

Infant feeding and HIV transmission

Randa J. Saadeh, Peggy Henderson and Cota Vallenias

*Consultation on Nutrition and HIV/AIDS in Africa:
Evidence, lessons and recommendations for action*

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Contents

1. Introduction.....	1
2. HIV transmission through breastfeeding	1
2.1. Risks of breastfeeding transmission	2
2.2. Mechanisms of breastfeeding transmission	3
2.3. Timing of postnatal transmission	3
2.4. Factors associated with risk of transmission through breastfeeding.....	4
2.4.1. Maternal factors	4
2.4.2. Infant factors	5
3. Infant feeding and HIV transmission: preventive aspects.....	7
3.1. Replacement feeding	8
3.2. Exclusive breastfeeding with early cessation	8
3.3. Other breast-milk options	9
3.3.1. Wet-nursing by a tested HIV-negative woman	9
3.3.2. Treatment of breast milk	10
3.3.3. Breast-milk banks.....	10
3.4. Antiretroviral drugs for HIV-infected women and/or their exposed infants	11
4. Current or planned research	11
4.1. Feeding practices	11
4.2. Antiretroviral drugs	12
4.3. Immunization against HIV infection	13
4.4. Antiretroviral prophylaxis combined with vaccination	14
5. Operational considerations and obstacles	14
6. Research gaps.....	14
7. Conclusion	16
8. References.....	16

1. Introduction

The Global Strategy for Infant and Young Child Feeding, adopted by the World Health Organization (WHO) and the United Nations Children's Fund, states that the optimal feeding pattern for overall child survival is exclusive breastfeeding for the first 6 months and continued breastfeeding for up to 2 years and beyond, with complementary feeding from age 6 months, together with related maternal nutrition and support (1). The Global Strategy contains specific recommendations for children in exceptionally difficult circumstances, including those born to HIV-positive women. For these women, avoidance of all breastfeeding is recommended if replacement feeding is acceptable, feasible, affordable, sustainable and safe. Otherwise, exclusive breastfeeding for the first months of life is recommended, followed by early breastfeeding cessation as soon as feasible, when the conditions for safe replacement feeding can be met. Mixed feeding with breast milk and other feeds has been suggested to be associated with a higher risk of HIV infection for the infant than is exclusive breastfeeding (2,3) and in any case should be avoided because it carries risks of diarrhoea and other infectious diseases as well as of HIV infection. HIV and infant feeding guidance also states that HIV-positive mothers should receive counselling, including general information about the risks and benefits of the various infant-feeding options and specific guidance in selecting the option most likely to suit their circumstances; they should also have access to follow-up care and support, including family planning and nutritional support (4). The mother's choice should always be respected and supported.

2. HIV transmission through breastfeeding

Transmission of HIV through breastfeeding has been well documented. The first reports indicating the possibility of HIV-1 transmission through breast milk were of breastfed infants of women who had been infected postnatally through blood transfusion or through heterosexual exposure (5-9). Other reports related to infants with no known exposure to HIV infection other than wet-nursing or pooled breast milk (10).

Where breastfeeding is common and prolonged, transmission through breast milk may account for up to half of the HIV infections in infants and young children (11,12). Available

antiretroviral prophylaxis interventions can substantially reduce the risk of transmission during pregnancy, labour and delivery but, so far, significant reduction of risk during breastfeeding has been less successful. Research into the prevention of breastfeeding transmission is concerned particularly with modifying breastfeeding practices as a means to prevent HIV transmission, and with the effect of antiretroviral prophylaxis on transmission, including the timing and duration of its administration; whether it is given to the mother or the infant or both; and drug resistance and other health consequences for mothers or infants.

2.1. Risk of breastfeeding transmission

The overall risk of mother-to-child HIV transmission in non-breastfeeding populations is 15-25% (without interventions to reduce transmission) and in breastfeeding populations 20-45% (13).

The risk can be reduced to less than 2% by antiretroviral prophylaxis during gestation, birth and the neonatal period together with elective caesarean section and avoidance of breastfeeding (14).

