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Breast-feeding and HIV transmission

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HIV-1 (subsequently referred to as HIV) infection may be transmitted to the infant during breast-feeding. The risk of transmission varies with stage of maternal infection, duration of breast-feeding, type of breast-feeding (i.e. exclusive or mixed breast-feeding), and breast pathology. Recent studies support the findings of a meta-analysis (Dunn *et al*. 1992) and indicate that when breast-feeding is practised for over 2 years, the risk of infection is about 14 %. Shorter durations of breast-feeding may therefore minimize the risk of transmission. Although the risk of infection appears to be greatest in the first 6 months this risk needs to be weighed against the excess risk of morbidity and mortality if children are not breast-fed in the first 6 months. In resource-poor settings any policy decision to replace breast-feeding with formula feeding in order to prevent postnatal HIV transmission needs to be balanced against the risks to the infant of malnutrition, morbidity and death if not breast-fed. New information suggests that exclusive breast-feeding, instead of the norm of mixed breast-feeding, may not increase risk of HIV transmission at 6 months and suggests that exclusive breast-feeding with early cessation may be a viable option for some women. The present review suggests options for reducing risk of HIV transmission through breast-feeding. Finally, current knowledge points to the dangers of large-scale replacement feeding programmes in contexts where women will have low education, poor access to water and health services, and strong cultural pressures to breast-feed. Emphasising replacement feeding in these contexts may fuel the mixed breast-feeding practice for mothers who will have no other choice than breast-feeding, yet will try to follow the recommendations applied to replacement feed.

Breast-feeding: HIV infection: Infant nutrition

Abbreviations: ARV, antiretroviral drugs; AZT, azidothymidine; MTCT, mother-to-child transmission; PCR, polymerase chain reaction; RCT, randomized controlled trial.

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Introduction

It is estimated that over 34 million individuals are living with HIV and AIDS and that an estimated 18·8 million individuals around the world have already lost their lives to the disease. Some 95 % of HIV-infected individuals live in developing countries, most of them in sub-Saharan Africa. Ironically, these same countries, which bear the brunt of the HIV epidemic, are also the countries which are identified by the World Bank as heavily indebted poor countries (UNAIDS, 2000). A large proportion of the HIV and AIDS burden is borne by women of reproductive age. Antenatal clinics are usually used as the sentinel sites for tracking the epidemic; information from sub-Saharan Africa reveals high prevalences of pregnant women infected with HIV (range 15–40 %). The risk of the infant being infected varies, and even for those children who escape perinatal infection, survival rates may decrease because of the loss of one or both parents to AIDS. In 1999 alone, an estimated 590 000 children throughout the world became infected with HIV, of which over 90 % were perinatally infected. More than 90 % of these HIV infections occurred in sub-Saharan Africa. Perhaps the saddest thing about the HIV epidemic is the dual burden that women must bear. Not only are they at increased risk of HIV infection because of their status and limited freedom (from sexual violence, poor education, poverty and dependence on men), but they must also bear the anguish of the possibility of transmitting the virus to their infants. The thought of transmitting the virus through breast-feeding is especially difficult to cope with, as breast-feeding is an integral part of a woman's motherhood. The present review will examine the risks associated with breast-feeding, methods of minimizing the risk, policy implications and research issues.

Background information on mother-to-child transmission of HIV

The present review will only consider transmission of HIV-1 (subsequently referred to as HIV), as mother-to-child transmission (MTCT) of HIV-2, through any route, is rare (Andreasson *et al*. 1993). HIV may be transmitted from mother-to-child by the following methods.

In utero *transmission*

It is estimated that about 7 % of infants are infected in this way. A positive HIV polymerase chain reaction (PCR) test within 48 h of delivery is indicative of *in utero* infection.

Intra-partum transmission

It is estimated that about 13 % of infants, vaginally delivered to mothers not on antiretroviral (ARV) treatment, are infected in this way. A negative PCR test within 48 h and positive HIV PCR test up to 6 weeks later is indicative of intra-partum transmission. *In utero* and intra-partum transmission can be substantially reduced by the use of ARV and elective Caesarean deliveries. The industrialized countries with sufficient funds, availability of personnel and good health services can provide both ARV and elective Caesarian sections for HIV-infected women. These strategies have proved to be so effective that transmission rates in the USA and Europe are now reported to be down to about 5–6 % (Mofenson & McIntyre, 2000). Developing countries do not, however, have access to these strategies and the most promising strategy which

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may be affordable is the use of nevirapine, first tested in Uganda and shown to have an efficacy of about 50 % (Guay *et al*. 1999). This regimen has recently been tested in South Africa as well, and has been reported to be as effective (Moodley, 2000).

