programmes aimed at decreasing infant HIV-1 need to do so in the context of promoting infant survival. Strengthening systems to promote infant health is critical.

Keywords

breastfeeding; HAART; replacement feeding

Introduction

During the past few years, an estimated 30–50% of approximately 500 000 infant HIV-1 infections worldwide occurring annually were acquired via breastfeeding [1–3]. More than approximately 200 000 infants annually acquired a completely preventable terminal infection because not breastfeeding was associated with the competing risks of morbidity, growth compromise and mortality. Neither infant HIV-1 infection nor death is an acceptable outcome, and conclusions regarding the best option to minimize both unacceptable outcomes differ between regions in Africa and between research and programmes [4,5]. During the past few years, peripartum antiretroviral regimens and shortened breastfeeding have been shown to decrease the risk of breast milk HIV-1 transmission substantially. This situation has altered the risk–benefit balance (infant HIV-1/death) to favour breast-feeding

over replacement feeding. The next frontier in infant feeding and HIV-1 is the issue of shortened breast-feeding and how to minimize the risk of infant HIV-1 or death after the cessation of breastfeeding. The issues surrounding shortened breastfeeding are reminiscent of replacement feeding and emphasize the need to frame infant HIV-1 risk in the larger context of infant health.

Breastfeeding HIV-1 transmission risk

HIV-1 transmission via breastfeeding occurs throughout lactation and is correlated with the duration of breastfeeding and HIV-1 levels in breast milk [6^{**}]. In the absence of antiretroviral therapy the risk of breast milk HIV-1 transmission is approximately 16% [7,8]. Breast milk transmission of HIV-1 is increased in mothers with advanced HIV-1 disease and may be increased in those with acute primary HIV-1 infection, mastitis, or mixed breastfeeding [6^{**},7,9–11,12^{*},13]. Antiretroviral regimens for the prevention of mother-to-child transmission of HIV-1 (PMTCT) alter breast milk HIV-1 transmission risk estimates. Studies including maternal/infant nevirapine yield lower breast milk HIV-1 transmission rates as a result of breast milk HIV-1 suppression or infant prophylaxis by nevirapine [14]. Studies that provide HAART to immunosuppressed women yield lower breast milk HIV-1 transmission risk estimates because the highest risk transmitters have received effective viral suppressive therapy [15^{**},16^{**}]. Because recent data suggest that current WHO guidelines recommending shortened breastfeeding (6 months) may compromise infant health, it is important to define breast milk HIV-1 transmission risk after 6 months in order to re-frame the competing risk assessment of shortened versus extended breastfeeding. Taha and colleagues [17^{**}] undertook a large cohort study to determine the timing and co-factors for late postnatal HIV-1 transmission occurring after 6 weeks of age. Transmission risk in that study was 9.7%, which was consistent with two previous studies estimating a late postnatal transmission risk (after 6 weeks) of 9.3% or 12.1% [10,18]. Importantly, in this cohort over 85% of late post-natal transmission occurred after 6 months postpartum suggesting that shortened breastfeeding may prevent substantial numbers of infants from acquiring HIV-1 [17^{**}].

Replacement feeding

Replacement feeding completely prevents any risk of HIV-1 transmission via breastfeeding, but may be associated with increased mortality and morbidity if incorrectly implemented [8,15^{**}]. In addition, maternal HIV-1 status may be inadvertently disclosed when mothers do not breastfeed in a setting in which breastfeeding is the norm. The safety of replacement feeding varies markedly between settings, with studies in urban African centers noting more safety than in settings with less developed infrastructure. Bequet and colleagues [19^{*}] in Côte d'Ivoire demonstrated comparable survival and morbidity between HIV-1-exposed uninfected infants who had prolonged breastfeeding and those with shortened or no breastfeeding. In contrast, massively increased replacement feeding-associated infant mortality (50-fold higher mortality among replacement feeding infants) was noted in Botswana in 2006 as a result of abrupt changes in water safety and the precarious supply and distribution of formula [20^{*},21]. In 2007, however, Botswana reported a less than 4% infant HIV-1 transmission risk in an unprecedented successful national PMTCT programme [22^{*}]. The PMTCT programme included expanded anti-retroviral drugs and replacement feeding, both of which may have contributed to the low infant HIV-1 risk. The contribution of replacement feeding may have been less important than antiretroviral agents in this setting. Thior and colleagues [15^{**}] in Botswana noted no benefit of replacement feeding in decreasing the risk of HIV-1/death compared with shortened breastfeeding with antiretroviral agents. The availability and efficacy of expanded antiretroviral drugs and the

unpredictability of water and the formula supply chain should motivate programmes to favour breastfeeding in regions that are susceptible to infrastructure failure.

