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Problems and advances in reducing transmission of HIV-1 through breast-feeding in developing countries

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Abstract. The additional risk of an infant acquiring human immunodeficiency virus type 1 (HIV) from its HIV+ mother during breast-feeding is about 15% after 24 months and depends on the duration of breast-feeding. This statistic has been exploited to inflate the disadvantages of breast-feeding. It may be more pertinent for health workers to quote a risk of about 5% if breast-feeding is practiced for 6 months, as will be the case in many programs that recommend shorter periods of breast-feeding for HIV-infected women. This review covers recent studies that highlight methodological complexities, the hazards of formula feeding in Africa, and the finding that the type of breast-feeding may influence transmission risks. Important additional risk factors include breast-milk cell-free viral load and breast health including subclinical mastitis. Interventions that have the potential to reduce breast-feeding transmission include safer obstetric practices, prevention and treatment of infant oral thrush, lactation management, shorter duration of breast-feeding, exclusive breast-feeding, antiretrovirals (to mother and infant) during breast-feeding, and heat treatment of expressed breast milk. HIV-infected mothers should be counseled to avoid any new HIV infection by abstaining from sex or using condoms.

Introduction

Overall transmission rates of human immunodeficiency virus type 1 (HIV) from mothers to their infants have recently been reported to be between 30% and 45% *(1)* and 14% to 42% *(2)*. However, mother-to-child transmission rates should be qualified by the presence or absence of breast-feeding. Mother-to-child transmission of HIV occurs during the intrauterine and intrapartum periods and during breast-feeding. In the absence of interventions, the absolute risk of transmission through each of these routes is about 7%, 13%, and 15%, respectively *(1)*.

Differentiating between intrapartum and early breast-feeding transmission of HIV will always be difficult because it is not possible to distinguish between the two in breast-feeding women. Data from studies of non-breast-feeding women suggest that intrapartum transmission of HIV is progressively detected up to about 6 weeks. This is probably due to HIV viral loads below the level of detection of currently available tests. We, therefore, have no guarantee, except in a randomized controlled trial (RCT), that the difference in the rate of HIV transmission at 6 weeks for women who breast-feed their children and for those who do not is due to transmission

through breast-feeding.

The advantages of breast-feeding for infant health have been well recognized and confirmed by a recent study *(3)*. The primary benefit to infants in poor countries is the protection afforded by immune factors against common infections of infancy. Avoidance of breast-feeding altogether would eliminate postnatal acquisition of HIV infection through breast milk; however, this is not feasible for many women in developing countries, such as Africa, for a number of reasons including the high cost of formula, fear of disclosure of HIV status, and the strength of cultural mores. Therefore, in developing countries, such as those in Africa, the risk of mother-to-child transmission of HIV during breast-feeding must be reduced, and factors increasing the likelihood of HIV transmission must be quantified. In industrialized countries, the risks attendant to formula feeding by HIV-infected women are negligible, and nearly all these women do not breast-feed. This paper, therefore, deals with developing countries.

Attempts to quantify risk of HIV transmission through breast-feeding

Many of the early studies quantifying risk of vertical transmission of HIV have inherent problems that probably affect results, such as failure to define type of breast-feeding (exclusive or mixed), mothers not breast-feeding their infants according to the study design, inadequate testing of the infants for HIV, and inappropriate sample sizes.

The type of breast-feeding has rarely been defined in HIV-transmission studies. Throughout the world, the overwhelming majority of women who breast-feed their infants are providing mixed breast-feeding *(4)*. It is, therefore, highly likely that most studies of HIV transmission during breast-feeding are based on mixed breast-feeding. For example, in a paper from Durban, South Africa, by Bobat *et al. (5)*, transmission rates at 18 months were given for formula, exclusive breast-feeding, and mixed breast-feeding; however, the definition used for exclusive breast-feeding was not in accordance with that proposed by the World Health Organization (WHO) *(6)*. In fact, women in the so-called "exclusive breast-feeding group" were mixed breast-feeding their infants *(5)*. Exclusive breast-feeding as defined by WHO *(6)* refers to the situation where the infant receives breast milk only with no other liquids or solids. Mixed breast-feeding refers to breast-feeding that is accompanied by the addition of any other liquids or solids (e.g., water, teas, juices, formula milk, cereals). No study of HIV transmission, prior to the Bobat paper, attempted to define type of breast-feeding.