Peripartum antiretroviral monotherapy alone can reduce the risk to about 15% at 3 months in breastfeeding infants. Combination therapy (zidovudine and lamivudine during the last 8 weeks of pregnancy, with the addition of single-dose nevirapine during labour and delivery) has been shown to reduce MTCT rates to less than 6% at 6 weeks in breastfeeding infants (15). Subsequent infection through breastfeeding, however, can increase the overall risk at 18-24 months to over 20%. The risk of mother-to-child transmission of HIV is substantially increased by deteriorating maternal health status - high HIV viral load in plasma, a low CD4+ cell count and AIDS - and to a lesser extent by vaginal delivery or prematurity. Recent maternal infection with HIV may raise the risk of transmission through breastfeeding to twice that of a woman with earlier established infection, probably because of the high viral load associated with recent infection.

Because breast milk can transmit HIV at any time during lactation, the rate of HIV infection in breastfed infants is cumulative and increases with duration of breastfeeding. An individual patient meta-analysis estimated that the cumulative probability of late postnatal transmission between 4 weeks and 18 months of age was 9.3%, or about 9 HIV infections per 100 child years of breastfeeding, and that the risk of transmission was constant throughout breastfeeding (16). In this meta-analysis, approximately 42% of all HIV infections were attributable to breastfeeding.

2.2. Mechanisms of breastfeeding transmission

The mechanisms by which breastfeeding transmits HIV are not well understood. Possible portals of virus entry include M cells in the tonsils or overlying the intestinal lymphoid Peyer's patches, direct infection of the enterocyte or possibly direct passage through disruptions in mucosa or between immature mucosal junctions (17). The roles of cell-free and cell-associated virus in transmission and the association between virus levels in plasma and in milk have not been reliably quantified, though recent reports suggest that cell-associated virus may be more important than previously recognized (18).

2.3. Timing of postnatal transmission

Two factors make it difficult to determine the precise timing of HIV transmission and whether infection occurred during delivery (intrapartum) or, through breastfeeding, immediately postpartum: one is the persistence of maternal antibodies and the other is that during a certain period infection is undetectable by current technology. Some studies suggest that the first several weeks of life may be the highest-risk period for transmission. In a trial in Nairobi, Kenya where infants were randomized to breastfeed or formula-feed, most of the cumulative difference in HIV infection rates between breastfed and formula-fed infants had occurred by 6 weeks of age: the difference between groups was 10% at 6 weeks and 16% at 24 months (19). However, there were differences in the birth transmission rates between the breast-milk-fed and formula-fed groups, suggesting that randomization had not produced equivalent groups and hence a comparison of cumulative rates as described above is problematic.

The relative risk of HIV transmission by colostrum and mature breast milk is not clear (20-23). These types of milk differ with regard to the types of cells they contain and their levels of immune-modulating components (e.g. vitamin A, immunoglobulins and lactoferrin), and infants ingest much less colostrum than mature breast milk. The immune system of infants is less well developed at the beginning of lactation than later, and younger infants have an increased blood concentration of maternal antibodies. No evidence suggests that avoidance of colostrum would reduce the risk of HIV transmission to the infant.

2.4. Factors associated with risk of transmission through breastfeeding

2.4.1. Maternal factors

Many of the factors known to influence overall risk of transmission are also likely to influence transmission through breastfeeding: maternal RNA viral load in plasma and breast milk; HIV-related maternal immune status; breast conditions, including mastitis and abscesses; nutritional status of the mother; mode of infant feeding; infant factors (such as oral ulcers); and, possibly, protective elements in the milk.