Replacement feeding has been recommended for women with HIV-1 when it is deemed to be acceptable, feasible, affordable, sustainable and safe (AFASS). AFASS guidelines have been difficult to interpret and implement at the provider–client level [23*]. Doherty and colleagues [24**] evaluated 635 mothers with AFASS criteria, specifically assessing piped water, fuel and disclosure regarding HIV-1 status. Infants of women who met the criteria regarding water, fuel and disclosure who elected to replacement feed had the lowest risk of HIV-1 transmission or death; the risk of HIV-1 transmission/death was significantly higher both among breast and replacement feeding infants of mothers who did not meet criteria (hazard ratio >3.3). That study provided a potentially clear tool for counsellors to assess the suitability of clients for replacement feeding.

The perceived duality in the standard of care in WHO guidelines that do not consistently recommend replacement feeding for infants born to HIV-1-infected mothers led to a Rwandan programme that approached replacement feeding as a human right [25*]. Farmer and colleagues [25*] developed an approach previously piloted in Haiti, to optimize replacement feeding comprehensively for HIV-1-infected mothers including the provision of fuel and education on water safety. Because replacement feeding may compromise infant health if inappropriately implemented, however, it remains critical to determine the long-term effects of this approach on all potential infant adverse outcomes, including growth, morbidity and survival [26*].

Perhaps the most important recent studies regarding infant HIV-1 infection and feeding are those that demonstrate that replacement feeding is incrementally less beneficial or not beneficial in the setting of antiretroviral drugs and shortened breastfeeding, in contrast to previous studies in which replacement feeding offered a clear benefit versus unlimited breastfeeding and no antiretroviral agents [8,15**,16**]. In Botswana, the overall 18-month risk of HIV-1/death was the same among infants who were randomly assigned to replacement feed (13.9%) as those who breastfed for 6 months (15.1%; Table 1) [15**]. Mother–infant pairs in that study received short-course zidovudine and sometimes maternal and infant nevirapine, and breastfeeding infants received zidovudine while breastfeeding. When HAART became available nationally it was provided for immunosuppressed women in the study. Tonwe-Gold and colleagues [16**] in Côte d'Ivoire recently noted the high efficacy of a tiered antiretroviral approach (HAART for immunosuppressed and combined short-course zidovudine/nevirapine). In that study, the peripartum HIV-1 transmission risk was 2.2% and the cumulative 12-month HIV-1 transmission risk was 5.7% with a cumulative risk of death or HIV-1 of 11.7% by 12 months. Immunosuppressed mothers receiving HAART in that study had a similar HIV-1 transmission risk as non-immunosuppressed mothers receiving combined short-course antiretroviral regimens. Mothers had shortened breastfeeding in the cohort (median 5.4 months).

Because more effective antiretroviral agents (HAART or combined zidovudine/nevirapine) have resulted in a decreased risk of breastfeeding HIV-1 transmission, the current HIV-1 transmission risk/mortality balance favors 6-month breastfeeding over replacement feeding for mothers with HIV-1 who can access WHO currently recommended antiretroviral regimens. This message has not been disseminated evenly to providers in existing PMTCT programmes who may still believe that replacement feeding is beneficial [27**]. In addition, it is particularly important that mothers of HIV-1-infected infants be encouraged to continue to breastfeed as there is an increased risk of mortality in HIV-1-infected infants who do not breastfeed [28]. Unfortunately, this message is often lost at the programme level and

mothers of HIV-1-infected infants may still be inappropriately counselled to replacement feed.

Exclusive breastfeeding

The potential benefit of exclusive breastfeeding in the setting of maternal HIV-1 has been studied in South Africa, Zimbabwe, and Zambia [10,11,12*,13]. These studies have evaluated exclusive breastfeeding (defined in slightly different ways between studies) for the effect on HIV-1 transmission, both for early and later breast-feeding HIV-1 transmission. The studies had some limitations in design with an inability to exclude reverse causality and potential confounding. Exposure to exclusive breastfeeding during the first 3 months of life was determined to have a protective effect beyond the first 3 months after mixed feeding had been implemented. This finding would suggest that early exclusive breast-feeding provides protection that supersedes subsequent mixed feeding, a premise that may be consistent with residual confounding rather than extended protection from exclusive breastfeeding. In a recent comprehensive analysis adjusted for multiple potential confounders and using an approach to address potential reverse causality, Kuhn and colleagues [13] found a significantly increased HIV-1 transmission risk for mixed breastfeeding versus exclusive breastfeeding.