Post-partum transmission through breast-feeding

A small amount of breast-feeding transmission may also be contributing to the intra-partum transmission, but it is very difficult to distinguish breast-feeding transmission from that which occurs during the delivery process. It is generally accepted that transmission after 6 weeks is attributed to breast-feeding.

Evidence for breast-feeding transmission and attempts to quantify the risk

Transmission of HIV through breast-feeding was first described in women newly infected after delivery through blood transfusion or heterosexual exposure (Ziegler *et al*. 1985; Van de Perre *et al*. 1991). It has since been well documented that HIV may be transmitted through breast-feeding. A meta-analysis by Dunn *et al*. (1992) estimated that breast-feeding by women with established infection may increase the rate of transmission by 14 % (95 % CI 7, 22). The risk of transmission increases for the mother with a newly-acquired infection in the breast-feeding period; estimated to be 29 % (95 % CI 16, 42). In individual studies, late seroconversions in breast-fed children have been reported (Datta *et al*. 1992; Lepage *et al*. 1992; Bulterys *et al*. 1995; Bertolli *et al*. 1996; Ekpini *et al*. 1997; Karlsson *et al*. 1997). Some early published studies have also shown that breast-feeding compared with formula feeding (never exposed to breast-feeding) is associated with an increased risk for HIV transmission (De Martino, 1994; Bobat *et al*. 1997).

Using observational studies, the risk of postnatal transmission, including both early and late postnatal transmission of HIV, can only be reliably estimated using data from large prospective studies with frequent laboratory follow-up of children born to HIV-infected mothers, where postnatal transmission can be distinguished from intrauterine and intra-partum transmission by the use of frequent PCR tests. Most of the early studies comparing breast-feeding with formula feeding did not have early PCR testing to distinguish postnatal from intrauterine and intra-partum transmission, and so are not as useful. A further limitation of earlier studies was that sample sizes were small and the two infant feeding groups were very uneven in size.

Recently the results of three studies have been published in which both groups have at least 100 women. Two were observational studies (Tess *et al*. 1998; Coutsoudis *et al*. 2001); only one of which collected feeding information prospectively (Coutsoudis *et al*. 2001) and one was a randomized controlled trial (RCT; Nduati *et al*. 2000*a*). HIV infection results from these three trials are summarized in Table 1.

The study by Tess *et al*. (1998) was conducted in Brazil and HIV infection status was determined by ELISA at 18 months, no PCR tests were done and, therefore, the proportion of post-partum transmission is not known. The study shows, however, the increased risk of transmission related to breast-feeding. HIV infection was detected in 21 % of breast-fed infants compared with 13 % of formula-fed infants. The absolute rates of infection in both groups were lower than usual, presumably because of the nature of the study; only infants surviving and remaining in follow-up to 18 months or those under 18 months with obvious clinical signs of infection would be available for classification of HIV status. Of 553 children originally

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Table 1. Mother-to-child transmission rates (%) for HIV-1 in breast-fed and formula-fed infants*

Study	Mode of feeding	*n*	Age of infants: 1 d	6 weeks	3 months	6 months	15–18 months	24 months
Brazil (Tess *et al*. 1998)	Breast-fed	168					21	
	Formula-fed	264					13	
South Africa (Coutsoudis *et al*. 2001)	Breast-fed	157	6·9			24·2	31·6	
	Formula-fed	394	7·6			19·4	19·4	
Kenya (Nduati *et al*. 2000*a*)	Breast-fed	191	7·0	19·9	24·5	28·0		36·7
	Formula-fed	193	3·1	9·7	13·2	15·9		20·5

*Breast-fed infants were predominantly mixed breast-fed; formula-fed infants were never breast-fed. Results are from studies with at least 100 infants per group.

followed, infection status was only available for 434 children. The absolute risk of breast-feeding transmission compared with formula feeding was 8 % at 18 months. This risk level was probably lower than expected because, as already mentioned, no early PCR testing was done and also the duration of breast-feeding was very low (median duration 30 d).

The study from South Africa (Coutsoudis *et al*. 2001) was an observational study in which feeding data were collected at 1 week, 6 weeks and 3 months after delivery, and thereafter 3-monthly until 15 months of age. At each of these visits blood samples were available for PCR testing for HIV. Included in the study were 394 infants who were breast-fed and 157 infants who were formula-fed. At 15 months of age 31·6 % of breast-fed infants were HIV-infected compared with 19·4 % in the formula-fed group, representing an excess absolute risk of HIV transmission through breast-feeding of 12·2 % after 15 months. The median duration of breast-feeding was 6 months; the probability of still breast-feeding at 12 months was 27 %.

The Kenyan RCT (Nduati *et al*. 2000*a*), using an intent to treat analysis, showed that at 24 months of age, 36·7 % of breast-fed infants were infected compared with 20·5 % of the formula-fed infants, representing an excess absolute risk of HIV transmission of 16·2 % after 24 months. The median duration of breast-feeding was 17 months.