The risk of transmitting HIV through breastfeeding is strongly associated with HIV RNA levels in the milk (24). In South Africa and Malawi, women with a detectable RNA viral load in their milk at any time during the first 6 months postpartum were more likely to transmit HIV than were women in whose milk RNA virus was not detected (24,25). In West Africa, the rate of late postnatal transmission increased 2.6 times for every \log_{10} increase in plasma RNA viral load measured in late pregnancy (26). Studies by Willumsen et al. (27,28) in South Africa indicate that, in general, RNA viral load in milk is lower than in plasma, and often lower than the detectable limit of the assays used. The amount of HIV found in human milk samples differed between breasts and over time, suggesting that virus shedding into breast milk is variable (27).

Studies have consistently shown a relationship between maternal CD4+ cell count around the time of delivery and risk of postnatal HIV transmission. In the BHITS meta-analysis, a strong association was observed between risk of postnatal infection after 4 weeks of age and maternal CD4+ cell count: transmission increased 8 times at counts less than 200×10^6 cells/L and 3.5 times at counts between 200 and 500×10^6 cells/L compared with the reference group of CD4+ cell count greater than 500×10^6 cells/L (16). Low plasma CD4+ counts have been associated with detection of HIV DNA in breast milk (29).

Clinical and subclinical mastitis are associated with HIV transmission risk. Subclinical mastitis is not necessarily an infection and may occur with milk stasis and breast engorgement, and may be associated with increased milk RNA load and cytokines (25,30). Mastitis is more likely to occur when the milk first comes in after birth, with inadequate milk drainage as well as with mixed feeding, with poor attachment or weak suckling by an ill infant and with rapid weaning (31-33).

Whether treatment of mastitis and other breast lesions reduces the rate of transmission at the population level is still a subject of research.

Maternal nutritional status may influence risk of transmission overall and during breastfeeding. Early observational studies reported that mothers with low serum retinol levels were more likely to transmit HIV to their infants (22). This observation led to the implementation of several clinical trials in Africa on the impact of vitamin A supplementation with or without other micronutrients on mother-to-child HIV transmission. Results of these studies have varied and are reported in greater detail in the micronutrient paper by Friis (34). In one study, preformed vitamin A given together with β -carotene was associated with a slight increase in transmission rates overall and an increased risk of breastfeeding transmission (35). On the other hand, multivitamins (excluding vitamin A) were associated with a nonsignificant reduction in breastfeeding transmission and mortality in the first 2 years of life. The children of women who had been randomly assigned to receive multivitamins during pregnancy and lactation had a significantly lower risk of diarrhoea ($P=0.03$) and a substantially higher mean CD4⁺ cell count ($P=0.006$) than those who did not receive multivitamins (36). HIV-positive and -negative children benefited alike. Vitamin A given to the mother reduced the risk of respiratory infections in the child significantly ($P=0.03$) but did not affect diarrhoea. Other studies have shown no effect of vitamin A supplementation during pregnancy on risk of breastfeeding transmission (37,38). In the ZVITAMBO trial in Zimbabwe, single, high-dose postpartum vitamin A supplementation had no effect on postnatal HIV transmission risk (2). Maternal mid-upper arm circumference, however, was associated with a significantly reduced risk of HIV transmission during breastfeeding, after taking into account maternal immune status and other feeding and health variables (2). In that same study, severe maternal anaemia ($Hb < 70$ g/L), although uncommon, was associated with a nearly 7-fold increased adjusted risk of postnatal HIV transmission from 6 weeks to 6 months (2).

2.4.2. Infant factors

Damage to the mucous membrane of infants (e.g., by oral thrush) may increase the risk of HIV transmission by breastfeeding. Which is cause and which effect, however, may be unclear, for thrush may occur with early HIV-1 infection (31,39). Oral thrush can also cause nipple thrush and

fissures. The intestinal mucosa may be damaged by cow's milk, allergic reactions to complementary foods, and infection. Mode of feeding may affect the intestinal permeability of the young infant (40): exclusively breastfed infants may have a less permeable and therefore healthier gut lining than those not breastfed. Feeding mode in children born to HIV-positive mothers, however, has not been found to be associated with intestinal permeability in infants (measured with lactulose-mannitol ratios, i.e. dual sugars), but infants diagnosed with HIV infection at 14 weeks had higher permeability at 6 and 14 weeks than uninfected infants (41). Only one study was done on this issue and further research is needed.

