HIV transmission through breastfeeding

A REVIEW OF AVAILABLE EVIDENCE

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A review of available evidence

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Glossary of terms

AZT (azidothymidine, also known as zidovudine [ZDV]): an antiretroviral drug that inhibits HIV replication. It was the first drug licensed to treat HIV infection. Today, it is commonly used in combination with other antiretroviral drugs to treat HIV infection, and, alone or in combination, in the prevention of mother-to-child transmission of HIV infection.

Breast-milk substitute: any food being marketed or otherwise represented as a partial or total replacement for breast milk, whether or not suitable for that purpose.

CD4+ cells (also known as "T4" or "helper T cells"): CD4+ lymphocytes (a type of white blood cell) are key to both humoral and cell-mediated immune responses. They are the main target cells for the HIV. Their number decreases with progression of HIV infection, and their level is used as a marker of severity of the infection.

CD8+ cells are also a subtype of T lymphocytes, which have an important function in fighting infection. Their number may increase with progression of HIV infection.

Cell-associated virus: HIV which lives inside the cell, measured as HIV-DNA.

Cell-free virus: parts of the virus (virions) not associated with a cell, measured as HIV-RNA.

Cessation of breastfeeding: completely stopping breastfeeding, including suckling.

Colostrum: the thick, yellow milk secreted by the breasts during the first few days after delivery. It gradually changes into mature milk at 3–14 days postpartum; it contains more antibodies and white blood cells than mature breast milk.

Commercial infant formula: a breast-milk substitute formulated industrially in accordance with applicable Codex Alimentarius standards to satisfy the nutritional requirements of infants during the first months of life up to the introduction of complementary foods.

Complementary food: any food, whether manufactured or locally prepared, used as a complement to breast milk or to a breast-milk substitute.

DNA: deoxyribonucleic acid, the carrier of genetic information, found in cell nuclei.

Enterocytes: the cells that form the lining of the intestinal wall.

Exclusive breastfeeding: an infant receives only breast milk, and no other liquids or solids, not even water, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines.

HAART: Highly Active AntiRetroviral Therapy, a combination of three or more antiretroviral drugs used in the treatment of HIV-infected people to reduce viral load.

Human immunodeficiency virus (HIV): the virus that causes AIDS. In this document, the term HIV means HIV-1. Mother-to-child transmission of HIV-2 is rare.

Immunoglobulins: the five distinct antibodies present in the serum and external secretions off the body (IgA, IgD, IgE, IgG and IgM).

Infant: a person from birth to 12 months of age.

Intrapartum: the period during labour and delivery.

Lamivudine, or 3TC: an antiretroviral drug often used in combination with zidovudine (AZT)

Lipid: any one of a widely varied group of fats and fat-like organic substances.

Macrophage: a type of white blood cell that ingests foreign material. Macrophages help destroy bacteria, protozoa and tumour cells and stimulate other cells of the immune system.

Mature breast milk: milk produced from about 14 days postpartum.

Mixed feeding: feeding both breast milk and other foods or liquids.

Mother-to-child transmission: transmission of HIV to a child from an HIV-infected woman during pregnancy, delivery or breastfeeding. The term is used here because the immediate source of the child's HIV infection is the mother. Use of the term *mother-to-child transmission* implies no blame, whether or not a woman is aware of her own infection status. A woman can contract HIV from unprotected sex with an infected partner, from receiving contaminated blood, from non-sterile instruments (as in the case of injecting drug users), or from contaminated medical procedures.

Neonatal: denotes the period from birth through the first 28 days of life.

Nevirapine (NVP): an antiretroviral drug commonly used either to treat HIV infection or as prophylaxis, alone or in combination with other drugs, to prevent mother-to-child transmission.

PCR: polymerase chain reaction, a qualitative or quantitative laboratory method in which the genetic material (DNA or RNA) of the virus is detected and amplified.

Peripartum transmission: mother-to-child transmission of HIV occurring shortly before, during or immediately after delivery.

Postnatal transmission: mother-to-child transmission of HIV after delivery, through breastfeeding.