The South African (Coutsoudis *et al*. 2001) and Kenyan (Nduati *et al*. 2000*a*) study results confirm the results of the early 1992 meta-analysis (Dunn *et al*. 1992) of approximately 14 % breast-feeding transmission over 2 years of breast-feeding. This value will obviously vary according to duration and type of breast-feeding practice, which will be discussed later (see pp. 195–197).

Some important points have emerged from the Kenyan RCT (Nduati *et al*. 2000*a*), and these points need to be highlighted as they shed some light on the dilemma facing HIV-infected women. The trial has shown that to examine infant feeding and its effect on postnatal transmission, an RCT may not be the best study design because of the difficulty with randomizing behaviours. In the formula-feeding arm 30 % of women reported also breast-feeding, and if one examines the accumulation of new infections in this group (see Table 1) it suggests that possibly up to 60 % of women were in fact breast-feeding as well as giving formula. The results of this study have underscored the importance of balancing risks when HIV-infected women make decisions on infant feeding. In the formula-feeding group, who relative to most other women in Africa were well-off, had access to clean water, free formula and frequent support of health workers, the risk of HIV infection appears to have been surpassed by the risk of morbidity and

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mortality from other infectious diseases. During the first 3 months of life, infants in the formula-fed arm had an increased risk of diarrhoea (relative risk 2·7, 95 % CI 1·6, 4·6), dehydration (relative risk 11·9, 95 % CI 1·6, 91·8), and upper respiratory infections (relative risk 1·3, 95 % CI 1·1, 1·7; Mbori-Ngacha *et al*. 2000). Similarly, the cumulative mortality at 6 weeks and 3 months was higher in the formula-fed group compared with the breast-fed group (3·9 % *v*. 1·0 % at 6 weeks and 6·4 % *v*. 4·1 % at 3 months). In the first 3 months this increased morbidity and mortality was most obvious in the uninfected formula-fed infants. Similarly, mortality in the first 6 months of life for infants not infected with HIV was highest in formula-fed babies (5 %) compared with breast-fed babies (0·8 %). This study therefore suggests that serious consideration needs to be given to the wisdom of replacement feeding in developing countries.

Breast-milk transmission of HIV according to specific breast-feeding pattern

Most studies attempting to document the risk of MTCT transmission of HIV attributable to breast-feeding have made no attempt to define the pattern of breast-feeding. Just as it is important to specify the duration of breast-feeding when assigning risk, so too is it important to specify the type of breast-feeding that is being practised. In most studies insufficient information has been collected in order to classify infants as exclusively breast-fed. Many researchers have used arbitrary definitions of exclusive breast-feeding and not the accepted World Health Organization (1991) definition, which defines exclusive breast-feeding as breast milk only, with no other solids or liquids. Researchers commonly have allowed consumption of waters, teas and other non-milk liquids or solids in their definition of exclusive breast-feeding (Bobat *et al*. 1997). Three studies have attempted to classify infants according to breast-feeding pattern. The first study, a South African study (Bobat *et al*. 1997), as already mentioned, used a definition of exclusive breast-feeding which allowed the infant to receive cereals and any other non-milk liquids, provided that no artificial milk was given concurrently with breast milk. The 18-month results of this study showed that, using their definition, 39 % of infants who received only breast milk were infected compared with 34 % in those receiving breast milk and formula; as expected the difference was not significant. However, the risk compared with formula feeding in the two breast-feeding groups was much higher presumably because the majority of infants were not exclusively breast-fed.

The second study which was conducted in Brazil by Tess *et al*. (1998) found that infants who were breast-fed exclusively had a lower risk of HIV transmission. This study used the correct World Health Organization (1991) definition of exclusive breast-feeding; however, a limitation of this study was that feeding data were collected retrospectively (at least 18 months after birth).

The third study, also a South African study (Coutsoudis *et al*. 2001), included HIV-infected pregnant women participating in a RCT of Vitamin A (Coutsoudis *et al*. 1999). Women received counselling antenatally according to the Joint United Nations Programme on HIV/AIDS (2000) guidelines and chose to either breast-feed or formula-feed. Those women who chose to breast-feed were encouraged to practise exclusive breast-feeding as a possible way of reducing risk of HIV infection. Of the 551 mother–baby pairs included in the study, 157 (28·5 %) were never breast-fed and 394 (71·5 %) were ever breast-fed (median duration of all breast-feeding was 6 months and that of exclusive breast-feeding was 3 weeks). Ever breast-feeders were separated into 118 women who exclusively breast-fed to $\geqslant$ 3 months and 276 women who mixed breast-fed. The three feeding groups did not differ in any risk factors for MTCT and the probability of detecting HIV at birth was similar. The women in the three groups were similar in terms of all