At population level, mode of infant feeding has particular relevance to rates of HIV transmission. In most populations, breastfeeding is usually initiated but is soon supplemented with water or other drinks or feeds; exclusive breastfeeding beyond the first few months is rare (42).

A study in South Africa found that infants who received both breast milk and other feeds were significantly more likely to be infected by 15 months of age (36%) than those who had been exclusively breastfed for the first three months (25%) or formula fed (19%) (3). Exclusive breastfeeding carried a significantly lower risk of HIV infection than mixed breastfeeding. An increased risk of postnatal HIV transmission associated with early mixed feeding was also recently reported in the ZVITAMBO trial. In that study of 2060 HIV-positive mothers with infants who were HIV-PCR negative at 6 weeks, the rates of postnatal HIV transmission were 5.1, 6.7, and 10.5 per 100 child years of exclusive, predominant, and mixed breastfeeding, respectively (2). The protective effects of early exclusive breastfeeding were greatest in the first 6 months, even after controlling for maternal immune and nutritional status, but continued throughout the 18 month follow-up period. Further studies are under way to confirm these findings, which have obvious implications for infant-feeding recommendations and for advice to HIV-positive women in settings where it is not acceptable, feasible, affordable, sustainable or safe to refrain from breastfeeding.

Result from a large meta-analysis showed that maternal CD4+ cell counts and child gender were significantly associated with postnatal transmission after 4 weeks of age; females were 40% less likely than males to become infected through breastfeeding after 4 weeks of age (16). The risk was highest for males breastfed by mothers with CD4+ cell counts less than 200×10^6 cells/L, followed by

males whose mothers had counts of $200\text{--}499 \times 10^6$ cells/L and then by females breastfed by mothers with counts less than 200×10^6 cells/L. Duration of breastfeeding was similar for both sexes but age of introduction of other foods or type of food was unknown. The sex difference in risk of late postnatal transmission may have been due to males receiving complementary feeds at an earlier age, thus making them mixed feeders, which could raise their risk of becoming infected, or it could indicate a difference of timing of acquisition of infection following suggestions by other studies that girls are more likely to acquire infection in utero than boys (43). There was no association between infant sex and risk of postnatal HIV transmission in the ZVITAMBO trial (2,44).

3. Infant feeding and HIV transmission: preventive aspects

Prevention of HIV transmission associated with breastfeeding should be considered in a broad context that takes into account the need to promote breastfeeding of infants and young children in the general population. Infant-feeding options designed to prevent mother-to-child transmission are fully described in other documents (45,46). Several investigators have attempted to use mathematical models to guide policy-makers in weighing the relative risks and benefits of breastfeeding and other infant-feeding options in this context (47,48). Models to balance these risks are limited by the scarcity of data on the risks associated with various methods of infant feeding, particularly in the first weeks of life, the risks associated with not breastfeeding in populations where HIV is prevalent, and by the inability of models to take into account all factors that influence individual decisions about infant feeding. In any case, counselling for individual women should be based on their unique circumstances.

The infant-feeding options for HIV-positive mothers are replacement feeding with commercial infant formula or home-modified animal milk; exclusive breastfeeding with early cessation; and wet-nursing, expressing and heat-treating breast milk, and breast-milk banks where available. Of paramount importance are finding ways to make feeding safer for infants of HIV-positive women, and finding effective strategies for supporting women in their infant-feeding choices. Counselling HIV-positive women on infant feeding should consider their personal circumstances and their disease progression: the rate of postnatal transmission in women with advanced disease is very

high. Finally, interventions are needed at the community level to increase the acceptability of feeding practices different from the cultural norms (e.g., exclusive breast milk or replacement feeds).