In studies from South Africa, mothers who 'mixed breastfed' during the first 3 months had a 15-month HIV-1 transmission risk of 35.9% in contrast to 24.9% for exclusive breastfeeding mothers and 19.4% for replacement feeding mothers [11]. In Zimbabwe, the late post-natal HIV-1 transmission risk occurring after 6 weeks postpartum for mixed breastfeeding mothers was 13.9% (by 18 months) [10]. Given that the majority of women (>70%) in those two studies in South Africa and Zimbabwe mixed breastfed their infants rather than either exclusive breastfeeding or replacement feeding, the 'spillover' from non-exclusive breastfeeding resulted in an estimated 197 HIV-1-infected infants (13.9% transmission risk after 6 weeks, 1414 infants) in Zimbabwe and 39 HIV-1-infected infants in South Africa (14% transmission risk after 6 weeks, 276 infants). This risk emphasizes the reality that programmes that are unsuccessful in the promotion of exclusive breastfeeding may result in appreciable numbers of infants infected with HIV-1. As a result, newer studies have aimed to increase the uptake of exclusive breastfeeding [29*]. Whereas earlier studies noted that exclusive breastfeeding was successfully implemented in only a minority of mothers (<10% by 6 months), recent studies with more intensive counselling and home visits have noted an increased uptake of exclusive breast-feeding [10,11,12*,13,30*]. The combination of increased counselling to promote exclusive breastfeeding and more liberal definitions of exclusive breastfeeding have resulted in increased reported rates of exclusive breastfeeding [16**,17**]. A recent study by Coovadia and colleagues [12*] noted exclusive breastfeeding among 82% of mothers at 6 weeks but 40% at 6 months. Similar results have been reported by Kuhn and colleagues [13] in Zambia with more than an 80% uptake of exclusive breastfeeding. Those studies suggest that with concerted efforts, including home visits and more intensive counselling, exclusive breastfeeding rates can be increased. Similar to replacement feeding, however, exclusive breastfeeding cannot be implemented without an appropriate infrastructure to optimize uptake, and this scenario involves cost and prioritization at the programme level. Exclusive breast-feeding also has areas of confusion at the provider-client interface. Programmatically, it is unclear what message to give women who 'fail' in exclusive breastfeeding during the first 3 months; have they now inexorably increased their infants' long-term risk of HIV-1 acquisition? Once they have 'mixed breastfed' is there any point in reverting to exclusive breastfeeding?

To date, exclusive breastfeeding studies have been conducted in cohorts with either no antiretroviral drugs or single-dose nevirapine. Because recent studies with combined

zidovudine/nevirapine or HAART demonstrated a low risk of breast milk HIV-1 transmission in women, without complex efforts to promote exclusive breastfeeding the promotion of exclusive breastfeeding 'to reduce HIV-1 transmission' may be unnecessary in programmes implementing current WHO-recommended combination PMTCT regimens. Certainly exclusive breastfeeding should be promoted for all breastfeeding infants regardless of maternal HIV-1 infection, but the concerted costs and efforts of exclusive breastfeeding programmes specific to HIV-1 may be redundant. In efforts to standardize simple and clear messages in an already muddled policy area, it may be wisest simply to reiterate that all breastfeeding women, regardless of HIV-1 infection, should be supported in exclusive breastfeeding with enhanced national programmes to promote this effort.

Early cessation of breastfeeding

Cost-effectiveness analyses resulted in WHO recommendations to suggest shortened breastfeeding as a means to balance the competing risks of breastfeeding HIV-1 transmission against replacement feeding mortality [31]. After 6 months of age, appropriate alternative feeding strategies were deemed to be sufficient to provide adequate nutrition without increased mortality risk, and were considered to be much less risky than for younger infants. Recent studies have, however, suggested that the same issues that plague replacement feeding from birth also affect women who stop breastfeeding at 6 months. Several not yet published studies suggest that early cessation of breastfeeding is associated with substantial morbidity and growth compromise. These studies from Kenya, Malawi, Uganda, and Zambia provide worrisome new evidence that the cessation of breastfeeding at 6 months needs to be supported by appropriate measures to minimize infant risk of death, morbidity, and growth failure (Table 2) [28,32–36].