Replacement feeding: feeding infants who are receiving no breast milk with a diet that provides the nutrients the infants need until the age at which they can be fully fed on family foods. During the first six months of life, replacement feeding should be with a suitable breast-milk substitute. After six months the suitable breast-milk substitute should be complemented with other foods.

RNA: ribonucleic acid, a substance present in the nucleus of all living cells and in many viruses. It is an intermediate form of DNA. It is the medium by which genetic instructions from the nucleus are transmitted to the rest of the cell.

RNA viral load: the result of a laboratory method, expressed as copies of RNA per ml of plasma or other body fluid; it reflects the amount of actively replicating virus in the body. Temporary high levels of viral RNA occur immediately after contracting infection. Later, levels increase with progression of disease. High levels are associated with high rates of mother-to-child transmission.

Transcytosis: a process by which specific macromolecules, such as nutrients or antibodies, are absorbed via polarized epithelial cells, which transport the macromolecule into the cell, transfer it across the cell, and release it to the other side.

Wet-nursing: breastfeeding by a woman other than the infant's mother.

Executive summary

Exclusive breastfeeding – breastfeeding with no other food or drink, not even water – is the ideal mode of infant feeding for the first six months of life. For optimal growth, development and health, infants should be exclusively breastfed for their first six months, and should then receive nutritionally adequate and safe complementary foods, while breastfeeding continues up to 24 months or beyond. With the onset of the HIV/AIDS epidemic, however, and the recognition that HIV-infected mothers can transmit HIV to their infants through breastfeeding, specific recommendations apply to infants born to HIV-infected mothers. The overall aim of these recommendations is to achieve the ultimate goal of increasing child survival, while reducing HIV infection in infants and young children.

Mother-to-child transmission of HIV can occur during the second and third trimesters of pregnancy, during delivery, or at any point during breastfeeding. The risk through breastfeeding is cumulative; the longer the HIV-infected mother breastfeeds, the greater the additional risk of transmission through breastfeeding. Where breastfeeding is common and prolonged, transmission through breastfeeding may account for up to half of HIV infections in infants and young children. Available interventions can reduce substantially the risk of transmission during pregnancy, labour and delivery, but, so far, risk reduction during breastfeeding has been much less successful. Research into prevention of breastfeeding transmission is concerned particularly with the effect of antiretroviral prophylaxis on either the uninfected infant or the infected mother during breastfeeding. Early findings show a low rate of transmission through breastfeeding in the first three months in infants receiving prophylaxis with either lamivudine or nevirapine.

The risk of transmission by an infected mother occurring before or during birth (without interventions to reduce transmission) is 15–25%. Breastfeeding by an infected mother increases the risk by 5–20% to a total of 20–45%. The risk can be reduced to under 2% by a combination of antiretroviral prophylaxis during pregnancy and delivery and to the neonate with elective caesarean section and avoidance of breastfeeding. Peripartum antiretroviral monotherapy alone can reduce the rate to about 15% at three months, and triple combination therapy to under 6% at six weeks. Subsequent infection through breastfeeding, however, can increase the overall rate at 18–24 months to over 20%. The overall risk of mother-to-child transmission of HIV is substantially increased by maternal factors – high HIV viral load in plasma, a low CD4+ cell count, and AIDS – and by vaginal delivery or prematurity. Maternal factors are also associated with increased risk of transmission during breastfeeding. Recent maternal infection with HIV may raise the risk of transmission through breastfeeding to twice that of a woman with earlier established infection, owing probably to high viral load associated with recent infection.

It is not clear whether, or to what extent, the protection that breastfeeding normally confers against common childhood infections applies to breastfeeding of HIV-infected infants by HIV-infected mothers. Recent research in sub-Saharan Africa indicates that mortality in the first 12–18 months is similar in HIV-infected breastfed and non-breastfed infants. Nor is it clear whether, or in what ways, overall morbidity or mortality up to two years of age is related to different infant feeding practices; more studies are needed to clarify this issue.

Prevention of mother-to-child transmission

HIV-infected pregnant women should consider their infant feeding options. They should seek to balance the nutritional and other benefits of breastfeeding with the risks of transmitting HIV to their infants and choose between exclusive breastfeeding and replacement feeding (commercial infant formula or home-modified animal milk) or other breast-milk options (heat-treated expressed breast milk, wet-nursing, or donors' milk from a milk bank).