3.1. Replacement feeding

Replacement feeding means feeding an infant receiving no breast milk a diet that provides the necessary nutrients. Suitable breast milk substitutes include commercial infant formula or home-modified animal-milk (46). Little is known about how replacement feeding affects infant morbidity or mortality in the context of PMTCT programmes (49-51); the indications are that mortality is high for both uninfected and infected infants of HIV-positive mothers (52).

Avoidance of all breastfeeding is recommended for HIV-positive mothers when replacement feeding is acceptable, feasible, affordable, sustainable and safe. Otherwise, exclusive breastfeeding for the first months of life is recommended. Support for adequate replacement feeding is needed throughout the first 2 years of life, when breast milk is normally recommended and the child is at greatest risk of malnutrition. From birth to 6 months, some form of milk is generally considered essential; after 6 months additional replacement-feeding options may be used; they should include solid foods, preferably still with milk in some form (53).

3.2. Exclusive breastfeeding with early cessation

Exclusive breastfeeding means nourishing an infant on breast milk alone with no other liquids or solid foods apart from human milk, although prescribed medicines and vitamin-mineral supplements are allowed within this definition. Early cessation means completely stopping breastfeeding before age 2 years and, ideally, it occurs among HIV-positive mothers as soon as replacement feeding is acceptable, feasible, affordable, sustainable and safe, as a strategy to reduce the risk of HIV transmission by limiting the infant's exposure to HIV infection through breast milk (54). However, there are limited data on the impact of early breastfeeding cessation on infant HIV-free survival and studies are currently underway to examine this issue in Zambia and South Africa (33). Support is still needed, however, to ensure adequate nutrition during the first years of life. Some mothers may be unable to provide replacement feeding even from 6 months onwards because suitable replacement foods may be hard to obtain. In such situations, early cessation may increase malnutrition in infants and young children (53).

It is important to bear in mind that many countries have relatively low population rates of exclusive breastfeeding up to 6 months of age; yet longitudinal and randomized controlled studies in different settings have shown that breastfeeding counselling increases those rates (55). Some countries have successfully increased such rates with combined action at different levels. In the ZVITAMBO trial, clinic-based education and counselling on safer breastfeeding practices in areas of high antenatal HIV prevalence resulted in an 8-fold increase in the practice of exclusive breastfeeding for at least 3 months among mothers of known and unknown HIV status alike (56).

Other programmes have met with mixed success in promoting either exclusive breastfeeding or exclusive replacement feeding. Early evidence from a PMTCT pilot programme in Botswana, where free infant formula was provided to HIV-positive mothers, indicated that about 90% of the HIV-positive participants were exclusively formula feeding (57). Of the 10% who breastfed, only 20% did so exclusively. Mothers who stopped breastfeeding around 3–4 months experienced greater criticism and more breast health problems (e.g., engorgement) than those who stopped breastfeeding around six months. The study included only women still attending the programme and not those who were noncompliant or had dropped out; and thus the results may have been biased toward formula feeding (Rollins NC and Willumsen JF, unpublished, 2001). In another trial, exclusive breastfeeding was better maintained if the partner knew of the mother's HIV status and was party to the decision to breastfeed or formula feed (49).

3.3. Other breast-milk options

The other breast-milk options to reduce HIV infectivity are wet-nursing by a tested, HIV-negative woman; rendering breast milk noninfectious; and use of breast-milk banks.

3.3.1. *Wet-nursing by a tested HIV-negative woman*

Wet-nursing may be considered in communities where this option is accepted. The wet-nurse must understand and agree to the implications of HIV testing and counselling, as she will need HIV testing before wet-nursing and 6–8 weeks after starting. In addition, she should be counselled about HIV infection and how to avoid infection during breastfeeding. There is anecdotal evidence of infected infants transmitting HIV to their HIV-negative breastfeeding mothers (58,59).