An RCT may not be the best study design to examine infant feeding and its effect on postpartum transmission of HIV because of the difficulty with randomising this type of behavior. For example, in an RCT conducted in Kenya *(7)*, more than 25% of women randomized to the formula-feeding group were reported to have also breast-fed their infants. The reasons women may prefer not to be randomized to formula are not known but probably include fear of disclosure of their HIV status and adherence to deeply held cultural beliefs.

Inadequate testing of infants may have restricted interpretation of data in some studies. Most of the early studies comparing breast-feeding to formula feeding did not have early or frequent polymerase chain reaction (PCR) testing to distinguish postpartum from intrauterine and intrapartum transmission *(8)*. Earlier studies are further limited because the numbers of infants

in the two feeding groups were very different *(9)*.

The earliest attempt to quantify the risk of HIV transmission through breast-feeding in both developing and developed countries was a meta-analysis published in 1992 *(9)*. It was estimated that breast-feeding by women with established HIV infection increased the rate of transmission by 14% (95% confidence interval (CI), 7%-22%). Recent studies in Kenya and South Africa *(7,10)* reinforce the results of the meta-analysis *(9)*. Unlike previous studies, both these studies had at least 100 women in each group: One group breast-fed their infants, and the other fed only formula and no breast milk. Both feeding groups were followed for at least 15 months. The Kenyan RCT study used an intent-to-treat analysis, and mixed breast-feeding was the norm in those women who breast-fed *(7)*. When the infants were 24 months old, the estimated increased risk of HIV-1 transmission through breast-feeding was 16.2% (95%, CI, 6.5%-25.9%) *(*Table 1*)*. The risk may be higher in this study because about 25% of the women who were assigned to the formula-feeding group were reported to have also been giving breast milk.

The South African study *(10)* was observational, and data were collected prospectively at 1 week, 6 weeks, 3 months after delivery and, thereafter, every 3 months until the infants were 15 months old. At each of these visits, blood samples were available for testing for HIV. After 15 months, the excess absolute risk of HIV transmission through breast-feeding was 12.2% *(10,* Table 1*)*. The median duration of breast-feeding was 6 months, and the percentage of women still breast-feeding at 15 months was 18%.

Table 1. Mother-to-child transmission rates of HIV. Infants were either breast-fed (predominantly mixed breast-fed) or fed formula (never breast-fed).*

Study	Group	Rate of infant HIV infection (%)					
		At birth	6 weeks	Months			
				3	6	15-18	24
South Africa *(10)*	Breast-fed (*n* = 394)	6.9	19.9	21.8	24.2	31.6	---
	Formula (*n* = 157)	7.6	18.0	18.7	19.4	19.4	---
Kenya *(7)*	Breast-fed (*n* = 191)	7.0	19.9	24.5	28	---	36.7
	Formula (*n* = 193)	3.1	9.7	13.2	15.9		20.5
Brazil *(8)*	Breast-fed (*n* = 168)	---	---	---	---	21	---
	Formula (*n* = 264)	---	---	---	---	13	---

* Note: This table only includes cohorts that had at least 100 infants in each of the two feeding groups.

Another observational study, this one in Brazil, had at least 100 women in each feeding group *(8,* Table 1*)*. Data were collected retrospectively, and the study was undertaken before routine PCR testing was available; therefore, the proportion of infants infected with HIV during early postpartum is unknown. The HIV status of infants was only determined for those surviving and remaining in follow-up for 18 months and for those under 18 months with obvious clinical symptoms of HIV infection. These factors were included in the sensitivity analysis of rates of mother-to-child transmission of HIV *(8)*. The Brazilian study does, however, show the increased rate of transmission related to breast-feeding in a population with a short duration of breast-feeding. The absolute rates of infection in both the breast-fed and the formula-fed groups (Table 1) were lower than those in Africa *(5 , 7, 10-12)* and similar to those in Europe *(9, 13)*.