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the possible risk factors for MTCT of HIV (i.e. viral load, CD4, mode of delivery, prolonged rupture of membranes and preterm delivery). However, two of the risk factors (low serum retinol and positive syphilis test) were higher in the breast-fed group, but this result would therefore favour the formula-fed group to have a lower transmission risk. At birth, transmission rates in the never, exclusive and mixed breast-feeding groups were similar: 0·076 (95 % CI 0·042, 0·125)/100 among never breast-feeders; 0·068 (95 % CI 0·032, 0·123)/100 among exclusive breast-feeders; and 0·069 (95 % CI 0·043, 0·103)/100 among mixed breast-feeders. The cumulative probabilities of HIV infection remained similar among never and exclusive breast-feeders up to 6 months: 0·194 (95 % CI 0·136, 0·260) and 0·194 (95 % CI 0·125, 0·274) respectively, whereas the probabilities among mixed breast-feeders soon surpassed both groups reaching 0·261 (95 % CI 0·205, 0·319) by 6 months. New infections were detected among previously exclusively breast-fed infants following cessation of all exclusive breast-feeding by 6 months. However, by 15 months the cumulative probability of HIV infection remained lower among those who exclusively breast-fed $\geqslant$3 months (0·247 (95 % CI 0·160, 0·344)) than among other breast-feeders (0·359 (95 % CI 0·267, 0·451)). In a time-dependent Cox model, exclusive breast-feeding carried a significantly lower risk of HIV transmission than mixed feeding (hazard ratio 0·56 (95 % CI 0·32, 0·98)) and a similar risk to never breast-feeding (hazard ratio 1·19 (95 % CI 0·63, 2·22)). Infant morbidity and pre-HIV infection did not explain change from exclusive to mixed breast-feeding (Coutsoudis *et al*. 2001). The results from this study suggest very strongly that the vertical transmission of HIV through breast milk is dependent on the pattern of breast-feeding and not simply on breast-feeding *per se*. A limitation of this study was the difficulty in being able to measure adherence to the reported feeding practice. The strongest evidence the authors suggest for women adhering to the feeding pattern reported is the fact that in the formula-fed group there were only two new infections after 6 weeks; one was in a child tested for the first time at 4 months. In addition, infants in the exclusively breast-fed groups began acquiring infection after 6 months once all exclusive breast-feeding had ceased. Measuring adherence will always be difficult; however, in future studies frequent monitoring (at least weekly) may help to improve the validity of the maternal recall.

Preliminary results from a recent study in Kisumu, Kenya (Taren *et al*. 2000) also seem to indicate that introduction of other solids and liquids during the early months of breast-feeding is a risk factor for breast-milk transmission. Their study included a sample of 220 HIV-infected mothers whose infants were not HIV-positive on their first PCR test, and showed that the incidence rate of HIV infections was greater (P<0·07) for infants who started mixed feeding before 30 d compared with infants who started mixed feedings after 30 d. Similarly, incidence of HIV infections was greater (P<0·05) for infants who started mixed feedings before 120 d compared with those who started after 120 d.

These preliminary observations, if confirmed, have important implications, and therefore several studies have recently commenced in order to test them. The sites at which these studies will be conducted are South Africa, West Africa, Ethiopia, and Zambia.

Timing of breast-feeding transmission

There has been considerable debate as to the exact timing of HIV transmission through breast milk. Colostrum has been considered to be more infectious than later milk, because of its higher lymphocyte count; however, many of the protective substances of breast milk are present at higher levels in colostrum than in mature milk, i.e. secretory immunoglobulin A, secretory leucocyte protease inhibitor and lactoferrin (Van de Perre, 1999).

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In a recent meta-analysis of pooled data from eight cohorts, the risk of post-partum transmission (after the age of 4 months) was 3·2 % per year of breast-feeding (Leroy *et al*. 1998). A study in Malawi demonstrated that the risk of early breast-milk transmission (i.e. in the first 6 months) was higher than the risk at a later stage (Miotti *et al*. 1999). This study, conducted between 1994 and 1997, examined the HIV status of 672 infants born to infected women. Only infants who were not infected at the first visit, when they were about 4 weeks of age, were eligible for the study. The HIV infection rates in the first 2 years of life declined significantly over time, falling from 0·7 % per month in months 1–5 to 0·6 % per month in months 6–11, and to only 0·3 % when the babies were over 12 months old. The estimated risk of late postnatal transmission was similar to that estimated by Leroy *et al*. (1998). These risks could be related to increased infant susceptibility in the early months, especially in the situation where the infant does not receive exclusive breast-feeding, or it could be an indication of bias due to surveillance biases, which would tend to have closer surveillance in the early months of life than at a later stage.