When replacement feeding is acceptable, feasible, affordable, sustainable and safe, HIV-infected mothers should avoid breastfeeding completely. When these conditions are not present, HIV-infected women who choose to breastfeed are recommended to do so exclusively for the first few months, and then, over a period of a few days to a few weeks rather than abruptly, to stop breastfeeding (exclusive breast-

feeding with early cessation), provided the conditions for replacement feeding or other breast-milk options are in place.

In an observational study in South Africa, exclusive breastfeeding during the first three months of life was associated with a lower transmission risk than mixed feeding, and a number of studies are under way to investigate further the association between infant feeding modality, risk of transmission through breastfeeding and infant health.

Prevention of HIV transmission during 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.

Current or prospective research into mother-to-child transmission

The main current public-health research question is whether breastfeeding by HIV-infected mothers can be made safer as to transmission risk, given the possible adverse effects of refraining from breastfeeding. Various ongoing or planned trials and studies concern either mode of infant feeding (exclusive or mixed) or antiretroviral therapy to either the mother or the infant over the breastfeeding period.

Other related topics on which research is under way or planned are: the mechanisms of breastfeeding transmission, in particular the parts played by cell-free and cell-associated HIV; the association between virus levels in plasma and milk; the possibly protective effect of HIV-specific cells with immune function in the breast milk of HIV-infected women; the correlation between risk of transmission and the presence of anti-infective substances in the breast milk of HIV-infected women, including immunoglobulins, lactoferrin, and mucins; the effect of antiretroviral prophylaxis on either the uninfected infant or the breastfeeding mother; whether, or to what extent, the protection against common childhood infections normally conferred by breastfeeding applies to breastfeeding of HIV-infected infants by HIV-infected mothers; survival rates associated with the various treatment modalities; and assessment of the health benefits of nutritional support to breastfeeding HIV-infected women.

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 and oral thrush), nipple fissures or clinical or subclinical mastitis may increase the risk of transmission through breastfeeding. Current research is investigating this possible association, its strength, and its possible impact on public health.

Introduction

Action to reduce child morbidity and mortality and to promote family health has greatly improved child health (World Health Report, 1999; Walker et al., 2002, Black et al., 2003). Promotion of breastfeeding has contributed significantly in that it provides optimum nutrition, protects against common childhood infections, reduces mortality significantly, and has child-spacing effects (Nicoll et al., 2000; WHO Collaborative Study Team, 2000). Nearly all infants in developing countries are initially breastfed, and most continue until at least six months of age but often into the second year (Nicoll et al., 2000, WHO Collaborative Study Team, 2000). Continued breastfeeding (beyond six months) is common in sub-Saharan Africa and Asia, but much less so elsewhere. Up to 94% of infants in the world are estimated to be ever breastfed, 79% to continue at one year, and 52% at two years, with an estimated median duration of breastfeeding of 21 months. Overall, an estimated 41% of infants under four months of age and 25% under six months are exclusively breastfed; in sub-Saharan Africa 23% of infants under six months of age are exclusively breastfed (WHO Global Databank on Breastfeeding and Complementary Feeding, 2003).

In 2001 the World Health Assembly endorsed the recommendation that infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health. After six months, they should receive nutritionally adequate and safe complementary foods while breastfeeding continues up to 24 months or beyond (World Health Assembly resolution 54.2, 2001). This recommendation takes into account the considerable benefits of breastfeeding, as well as the adverse effects of artificial feeding at an early age. Exclusive breastfeeding is the best form of feeding for the infant during the first six months of life (WHO, 2001a). Also, it helps the mother space her pregnancies. A woman who exclusively, or almost exclusively, breastfeeds during the first six months and who has not resumed menstruation has a less than 2% risk of becoming pregnant (WHO, 2000).

Exclusive breastfeeding on a population basis has been shown to be feasible with adequate support and training of health-care professionals (Kramer et al., 2001; Bhandari et al, 2003).