3.3.2. Treatment of breast milk

The modification or treatment of breast milk to render it non-infectious involves expressing milk, and lactating women have to be taught and supported to sustain this process for long periods. The option should nevertheless be offered; opting women should be counselled on infant feeding, hygiene must be ensured and stigma must be prevented. Expression and heat treatment can be a temporary measure in periods of increased risk of transmission due to cracked nipples or breast abscess, for example, or for low-birth-weight or sick infants, for whom replacement feeding would represent increased risk, as well as during transition from exclusive breastfeeding to replacement feeding (45).

In vitro studies have shown that when breast milk to which a known quantity of HIV has been added is heat-treated the infectious titre of cell-free and cell-associated virus is substantially reduced (60). Methods of heat treatment suitable for domestic use, such as the Pretoria pasteurization method or flash heating method (61-63) are being looked at.

Heat treatment at high temperatures reduces many immune and protective components of breast milk (64). Breast milk contains substances that inhibit infectious agents (64). Several studies have indicated that HIV is inactivated when milk is left to stand at room temperature for 30 minutes (63,65); the inhibitory effects of breast milk were attributed to a factor activated by milk lipase, which released fatty acids that seemingly dissolved or disrupted the viral envelope. Newburg et al. (65) demonstrated that human milk glycosaminoglycans inhibited binding of HIV glycoprotein gp120 to host-cell CD4+ receptors. HIV may be inactivated by adding microbicides to breast milk and letting it stand for 5–10 minutes. Evaluation is needed of alternative methods of breast-milk treatment that use or enhance the action of naturally occurring anti-HIV factors.

3.3.3. Breast-milk banks

Experience with breast-milk banks in Latin America, especially in Brazil (66), has been positive though limited in relation to HIV infection. Breast-milk banks may be very useful for HIV-infected women where they are already established. Heat treatment of breast milk is recommended for all milk banks. Whether milk banks should systematically screen donors for HIV remains to be explored.

3.4. Antiretroviral drugs for HIV-infected women and/or their exposed infants

Given the significant added transmission risk for children breastfed by women with low CD4+ counts, several research trials are presently investigating the impact of giving antiretroviral drugs to women while they are breastfeeding and or to the child during the period of breastfeeding exposure. Results are expected in the near future (67; Vyankadondera J et al., unpublished data, 2004).

4. Current or planned research

The overriding research priority with regard to infant feeding and HIV infection is to find a means of reducing substantially or eliminating the risk of transmission of HIV infection through breastfeeding. Such research is concerned with mode of infant feeding (exclusive breastfeeding or mixed feeding) and with the response of the mother and the infant to antiretroviral drugs over the breastfeeding period (68). The safety of replacement feeding after early cessation using locally available foods or supplements is another important research question. Current or planned studies are designed to develop interventions that will substantially reduce the risk of HIV transmission through breastfeeding in the first months of life to infants in resource-poor settings, born to HIV-positive women for whom refraining from breastfeeding is not an option.

4.1. Feeding practices

Research is indicated to assess morbidity and mortality among HIV-positive and -negative breastfed and non-breastfed infants of HIV-positive mothers to further inform the debate about how best to counsel HIV-positive women about infant feeding. Other research questions in this context are whether, or the extent to which, the recommended infant-feeding options result in increased or reduced HIV-free child survival at age 2 years; whether, or to what extent, the protection against common childhood infections normally conferred by breastfeeding applies to breastfeeding of HIV-positive infants by HIV-positive mothers; the optimal duration of exclusive breastfeeding and the process of cessation; and how to safely feed infants after early breastfeeding cessation. Current studies in sub-Saharan Africa are expected to provide much-needed data to inform practical recommendations on all aspects of early cessation.

4.2. Antiretroviral drugs

Antiretroviral prophylaxis is aimed at preventing HIV infection in the fetus or infant.

Antiretroviral drugs are provided to the HIV-positive mother during pregnancy and during the birth process, to the infant in the neonatal stage, or to both mother and infant.