Issues to be considered by HIV infected women when making infant-feeding options

In view of the risk of HIV transmission the obvious response would be that HIV-infected mothers should be counselled not to breast-feed their infants. However, this decision is not straightforward, because of the benefits of breast-feeding (notwithstanding the risk of HIV transmission) and the risks of replacement feeding. Clearly, there is a need to balance the risks, and the balance will vary with each woman's situation. Thus, mothers need to be well informed of the risks and benefits of breast-feeding and replacement feeding in their particular situation before they can make their decision.

Benefits of breast-feeding

Breast milk contains protective anti-infective substances such as lactoferrin (Harmsen *et al*. 1995), lysozyme, mucins, immunocompetent T-cells, complement, glycosaminoglycan (Newburg *et al*. 1992), and secretory leucocyte protease inhibitor. Secretory leucocyte protease inhibitor, a serine protease inhibitor, is present at potentially-active concentrations (>100 ng/ml) in colostrum and transition milk, and it can inhibit HIV entry into host cells *in vitro* (Wahl *et al*. 1997).

The composition of breast milk fulfils the infant's total nutrient requirements for the first 6 months of life (Lawrence, 1994), and remains a valuable source of nutrition up to 2 years of age and beyond. Breast-feeding is obviously the most economic and safe mode of infant feeding, and is important in promoting the mother–infant relationship and may enhance the child's intellectual development (Lucas *et al*. 1992; Lanting *et al*. 1994). However, the greatest benefit probably comes from the protection it provides the mother (Gwinn *et al*. 1990; Thomas & Noonan, 1993; Newcomb *et al*. 1994) and child against illness and death (Thapa *et al*. 1988). The more well-known benefit of breast-feeding to the infant is the reduction in the risk of infection, especially diarrhoea and pneumonia. The benefits of breast-feeding are widely recognised, and have been reinforced by a recent meta-analysis (World Health Organization Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality, 2000). In this meta-analysis, which included studies from Brazil, Pakistan and the Philippines, breast-feeding was shown to protect against child mortality, especially in the early months (odds ratio for infants <2 months of age was 5·8). From their results the authors of this study concluded that 'it will be difficult, if not impossible, to provide safe

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breastmilk substitutes to children from underprivileged populations'. The benefits of breast-feeding in terms of reduction of mortality from infections are unlikely to be as important in well-resourced industrialized countries where the risks of artificial feeding can be minimized. However, even in developed countries breast-feeding may protect against less common conditions such as early onset diabetes (Karjalainen *et al*. 1992) and sudden infant death syndrome (Ford *et al*. 1993).

Whether rich or poor, all women will have to face the same dilemma: in order to prevent HIV infection in a possible 0–15 % of infants **(**depending on pattern and duration of breast-feeding), 85−100 % of infants will have to be formula-fed and therefore subjected to the possibility of more disease, more allergy and lower intelligence than breast-fed babies (Lawrence, 1994). The mothers too will have higher risks for certain cancers and will be denied the psychological benefits of bonding with their infants (Lawrence, 1994). Depending on availability of interventions to reduce MTCT of HIV, some 5–20 % of infants may already be infected either *in utero* or intra-partum, therefore mothers both rich and poor also need to face the dilemma of denying the infant who is already infected the possible benefits of breast-feeding. Difficult as these decisions will be for women who have the economic means to afford artificial milk and all the attendant prerequisites to ensure maximum possible safety (clean safe water, fuel supplies, refrigeration facilities, hygienic environment and easy access to good health care facilities), poor women and disempowered women often do not have the opportunity to make a choice.

Implications for poor countries

World Health Organization Joint United Nations Programme on HIV/AIDS UNICEF (1998) issued a joint policy statement on HIV and infant feeding, which states that: 'As a general principle, in all populations, irrespective of HIV infection rates, breastfeeding should continue to be protected, promoted and supported' and: 'counselling for women who are aware of their HIV status should include the best available information on the benefits of breastfeeding, on the risk of HIV transmission through breastfeeding, and on the risks and possible advantages associated with other methods of infant feeding'. However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases children's risk of illness and death.

Policy makers considering implementing replacement feeding for HIV-infected women in poor communities need to bear in mind the unpredictable risks. Poor countries often have limited resources to respond promptly to these unpredictable situations; rural health centres may be prevented from getting supplies because of fuel restrictions; this has been the case recently in the Zimbabwean election crisis of June 2000. The floods in Mozambique in early 2000 also highlighted the perils of formula feeding in countries which cannot respond promptly to disasters, when many of the population were cut off for several days and even weeks without resources and clean water; such a situation puts a young artificially-fed infant in extreme peril. Even in countries less economically deprived, such as South Africa, the majority of mothers involved in a Provincial Health Department MTCT pilot programme reported that the formula provided by the programme was insufficient, and as a result they had to supplement their babies with fruit juice or sugar water (Chopra *et al*. 2000).