It is well established that peripartum treatment of the mother with antiretrovials can substantially reduce the risk of an infant acquiring HIV. It is important to note that the benefit of short-course antiretroviral interventions was not overridden when infants were breast-fed during the first and second year of the infant's life *(14, 15,* Table 2).

Table 2. Mother-to-child transmission rates of HIV. Mothers received placebos or antiretroviral drugs antepartum and intrapartum. Infants were predominantly breast-fed.

Study	Group	Rate of infant HIV infection (%)					
		1 day	6-8 weeks	Months			
				3	13	18	24
West Africa *(14)*	AZT antepartum and intrapartum	6.6	14.1	16.4	18.5	21.6	22.1
	Placebo	8.4	23.2	25.3	28.5	30.1	30.1
Uganda (*15*)	Nevirapine intrapartum	8.1	11.8	13.6	15.7	---	---
	AZT intrapartum (placebo equivalent)	10.3	20.0	22.1	24.1	---	---

Timing of HIV transmission through breast-feeding

Considerable debate exists about when HIV is most likely to be transmitted through breast milk. In the recent LeRoy *et al.* *(13)* meta-analysis of pooled data from eight cohorts, the risk of postpartum HIV transmission (after 4 months of age) was 3.2% per year of breast-feeding. The data were from cohorts in the United States, Switzerland, France, Europe, Rwanda (2 cohorts), Ivory Coast, and Kenya. In a study from Malawi *(11)*, risk of early breast-milk transmission (in the first 1 to 6 months) was higher than the risk later on. The risk of HIV infection due to breast-feeding during the first 2 years of an infant's life declined significantly over time and decreased from 0.7% per month between month 1 and month 5 to 0.6% per month between month 6 and month 11, and to only 0.3% when the infants were more than 12 months old *(11)*. After 12 months, the risk of HIV infection in the Malawi study was similar to that determined by Leroy *et al.* *(13)*.

The higher rates of HIV transmission through breast-feeding during the first few months of life reported in these studies *(11, 13)* could be related to increased infant susceptibility during the early months, or these rates could be an indication of surveillance bias. Infants could have been monitored more closely during their early months of life compared to later. The type of breast-feeding (exclusive or mixed) and/or amount of milk consumed may also be a risk factor accounting for the higher rates of early transmission.

The Kenyan RCT *(7)* and the SAINT study *(16)* suggest that breast-feeding transmission is higher in the first 2 months than later. In the Kenyan study during the period between delivery and 6 to 8 weeks of age, the breast-feeding group had 6.3% more new HIV infections than the formula-fed group. In the SAINT study during the period between delivery and 6 to 8 weeks of age, the breast-feeding group had 5.6% more new HIV infections than the formula-fed group *(16)*.

Although an RCT is the only way we can be sure of the risk of breast-feeding transmission during the first 6 weeks, the only RCT had inherent flaws *(17);* therefore, the data cannot be interpreted reliably enough. Thus, the only data that we have currently available to estimate transmission in the first 6 months is to calculate the rate of new infections between 6 weeks and 6 months in mixed-breast-feeding populations in five recent, large studies (Table 3). Using this method, we estimate that the risk of HIV transmission during breast-feeding is between 3.1% and 8.1%. At a public health level, information to mothers could be rounded off to suggest that mixed breast-feeding during the first 6 months carries a risk of about 5% transmission.

Table 3. Accumulation of HIV infection in the first 6 months in predominantly mixed-breast-fed infants (percent).