From the beginning of the HIV pandemic through 2002, four million children under 15 years of age worldwide became infected. During 2003 an estimated 700 000 (590 000–810 000) were newly infected (UNAIDS/WHO, 2003), mostly in sub-Saharan Africa; in this region the majority of HIV-infected children die before their fifth birthday, and HIV is already contributing to increased rates of childhood mortality (Dabis and Ekpini, 2002; UNAIDS/WHO, 2002; Walker et al., 2002). Although HIV transmission during breastfeeding is only partly responsible for this increase, the impact of HIV infection on infant feeding practices is a significant public-health issue, for two reasons: malnutrition is an underlying cause in 60% of child deaths, and underweight is the leading underlying cause of disability and illness worldwide; this is particularly the case in countries with high adult and infant mortality, where sub-optimal feeding practices are a major cause of underweight (World Health Report 2002).

Without antiretroviral prophylaxis or other effective interventions for pregnant women with HIV infection, breastfeeding for two years or more can double the overall risk of mother-to-child transmission of HIV to about 40% (Nduati et al., 2000; Newell, 1998). An estimated 5–20% of infants are infected postnatally, and the risk increases with duration of breastfeeding. Breastfeeding may thus be responsible for one third to one half of HIV infections in infants and young children in Africa (De Cock et al., 2000). Available interventions can substantially reduce the risk of transmission during pregnancy, labour and delivery, but not yet during breastfeeding – peripartum antiretroviral prophylaxis does not prevent transmission through breastfeeding. Given the risk from breastfeeding, reduction of such HIV transmission is one of the most pressing public health challenges confronting researchers, health-care professionals, health policy-makers and HIV-infected women in many parts of the world, especially in developing countries. Efforts to prevent transmission by breastfeeding should take into account the need to promote breastfeeding of infants and young children in the general population. Countries need to develop (or revise) a comprehensive national infant and young child feeding policy

to include HIV and infant feeding, while continuing to protect, promote and support early, exclusive and continued breastfeeding for infants of women who are HIV-negative or of unknown HIV-infection status.

The risk of mother-to-child transmission and infection in infants and young children can now be reduced, and considerable effort is under way to expand preventive interventions to a wider population.

The Declaration of Commitment, endorsed by 189 countries at the United Nations General Assembly Special Session on HIV in June 2001, set the goal of reducing the proportion of infants infected with HIV by 20% by 2005 and 50% by 2010 (United Nations, 2001). Such a large decrease can be achieved only through a comprehensive approach that includes a substantial reduction in the number of young women becoming HIV-infected (De Cock et al., 2002). The UN Special Session set goals of a 25% reduction among young people of 15 to 24 years in the most affected countries by 2005 and globally by 2010, as well as to ensure that 80% of pregnant women who receive antenatal care have access to HIV-prevention services.

Where mothers are being screened and diagnosed as HIV-infected, their care and that of their infected and uninfected children will have to be assured. Guidance on infant feeding for women known to be HIV-infected will need to be personal to the individual woman. Such guidance should take account of its possible effect on women who are uninfected or of unknown HIV status; these should continue to be encouraged and supported to breastfeed. When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life and then discontinued as soon as it is feasible to do so. To help HIV-positive mothers make the best choice, they should receive counselling that includes information about both the risks and the benefits of various infant feeding options, based on local assessment, and guidance in selecting the option that best suits their circumstances. They should also have access to follow-up care and support, including family planning and nutritional support (WHO, 2001b). Also to be considered and researched are the longer-term health of both infected and uninfected children and their mothers, the mortality of children living in families with HIV, and the plight of increasing numbers of orphans (UNAIDS, 2002). The corresponding interventions need to be monitored and their impact evaluated.

This publication is one of a series on HIV and infant feeding. It presents the scientific evidence relating to the transmission of HIV infection by breastfeeding; this evidence constitutes the basis of the guidelines for decision-makers and health-care managers, issued as separate documents in the series (WHO/UNICEF/UNFPA/UNAIDS 2003a, 2003b). It describes briefly the benefits of breastfeeding for mothers and infants in general. Transmission by breastfeeding is discussed in the light of overall mother-to-child transmission of HIV-1 infection.