It should be borne in mind that counselling and empowering women to make an informed choice on infant feeding is not simply a matter of informing or educating them about the theoretical risks and different feeding options. It requires a deep understanding of the social issues,

compassion, knowledge of the household situation, the ability to translate complex scientific concepts on risk in a way that is understood by women who do not have grasp of these concepts, as well as the ability to emotionally support women in a decision that affects themselves, their children, and the rest of their family.

The push to encourage women to take up replacement feeding in pilot programmes in some settings may lead to a loss of support for initiatives to promote breast-feeding, and to some women avoiding breast-feeding even if they do not know their HIV status. This situation can have serious consequences in poor communities.

Mathematical modelling exercises have helped to quantitatively compare the risks of HIV transmission via breast-feeding against the increased risks of non-HIV mortality associated with not breast-feeding. Results of such exercises have shown that where the background infant mortality rate is over 70/1000 it is estimated that the risk of infant deaths from infectious diseases due to replacement feeding will surpass the risk of acquisition of HIV by breast-feeding (Kuhn & Stein, 1997). This model and others have consistently concluded that complete avoidance of breast-feeding is almost always contraindicated when HIV status is unknown. A recent preliminary modelling exercise, taking into account the recent results of reduction in breast-milk transmission with exclusive breast-feeding, lowers the threshold infant mortality rate above which breast-feeding would be favoured compared with breast-milk substitutes. The authors estimated that this threshold infant mortality would be 42–80/1000 (Smith & Kuhn, 1999), i.e. in a situation of HIV risk, even if infant mortality rate is as low as 42–80, replacement feeding would pose more of a threat to infant survival than exclusive breast-feeding.

For women who choose to breast-feed it is important that they are given information on factors which increase the risk of breast-milk transmission of HIV and, following on from this approach, information on what suggestions there are for them to minimize this risk.

Possible risk factors for breast-feeding transmission

High plasma and breast-milk viral load (Semba *et al*. 1999; Pillay *et al*. 2000) and breast-milk pathology such as mastitis and cracked bleeding nipples (Ekpini *et al*. 1997; Tess *et al*. 1998; Embree *et al*. 2000) are considered to increase the risk of transmission of HIV. Additionally even subclinical mastitis (measured by elevated breast-milk Na levels) may be associated with increased risk for breast-feeding transmission (Semba *et al*. 1999). Similar associations, between elevated Na:K in breast milk and HIV viral load in breast milk, have been reported by Willumsen *et al.* (2000).

Suggested methods to minimize breast-feeding transmission

Many of the following methods are based on reasonable clinical practice rather than on firm evidence.

Improvement in obstetric practice

Suctioning out of an infant's mouth should not be carried out routinely. 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.

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Prompt treatment of oral thrush

Treatment of oral thrush with appropriate anti-fungal drugs should be given immediately, as any breaks in the mucosal barrier would pose a risk for HIV transmission.

Shorter duration of breast-feeding

A 3-month period of breast-feeding may be appropriate for HIV-infected women, as modelling exercises have estimated that the optimum time for early weaning may be 3 months; this practice balances the risk of HIV transmission with the benefits of breast-feeding.

Exclusive breast-feeding for up to 6 months

The overwhelming majority of women in Africa give mixed feeds to their babies; exclusive breast-feeding is uncommon (Labbock *et al*. 1997). Accordingly, if the results of the South African study (Coutsoudis *et al*. 1999) are confirmed and are to be translated into practice, it would mean significant changes in infant feeding practices. These changes, however, would also have substantial benefits for non-HIV-related child health, in contrast to the negative consequences associated with formula feeding. A recent study in Mexico has shown that by using peer counsellors it is possible to bring about change in normal breast-feeding behaviour and encourage a switch to exclusive breast-feeding (Morrow *et al*. 1999). A recent review has documented the impact and lessons learnt from programmes promoting and supporting exclusive breast-feeding (Green, 1999), and has highlighted certain strategies for successful programmes. When these strategies are used, there is evidence that exclusive breast-feeding and related practices can be improved, and that such programmes, when properly designed and implemented, are cost-effective.

Expressing and heat-treating breast milk

There has been considerable resistance from policy makers to the idea of mothers expressing breast milk, because it is considered to be too difficult. Before the AIDS pandemic it was quite normal for mothers to express breast milk to be used for their own babies or for other infants in special need. A recent study from Chile (Valdes *et al*. 2000) has shown that it has been possible on a very large scale to implement a programme of breast-milk expression for working women; these mothers 'exclusively' breast-feed in this way. Once women and policy makers understand and accept that expressing breast milk is possible, heat treatment may not be an added burden.