Study	Anti-retroviral Treatment	6 weeks	3 months	6 months	Accumulation of infection from 6 weeks to 6 months
West Africa *(14)*	AZT	14.1	16.4	17.5	3.4
	Placebo	23.2	25.3	27.1	3.9

Uganda *(15)*	NVP	11.8	13.6	14.9	3.1
	AZT	20.0	22.1	23.1	3.1
Kenya *(7)*	Nil	19.9	24.5	28.0	8.1
South Africa *(10)*	Nil	19.9	21.8	24.2	4.3
Malawi *(11)*	Nil	0.7% per month			3.5
Range	---	---	---	---	3.1 - 8.1

Breast-feeding, formula feeding, and infant mortality

The results of the Kenyan RCT *(7)* underscore the importance of balancing risks when HIV-infected women in developing countries make decisions about infant feeding. Infants in the formula-feeding group whose mothers had access to clean water, free formula, and frequent support by health workers had a 40% lower risk of HIV transmission; however, their 24-month mortality was similar to that in the breast-fed group *(18)*. During the first 3 months of life, infants in the group fed formula had an increased risk of diarrhea [relative risk (RR), 2.7; 95% CI, 1.6 to 4.6], dehydration (RR, 11.9; 95% CI, 1.6 to 91.8), and upper respiratory infections (RR, 1.3; 95% CI, 1.1 to1.7). Similarly, the cumulative mortality at 6 weeks and 3 months was higher in the formula-fed group than in the breast-fed group (3.9% versus 1.0% at 6 weeks, and 6.4% versus 4.1% at 3 months). Mortality of infants uninfected with HIV in the first 6 months of life was higher for formula-fed infants (5%) than for breast-fed infants (0.8%) *(18)*.

Influence of pattern of breast-feeding on transmission

We have some other evidence that exclusive breast-feeding, as defined by the WHO carries no more risk of HIV transmission than formula feeding during the first 6 months of life *(10)*. In a prospective cohort study conducted in Durban, South Africa, involving 551 HIV-infected pregnant women, breast-feeding women were counseled and encouraged to practice exclusive breast-feeding for up to 6 months. The rates of transmission at 6 months were similar in the 157 infants who were formula fed and the 118 who had received three or more months of exclusive breast-feeding; 19.4% (CI, 13.6 to 26.0) and 19.4% (CI, 12.5 to 27.4) respectively. The rate in the mixed breast-feeding group (n = 276) was much higher: 26.1% (CI, 20.5 to 31.9). At 15 months, the transmission rate remained lower among those who exclusively breast-fed three or more months than among those who mixed breast-fed their infants (24.75% versus 35.9%, Figure 1). If confirmed in future studies, this observation has important implications for public health policy. New studies specifically designed to test this hypothesis on exclusive breast-feeding are planned at a number of sites in Africa (South Africa, West Africa, Ethiopia, Zambia).

Support for exclusive breast-feeding has also come from preliminary results from a recent study

in Kisumu, Kenya *(19)*. In this study, the incidence rate of HIV infections was greater ($P < 0.07$) for infants who started mixed breast-feedings before 30 days than for infants who started mixed breast-feedings after 30 days. Similarly, the incidence of HIV infections was greater ($P < 0.05$) for infants who started mixed breast-feedings before 120 days compared with those who started after 120 days. However, the effects of viral load and severity of maternal illness were not factored into the results.

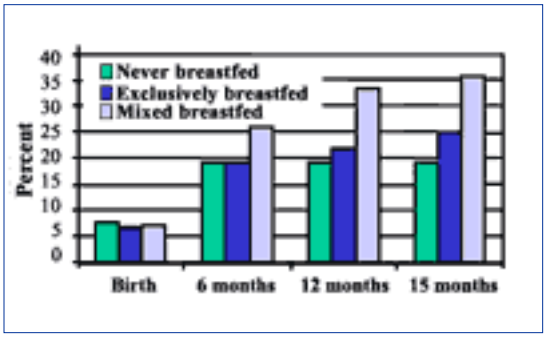

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Figure 1. Rate of HIV infection over time in 157 children never breast-fed; 118 children exclusively breast-fed; and 276 children mixed breast-fed.

Several potential mechanisms could account for the protective effect of exclusive breast-feeding *(20)*. These include the following: reduction in dietary antigens and enteric pathogens that may maintain integrity of the infant's intestinal mucosal barrier and limit inflammatory responses of the gut mucosa, promotion of beneficial responses of the gut mucosa, promotion of beneficial intestinal microflora that may increase resistance to infection and modulate the infant's immune response, alteration in specific antiviral or anti-inflammatory factors in human milk that may modulate maternal hormone or immunologic status, and maintenance of mammary epithelial integrity that may reduce viral load in breast milk.