Little is known about the safety for the breastfed infant of treating the mother or the infant with antiretroviral drugs (69). The provision of antiretroviral drugs as a prophylaxis to breastfed infants or as a continued viral-load suppressant to breastfeeding women is being evaluated. Trials are underway of several infant regimens to reduce transmission to breastfed infants: the administration for up to 6 months of nevirapine alone, of lamivudine alone, of nevirapine plus zidovudine, or of zidovudine plus lamivudine (67). The HIVNET023 phase-II trial in South Africa and Zimbabwe has shown that nevirapine has a good safety profile and maintains repeatedly high plasma concentrations when given daily or twice weekly to uninfected infants (69). Preliminary findings from the first of the infant prophylaxis trials suggest that the risk of postnatal transmission is about 1% in the first 3 months of life in infants who receive either nevirapine or lamivudine and who were born to women with relatively high CD4+ counts and low RNA viral load (70). Research is needed to confirm these rates, which compare with a 1.6% (95% confidence interval (0.3, 2.9) risk of late postnatal transmission between 4 weeks and 3 months without intervention (16).

Whether highly active antiretroviral therapy (HAART) beginning in late pregnancy or at or after delivery also reduces the risk of postnatal infection of the infant needs to be carefully examined. Markers of HIV progression such as low maternal CD4+ cell counts indicate that at least some women in resource-poor countries need HAART to delay progression of their own disease (70). The Treat 3 Million by 2005 Initiative launched by WHO and its partners is designed to make antiretroviral treatment available to 3 million people living with AIDS in poor countries by the end of 2005. This initiative is likely to increase substantially the number of HIV-positive pregnant women with access to antiretroviral drugs and, extended beyond 2005, may eventually ensure lifelong treatment for all mothers who need it. Some women on HAART may choose to breastfeed on the assumption that there is little or no risk of transmission; however, it is likely that even with HAART, there is a risk of transmission, albeit low.

An alternative approach being evaluated in several studies is to offer treatment during and after breastfeeding. In these trials, women who need HAART for their own health will be offered it long-term whether or not they are breastfeeding; these are mothers with evidence of advanced disease, such as CD4+ cell counts below 200×10^6 cells/L. This treatment is in line with current WHO recommendations, although its effect on rates of mother-to-child transmission is as yet unknown. The same trials are assessing the impact of HAART during breastfeeding for other categories of women, not yet in need of treatment for their own health, and are evaluating the safety of the antiretroviral intervention for infants exposed to HAART through breast milk. Pharmacokinetic studies of antiretroviral diffusion in breast milk are being carried out and are urgently needed. As regimens are developed for antiretroviral use during lactation, viral resistance in breast milk will become increasingly prevalent. In the planned maternal HAART studies (in which HIV-positive mothers receive HAART while breastfeeding) infants are likely to be exposed to sub-therapeutic levels of antiretroviral drugs through breast milk and some will become HIV positive. It is not known whether those who become infected will develop HIV resistance to antiretroviral drugs or whether such resistance will affect their future HIV treatment. For this issue to be assessed, therefore, HIV-positive children will need long-term follow-up.

To further understand and to prevent HIV transmission through breastfeeding, it is necessary to determine the mechanisms of viral resistance in breast milk. Resistance in breast milk may not be the same as resistance in plasma and may develop differently according to whether it is of viral origin or due to inadequate drug levels.

4.3. Immunization against HIV infection

Active (vaccine) or passive (immunoglobulins) immunization of infants is also being considered to reduce the risk of infection through breastfeeding in places where women cannot easily refrain from breastfeeding. This approach could complement the use of antiretroviral prophylaxis in the peripartum or early neonatal period (71). This is being evaluated in Ethiopia and Uganda but may actually be most helpful in combination with ARV, and early success is more likely to be due to the delay in disease progression rather than avoidance of infection.

4.4. Antiretroviral prophylaxis combined with vaccination

Ultimately, research aims at preventing HIV transmission by combining antiretroviral prophylaxis with vaccination. Research plans thus include the development of randomized trial protocols for vaccine testing to prevent infection during breastfeeding: infants of HIV-positive mothers will likely receive antiretroviral prophylaxis for perhaps 3 months during which they will receive three or more doses of vaccine (71).