There is evidence that the Holder method of pasteurization of milk used by milk banks, i.e. heating at 62·5° C for 30 min, is effective in destroying the HIV virus without destroying immunoglobulins and other protective factors in the milk. A group from Denmark and Tanzania (Jorgensen & Boisen, 2000) have developed a device for pasteurization of breast milk which can be powered by solar energy. A simpler method suitable for simple home settings using the principle of passive heat transfer was described by Jeffery *et al*. (2000). A novel idea for eliminating the HIV has recently been reported (Howett *et al*. 2000). Microbicides which are active against HIV are used to inactivate HIV in breast milk, and the microbicide is then removed without harm to the nutritional content or toxicity of the milk. This is an early report and much

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work is still needed to be sure that the microbicides can be completely removed without any possible toxicity. There is also a need to consider whether the work involved will not in fact be more difficult than the well-accepted method of heat treatment.

Avoiding new infections

The fact that viral load peaks immediately after infection has important implications for breast-feeding transmission, and therefore women should take steps (e.g. by using condoms) to prevent becoming infected while they are breast-feeding. In fact, in areas of high HIV prevalence all breast-feeding women should be encouraged to take steps to avoid HIV infection during the breast-feeding period.

Reducing risk factors associated with breast pathology

If women develop mastitis or cracked bleeding nipples, they should express milk from the affected breast and discard it, and only feed from the uninfected breast. Medical attention should be sought if the engorgement or blocked ducts do not resolve within 1 or 2 d, or if breast pain or fever develop. Cracked nipples and especially painful nipples need to be managed well; if candida infection is suspected prompt treatment of nipples with anti-fungal ointment should be started. If the infant has recurring oral candida and is exclusively breast-fed and the mother has sore nipples, the mother's nipples should be treated with anti-fungal ointment concurrently with the infant being treated to prevent re-infection. Although these measures are sensible and therefore should be employed for breast health in general, they have not been proven to reduce MTCT of HIV.

Lactation management

Improved lactation management may also be generally useful. This approach includes proper breast positioning and attachment of the infant to the breast and not just the nipple, which should minimize development of cracked and bleeding nipples. Proper emptying of the breasts will reduce milk stasis, engorgement and mastitis.

Concerns about the effects of antiretroviral drugs given to mothers during pregnancy on breast-feeding transmission

Data from the Thai study showed that in non-breast-fed populations, giving azidothymidine (AZT) to HIV-infected women during pregnancy from 36 weeks gestation reduced transmission risk by approximately 50 % (Shaffer *et al*. 1999). Concern has been raised that ARV therapies may not be as effective in breast-feeding populations, as the pool of children who could potentially be infected through breast-feeding will be enlarged, to include those who escape intra-partum infection as a result of maternal treatment. Since HIV levels in plasma rapidly return to, or even above, pretreatment levels when ARV therapy is discontinued (de Jong *et al*. 1997), the net effect of therapy may be a displacement of intra-partum infection to breast-feeding infection, without having an overall effect in reducing MTCT of HIV. The Retrovirun in Cote D'Ivoire study in West Africa (Wiktor *et al*. 2000) examined the change in HIV viral load in

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breast milk in the first 6 weeks post-partum in women receiving short-course antenatal AZT. They showed that there was a peak in breast-milk viral load at 2–3 weeks post-partum and this factor could raise the risk of postnatal transmission (Krou-Danho *et al*. 2000). However, the transmission results from this study do not show an increased risk of postnatal transmission in the AZT-treated group compared with the placebo group (see Table 2).

An intriguing observation was made in a South African study (Kuhn *et al*. 2000) which was examining whether fetal, cell-mediated immune responses to HIV provided protection against subsequent HIV transmission during delivery and breast-feeding, and whether short-course ARV had any impact on the development of these responses. The mothers of 115 infants were not exposed to ARV treatment and the mothers of forty-one infants were exposed to short-course AZT + lamivudine (Perinatal Trial in Africa study; Gray, 2000). HIV T-helper cell responses were observed in the cord blood of 34 % of infants not exposed to ARV and none of these infants were HIV-infected at 18 months. Only one ARV-exposed infant had detectable HIV T-helper cell responses ($P < 0{\cdot}007$). This study therefore suggests that newborn infants exposed to HIV *in utero* may have acquired immune responses to the disease, which protect them from future infection; however, exposure to short-course AZT + lamivudine reduces this protection, increasing the risk of future seroconversion. Interestingly, the study which showed no loss of efficacy with time (see Table 2) was the nevirapine trial (Owor *et al*. 2000) in which no ARV were taken antenatally, and which may tie up with the results found by Kuhn *et al*. (2000). This finding deserves further investigation.