The increased risks of shortened breastfeeding have led to the consideration of indefinite breastfeeding rather than early cessation. In the ZEBS cohort, a clinical trial comparing infants randomly assigned to early cessation versus indefinite breastfeeding, indefinite breastfeeding did not result in a higher risk of HIV-1 or death compared with early cessation of breastfeeding in a cohort that received single-dose nevirapine [28]. The late postnatal HIV-1 transmission risk estimates of Taha *et al.* [17**] suggest that an additional 8.8% transmission risk of HIV-1 after 6 months would result from indefinite breast-feeding. In the ZEBS study, HIV-1 transmission risk was offset by the mortality costs of shortened breastfeeding. As with replacement feeding, the morbidity, mortality, and growth costs of shortened breastfeeding depend on the safety net of care provided to children during the period off breastfeeding. It is plausible that breastfeeding for the first 6 months of life leaves mothers particularly unprepared for stopping breastfeeding, with even less support than a mother counselled to replacement feed from birth. In contrast to the ZEBS programme, others have demonstrated a minimal risk of infant mortality and HIV-1 after stopping breastfeeding at 6 months (Table 1, Fig. 1). The Botswana and Côte d'Ivoire studies observed a less than 2% risk of HIV-1 or death after 6 months, which is substantially lower than the 17 and 19% risk of HIV-1/death observed in ZEBS (after 4 months) [15**,16**]. The ZEBS study and the other studies noting post-6-month infant adverse events provide impetus to incorporate more careful maternal/infant support after the cessation of breastfeeding. The use of AFASS guidelines at 6 months may be useful in counselling mothers regarding shortened versus indefinite breastfeeding. Targeted transitional counselling, appropriate nutritional support, and monitoring may enhance the safety of infants whose mothers stop breastfeeding at 6 months.

Antiretroviral therapy during breastfeeding

Current WHO/UNAIDS guidelines for HIV-1-infected women recommend an approach tailored to maternal HIV-1 disease status. Women who meet the criteria for HAART initiation during pregnancy should be initiated on HAART for their own health and continue on this regimen indefinitely, including during lactation. Women who do not meet the WHO criteria for HAART initiation are recommended to receive combination zidovudine/nevirapine short-course therapy with a short combined antiretroviral 'tail' to minimize the development of nevirapine resistance. Early data from maternal HAART studies noted a low risk of HIV-1 transmission to infants, ranging from 1 to 5% [16^{**},37,38,39^{*}]. Current evidence does not yet suggest a marked incremental benefit for HAART versus combined short-course nevirapine/zidovudine to decrease infant HIV-1 transmission risk in non-immunosuppressed women (CD4 cell counts >200 cells/ml) [16^{**}]. Definitive randomized trials are ongoing to compare the relative merits of HAART during breastfeeding versus combined nevirapine/zidovudine for non-immunosuppressed mothers. The results of those studies will be important to establish future guidelines.

Infant feeding messages

The extraordinary efficiency of PMTCT research in identifying increasingly effective approaches to decrease mother-to-child transmission of HIV-1 has been a mixed blessing in terms of implementation [27^{**}]. Each new change in PMTCT approach requires changes in national policy, media messages, provider training, and awareness of HIV-1-infected mothers. The speed and complexity of changes have resulted in confusion at the programme and individual level. Over the past 10 years WHO guidelines have changed to incorporate rapid HIV-1 testing, single-dose nevirapine, short-course zidovudine, combined short-course zidovudine/nevirapine, HAART for immunosuppressed women, and antiretroviral 'tail' therapy to minimize resistance. Infant feeding counselling recommendations add a layer of complexity to this already confusing milieu of changing recommendations [27^{**}]. WHO guidelines have included recommendations for replacement feeding if AFASS qualified, exclusive breast-feeding, shortened breastfeeding, and antiretroviral drugs during breastfeeding. If conditions do not exist to permit infant safety with breastfeeding cessation at 6 months, the prevention of additional breastfeeding HIV-1 transmission risk may be offset by infant mortality as a result of not breastfeeding. Therefore, a well designed safety net to promote the prevention of diarrhea and to provide nutritional support after 6 months must exist within programmes recommending shortened breastfeeding to prevent HIV-1. In addition, clearer messages recommending breastfeeding for HIV-1-infected infants need to be incorporated.

Conclusion

The past 2 years have yielded critical information on infant feeding and HIV-1, particularly with respect to documenting substantially decreased breastfeeding HIV-1 transmission risk (~4%) with antiretroviral drugs and shortened breastfeeding. The overall infant HIV-1 transmission risk (~6%) with this approach is five to sevenfold lower than in the absence of interventions (35–45%) and can be implemented without the risks of early infant replacement feeding [8,12^{*}]. Emerging data suggest, however, that programmes will need to exert caution when advising shortened breastfeeding. Further development of systematic ways to gain the benefits of shortened breastfeeding without compromising infant health and survival is necessary. This situation may include the administration of AFASS criteria at 6 months, heightened nutritional counselling and supplements, closer infant monitoring in the peri-weaning period, or continued breastfeeding if residual issues compromising infant safety and growth cannot be overcome.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 202).