Other risk factors for HIV transmission through breast-feeding

High viral load in the mother's plasma, cell-free virus in breast milk *(21, 22)*, and breast pathology, such as clinically evident mastitis and cracked, bleeding nipples *(8, 12, 23, 24)*, are considered to increase the risk of transmission of HIV. Additionally, even subclinical mastitis (measured by elevated breast-milk sodium levels) may be associated with increased risk for transmitting HIV during breast-feeding *(25)*.

Willumsen *et al. (26)* also report associations between elevated Na/K ratios in breast milk and HIV viral load in breast milk. However, interpretation is complicated by their finding that Na/K ratios and viral loads vary between breasts at a given time and at different points in time *(26)*.

Guidelines for reducing mother-to-child transmission of HIV

The WHO/UNICEF/UNAIDS guidelines on HIV and infant feeding *(27)* are useful for women in developing countries. They state that "when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breast-feeding by HIV-infected mothers is recommended; otherwise, exclusive breast-feeding is recommended during the first months of life." In addition to these guidelines, reasonable clinical practices may reduce the transmission of HIV from mother to infant during breast-feeding. These include the following:

Improvement in obstetric practices

After delivery, infants' mouths should not be routinely suctioned. Similarly, care must be taken with tube feeding so that the infant's mucous membranes, which come into contact with breast

milk, are not damaged.

Prompt treatment of oral thrush

Oral thrush should be treated immediately with appropriate antifungals, because any breaks in the infant's mucosal barrier pose a risk for HIV transmission.

Shorter duration of breast-feeding

Early weaning off breast milk is a difficult in current circumstances and requires much more research. Weaning is usually a gradual process, and the length of time this takes varies in different parts of the world. Based on the results of the South African study *(10)*, it would appear prudent to aim to keep the mixed breast-feeding period as short as possible. However, if this period of transition is too short, it may have negative nutritional consequences for the infant and psychological consequences for the infant and mother. Further research is still needed to ascertain the best duration for this transition according to age of infant and/or environment. The WHO/UNICEF/UNAIDS guidelines advise that mothers should be provided with specific guidance and support when they cease breast-feeding to avoid harmful nutritional and psychological consequences *(27)*.

Exclusive breast-feeding for up to 6 months

Exclusive breast-feeding has substantial benefits for non-HIV-related child health in contrast to the negative consequences associated with formula feeding *(28-31)*. If the results of the South African study *(10)* are confirmed and are translated into practice, rates of exclusive breast-feeding could be improved. Recent studies have show that interventions that promote and support exclusive breast-feeding, such as peer counselors, can improve exclusive breast-feeding rates *(32-34)*.

Antiretrovirals during breast-feeding

The use of antiretrovirals (or other antiviral agents) given either to the infant or to the lactating mother during breast-feeding is another attractive option. Trials are under way to test this intervention. In one incomplete trial (HIVNET 023), nevirapine given to HIV-exposed infants on a daily or interrupted basis appears to be safe.

Expressing and heat-treating breast milk

Policy makers have considered that expressing and heat-treating breast milk is too difficult to be implemented on a large scale; however, there is evidence to the contrary. Before the AIDS pandemic, mothers frequently expressed breast milk to be used by their infants or by other infants in special need. A recent study from Chile has shown that a program of breast-milk expression can be implemented for working women *(35)*. This program would require testing in the field among populations where HIV incidence is high.

The Holder method of pasteurization of milk used by milk banks (heating breast milk at 62.5ºC degrees for 30 minutes) appears to be effective in destroying HIV virus with minimal destruction of immunoglobulins and other protective factors in the milk *(36)*, and methodology

exists for pasteurizing milk in a home setting *(37)*. Furthermore, Boisen and Jorgensen *(38)* have developed a solar-powered device for pasteurizing breast milk suitable for use in clinics.