Research issues

An early report by Nduati *et al*. (2000*b*) has raised concern, and demands further investigation because of the important implications. The investigators reported that breast-feeding women

Table 2. Mother-to-child transmission rates (%) for HIV-1 in breast-fed infants receiving antiretroviral treatment or a placebo

			Age of infants					
Study	Treatment	Timing of treatment	1 d	6–8 weeks	3 months	12 months	18 months	24 months
PETRA (Gray, 2000)	AZT+3TC	Ante- and intra-partum		9·2			20·7	
		Intra- and post-partum		12·6			24·4	
		Intra-partum		18·4			25·7	
	Placebo			19·2			26·6	
DITRAME and RETROCI, pooled; West Africa (Wiktor *et al*. 2000)	AZT	Ante- and intra-partum	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
HIVNET 012; Uganda (Owor *et al*. 2000)	Nevirapine	Intra-partum	8·1	11·8	13·6	15·7		
	AZT (placebo equivalent)	Intra-partum	10·3	20·0	22·1	24·1		

AZT, azidothymidine; 3TC, lamivudine; PETRA, Perinatal Trial in Africa; DITRAME, Diminution de la Transmission Mere-Enfant; RETROCI, Retrovirun in Cote D'Ivoire; HIVNET 012, HIV Network Study number.

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enrolled in the RCT in Kenya were more likely to die (eighteen of 197, relative risk 3·2 (95% CI 1·3, 8·1)) than mothers who formula-fed (six of 201). The baseline characteristics of the women in these two arms need to be examined more closely in order to determine whether randomization was in fact effective in producing two similar groups. Although biological markers of disease progression (CD4 counts and viral load) are important measures, the real test of degree of disease progression will be the MTCT of HIV. The women in the breast-fed group were more than twice as likely to infect their infants (birth infection rate was 7·0 in breast-feeders and 3·1 in formula feeders/100); this finding implies that the breast-feeders had more advanced disease, which was not necessarily picked up by biological markers. Similarly, at 6 weeks, which is usually the time period at which intra-partum infection is identified and there is very little evidence of transmission through breast-feeding, the breast-feeders were twice as likely to infect their infants. In fact, at 6 weeks the transmission rate in the formula-fed group was only 9·7 % which is surprisingly low; none of the other trials in the placebo arm had such low transmission rates at 6 weeks (Table 2). The two groups of women were therefore probably not similar, and this factor may have accounted for the increased mortality. The results of this study do, however, raise a possible research question of examining the effect, on maternal mortality and morbidity, of improving the nutritional status of breast-feeding women.

It is unlikely that any groups will attempt a RCT of feeding practices, as the recently completed Kenyan trial (Nduati *et al*. 2000*a*) showed clearly that it is very difficult to randomize a behaviour like breast-feeding, which is so inherently part of a woman's motherhood. Furthermore, it is now generally agreed that it would be unethical to conduct such a trial. Several large trials in South Africa, Zimbabwe, West Africa, Ethiopia, and Zambia are being planned to look closely at exclusive breast-feeding, with close monitoring of breast-feeding practices. Efforts are being made to try to coordinate the monitoring tool to allow for consistency in reporting across studies, so that results may be compared more adequately. Mothers and infants in the South African and Zambian studies will each receive one dose of nevirapine according to the HIV Network Study number 012 protocol (Guay *et al*. 1999). The Zambian study is, in addition, comparing the difference between complete cessation of breast-feeding at 4 months compared with gradual weaning off breast milk over 2 years.

The HIV Network Study number 027 trial in Uganda is a safety trial of ALVAC (canary pox) vaccine *v*. placebo given orally with nevirapine to newborn infants. Their mothers will receive nevirapine according to the HIV Network Study number 012 protocol (Guay *et al*. 1999).

A trial of passive immunization is also being planned for Uganda. Infants will receive hyper-immune HIV globulin during the period they are being breast-fed.

A Ghent Group/National Institute of Child Health and Development initiative has set up a Breastfeeding and HIV International Transmission Study. The study will pool data from RCT of interventions aimed at reducing MTCT of HIV in African populations where breast-feeding is common. This approach will enable an investigation into the acquisiton of HIV infection especially in the first few months of life, enabling clarification of the timing of breast-feeding transmission as well as identification of determinants of breast-feeding transmission.

Conclusion

In conclusion, it is clear that breast-feeding relative to replacement feeding carries an increased risk for MTCT of HIV. The magnitude of the risk appears to be dependent on the duration and pattern of breast-feeding, and on maternal factors such as breast health; as well as her nutri-

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tional, immunological and virological status. On the other hand, in developing countries, replacement feeding carries an increased risk for infant mortality. HIV-infected mothers in developing countries who are faced with a choice of how to feed their infants need to be presented with a balanced view of the risks of breast-feeding and replacement feeding in terms of HIV transmission and child survival. This approach will enable individual mothers to make an informed choice as to which option holds the greatest chance of her baby staying HIV-negative and alive. The reality is that the majority of HIV-infected women live in conditions which may necessitate their choosing to breast-feed; the onus is therefore on health workers and policy makers to increase efforts to make breast-feeding safer.

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