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Figure 1.
Risk of infant HIV-1 or death after 3–7 months

Table 1

HIV-1 and HIV-1-free survival for breastfed, replacement fed, and shortened breastfeeding among infants born to HIV-1-infected mothers with and without antiretroviral drugs in trials randomized on feeding practice

	Study design, duration, ART regimen	Risk of infant HIV-1	Risk of infant mortality	Risk of HIV-1 or death	Risk of HIV-1 or death after 1–6 months
No antiretroviral drugs					
Nduati <i>et al.</i> , 2000 [8]	RCT, <i>N</i> = 425 24 months	At 24 months BF vs FF 36% vs 20% (<i>P</i> = 0.001)	At 24 months BF vs FF 24.4% vs 20% (<i>P</i> = 0.3)	At 24 months BF vs FF 42% vs 30% (<i>P</i> = 0.02)	
Antiretroviral drugs					
Thior <i>et al.</i> , 2006 [15 ^a]	RCT, <i>N</i> = 1200 18 months; 6 months BF Regimen: Antenatal ZDV (some with maternal/infant NVP); BF infants ZDV	At 18 months BF vs FF 9.5% vs 6.0% (<i>P</i> = 0.02)	At 18 months BF vs FF 8.5% vs 10.7% (<i>P</i> = 0.21)	At 18 months BF vs FF 15.1% vs 13.9% (<i>P</i> = 0.60)	Risk of infant HIV-1 or death by 18 months After 1 month of life 9.1% BF vs 5% FF After 7 months of life ^a 2.2% BF ^b vs 1.4% FF
Kuhn <i>et al.</i> , 2007 (CROI 2007 abstract) [13]	RCT, <i>n</i> = 958 4 month BF vs indefinite BF 24 months Regimen: SD nevirapine				Risk of infant HIV-1 or death by 24 months Among HIV-1 uninfected at 4 months 17% early cessation BF vs 19% long BF

ART, Antiretroviral therapy; BF, breastfeeding; CROI, Conference on Retroviruses and Opportunistic Infections; FF, formula feeding; NVP, nevirapine; RCT, randomized controlled trial; ZDV, zidovudine.

^aMost stopped breastfeeding at 6 months.

^bMedian breastfeeding 5.4 months.

Table 2

Studies on infant feeding and HIV-1 transmission and infant survival in 2006 and 2007

	Location	Comments
Replacement feeding	Botswana [15**]	RCT showed no benefit for replacement feeding versus shortened BF/ZDV in decreasing risk of infant HIV-1/death in setting of peripartum ART and sometimes maternal HAART (if immunosuppressed)
	Côte d'Ivoire [16**]	Short or no BF comparable morbidity to prolonged BF
	DREAM programme in Mozambique, Tanzania, Malawi [38]	Low risk of infant HIV-1/death during first 6 months in BF and in replacement feeding infants
	South Africa [24**]	AFASS criteria predict risk of infant HIV-1/death
Exclusive feeding	South Africa [12*] Zambia [13]	Both studies noted: Exclusive BF can be increased by enhanced counselling Mixed BF increased HIV-1 transmission risk
Early cessation of BF	Zambia [28]	RCT HIV-1 and death risk relatively high (>17%) after 4 months, and comparable in early cessation versus indefinite BF
	Kenya, Malawi, Uganda [32–35]	Postcessation of BF associated with increased diarrheal morbidity
	Uganda, Botswana, Côte d'Ivoire [15**,16**,36]	HIV-1/death risk after 4–7 months with or without BF lower than observed in Zambia: Uganda risk of HIV-1/death between 3.5/4 months and 18 months 6.2% ZDV arm, 6% NVP arm (median BF duration 9.5 months and 8.8 months, respectively) Botswana risk of HIV-1/death between 7 months and 18 months 1.4% FF, 2.2% BF (median BF duration 5.9 months) Côte d'Ivoire risk of HIV-1/death between 6 and 12 months 0.9% (median BF 5.4 months)

ART, Antiretroviral therapy; BF, breastfeeding; FF, formula feeding; NVP, nevirapine; RCT, randomized controlled trial; ZDV, zidovudine.