5. Operational considerations and obstacles

From the time when the first reports indicated that HIV could be transmitted through breastfeeding, the public health community has been challenged by the dilemma of how to safely feed infants in areas where good water supply and sanitation are not available. The absence of data on key aspects of this dilemma has resulted in numerous debates and modelling exercises, each proposing a way forward. However, it has been the counsellor working in local clinics and the HIV-positive mother herself who has been confronted with the task of understanding the relative risks of breastfeeding or avoidance thereof and the day-to-day reality of feeding a child in societies with strong normative practices and values. The resultant challenge has been how to make infant feeding safer for the young HIV-exposed infant while not undermining arguably the most important child survival strategy for the vast majority of children worldwide. For the individual HIV-exposed child overall, survival and not avoidance of HIV transmission alone should be the over-riding consideration. In the light of this, the United Nations agencies formulated *A Global Strategy for Infant and Young Child Feeding*, which addressed the feeding of HIV-exposed children as part of the recommendations for all children (1).

6. Research gaps

The following are specific research issues:

- Effect of antiretroviral drugs on HIV transmission through breastfeeding:
 - as prophylaxis—effect on transmission; timing and length of administration, whether to mother or infant or both; and health consequences for mother and infant, including drug resistance;

- as treatment for the mother (e.g., HAART)—its effect on transmission and its short-term and long-term health consequences for the infant.
- Pharmacokinetic studies on antiretroviral diffusion in breast milk. Infants of HIV-positive mothers receiving HAART while breastfeeding may, through subtherapeutic exposure to antiretroviral drugs, develop resistance to those drugs; they need long-term follow-up to determine whether such resistance will affect their future HIV treatment.
- The mechanisms and rates of breastfeeding transmission, in particular the parts played by cell-free and cell-associated HIV, disruption of the epithelial integrity of the mucous membranes of the infant's mouth or intestine (caused by nutritional or infectious factors such as mixed feeding or oral thrush), and nipple fissures or clinical or subclinical mastitis.
- At population level, whether promotion of good breastfeeding practices to increase rates of exclusive breastfeeding while minimizing breast pathology reduces the rate of mother-to-child transmission of HIV infection.
- Whether or to what extent the protection against common childhood infections normally conferred by breastfeeding applies to breastfeeding of HIV-positive infants by HIV-positive mothers.
- Optimal duration for the process of early breastfeeding cessation (current studies in sub-Saharan Africa are expected to provide much-needed data to inform practical recommendations on all aspects of early cessation) and replacement feeding of the non-breastfed child after 6 months.
- The nutritional and developmental consequences of early cessation of breastfeeding.
- Whether nutritional status of the mother influences the rate of transmission of HIV-infection to the infant, and assessment of the health benefits of nutritional support to breastfeeding HIV-positive women.
- Community interventions to increase the acceptability of infant feeding choices by HIV-positive mothers and to reduce stigma

7. Conclusion

Few pandemics in history have had a more pernicious effect than the targeting by HIV of the fetus and the infant through the infected mother's plasma and milk and the vulnerability thus imposed on the infant in the peripartum process and postnatally. The infant is vulnerable particularly in that breastfeeding, the ideal form of sustenance—nutritional and psychosocial—is compromised as are its consequences in length and quality of life.

The pandemic has also stimulated a response that takes a variety of forms, from the sociopolitical and socioeconomic to education and public health and to the immunological, microbiological and technological. This chapter has outlined the basis of what is known about infant feeding and transmission of HIV: rates of transmission, mechanisms and timing, and the maternal and infant factors associated with risk of transmission through breastfeeding. Outlined also are the infant-feeding options for the prevention of transmission, the current and prospective roles of antiretroviral drugs in prevention and therapy, and the current research priorities. Clearly, there is scope for a variety of government sectors and voluntary bodies as well as an educated public to contribute to the prevention and management of the conditions that predispose to the transmission of HIV through breastfeeding.

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