Avoiding new infections

HIV-uninfected women who are breast-feeding their infants should take precautionary steps (e.g., sexual abstinence or using condoms) to avoid becoming HIV infected. Acute HIV infection in women is a greater risk factor for mother-to-child transmission of HIV during breast-feeding than chronic infection. This is because viral loads rise steeply and peak immediately after the onset of an HIV infection *(39)*.

Lactation management

Proper breast positioning and attachment of the infant to the breast and not just the nipple should minimize development of cracked and bleeding nipples. Proper emptying of the breasts will reduce milk stasis, engorgement, and mastitis.

Conclusion

We are compelled to conclude that there is no satisfactory solution to the problem of breast-feeding by the majority of HIV-infected women in developing countries. The individual woman has to make the extremely difficult choice between dealing with the likelihood of sickness and death from common infections when infants are not breast-fed against the prospect of transmitting a lethal disease to her child through breast-feeding. Better designed studies are urgently required to test the hypothesis that exclusive breast-feeding for 6 months carries no more risk than formula feeding and to establish more reliable estimates of risks of transmission of HIV in the first 6 months according to type of breast-feeding. Appropriate designs should include community mobilization, antiretrovirals to reduce perinatal mother-to-child transmission of HIV, and a large enough sample size of HIV-infected women to detect the impact of different feeding patterns and other risk factors on rates of transmission by 6 months. Additionally, future studies should include use of the standard WHO definition of type of breast-feeding, careful support and monitoring of exclusive breast-feeding, and frequent blood sampling of the infant for timely detection of HIV infection. Infant morbidity and mortality data should be collected after 24 months, and HIV-free survival determined at 24 months. A prospective cohort study with these elements is being undertaken at the Wellcome Trust's Africa Centre in a rural district in Kwazulu Natal, South Africa. A Zambian study is investigating rapid weaning.

For the present, we recommend adherence to WHO/UNICEF/UNAIDS Guidelines on infant feeding with the following modification: Mothers should be provided with information on advantages of exclusive breast-feeding and hazards of mixed breast-feeding, the probable risk of breast-feeding transmission of HIV after 6 months, and the option of early cessation of breast-feeding. Other options for reducing the risk of HIV transmission through breast-feeding include the following: lactation management to prevent cracked nipples and mastitis, prevention and treatment of infant oral thrush, antiretrovirals during breast-feeding, heat treatment of expressed breast milk, and prevention of new HIV infection by abstaining from sex or using condoms .

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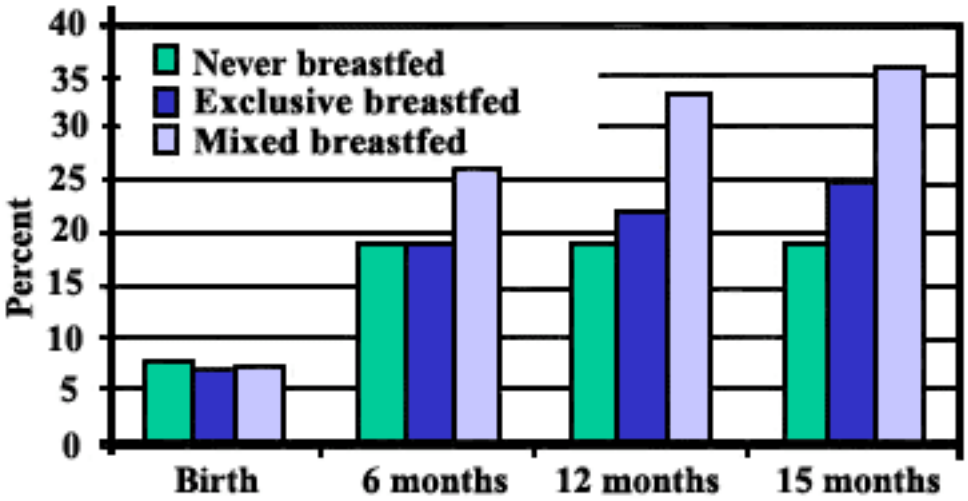
Never breastfed
Exclusive breastfed
Mixed breastfed
Percent
40
35
30
25
20
15
10
5
0
Birth
6 months
12 months
15 months