Background

The Global Strategy for Infant and Young Child Feeding (IYCF), adopted by the World Health Organization and UNICEF, states that the optimal feeding pattern for overall child survival is exclusive breastfeeding for the first six months, and continued breastfeeding for up to two years and beyond, with complementary feeding from age six months, together with related maternal nutrition and support (WHO, 2003). The Global Strategy contains specific recommendations for children in exceptionally difficult circumstances, including those born to HIV-positive women.

Benefits of breastfeeding in the general population

One of the most beneficial attributes of breast milk is that it protects against common childhood infections such as diarrhoea, pneumonia, neonatal sepsis and acute otitis media (Habicht et al., 1986 and 1988; Victora et al., 1987; WHO Collaborative Study Team, 2000). Whether it confers similar protection in areas of high HIV-prevalence is less clear, however. Results from a recently published pooled analysis of six studies carried out from 1983 to 1991 with data on all-cause death for 1123 children under the age of two years, in Brazil, Ghana, Gambia, Senegal, Pakistan, and the Philippines, confirm that breastfed infants are at lower risk of mortality than those who are not breastfed (WHO Collaborative Study Team, 2000). In the three non-African studies, in which outcomes for breastfed infants could be compared with those for infants who had not been breastfed, mortality rates were significantly higher for the non-breastfed through the first eight months of life. This was particularly striking in the first months of life, with a pooled odds ratio of 5.8 (95% CI 3.4–9.8) for infants less than two months of age, indicating a nearly sixfold increased risk of mortality for these young non-breastfed infants. During the first six months the protection conferred by breastfeeding against death from diarrhoea was increased sixfold, and from respiratory infection 2.4 times. This protective effect gradually diminished as the infant grew older. The estimates for the first year of life did not cover sub-Saharan Africa, because there were too few non-breastfed infants.

In an earlier study, in which 9942 urban infants in the Philippines were followed from birth to two years (between 1988 and 1991), deaths from diarrhoeal disease were found to be ten times higher in infants under six months who had never been breastfed or whose breastfeeding had been stopped than among breastfed infants, after controlling for demographic factors such as maternal education and socioeconomic status (Yoon et al., 1996).

Mode of infant feeding has been associated also with morbidity. In a study in Brazil, infants who were not currently breastfed were at 17 times higher risk of hospital admission for pneumonia (OR 16.7, 95% CI 7.7–36.0) than breastfed infants. In a cluster randomized trial of 17 046 mother–infant pairs at 31 hospitals in Belarus, half the sites made a special effort to encourage breastfeeding (Kramer et al., 2001). The intervention, which increased the rate of exclusive breastfeeding at six months and the duration of any breastfeeding, was associated with a significant reduction in the risk of gastrointestinal infections (OR 0.6, 95% CI 0.4–0.9) and of atopic eczema (OR 0.54, 95% CI 0.31–0.95) in the first year of life. Likewise, in a critical review of major studies on mode of infant feeding and infant-health outcomes in the United States of America and other industrialized countries since the 1970s, non-breastfeeding was reported to be associated with higher rates of diarrhoeal and acute lower respiratory disease among infants, and lower cognitive scores, than breastfeeding (Heinig and Dewey, 1996).

Anti-infective properties of breast milk of HIV-infected women

There is little information on whether, or the extent to which, breast milk from an HIV-infected woman protects her child, whether or not HIV-infected, from other infections. HIV-infected women may have immune dysfunction and be producing lower levels of protective antibody and cell-associated immunity against diarrhoeal and respiratory infections than women without HIV infection; in that case their milk would confer less protection against those infections than that of non-HIV-infected women.

Breast milk contains maternal antibodies, with all basic forms of immunoglobulin – IgG, IgM, IgA, IgD,

and IgE. The most abundant is secretory IgA (Lawrence, 1994). Investigation of the inhibiting action of breast-milk HIV-specific antibodies on transmission of HIV through breastfeeding has found that (i) the breast milk of women with established HIV infection has HIV-specific IgG, with a wide spectrum of activity against HIV proteins, comparable to HIV-specific IgG in serum; and (ii) the spectrum of activity of serum IgA against HIV is similar to that of serum IgG, but that of HIV-specific secretory IgA (sIgA) in breast milk affects only a limited number of viral proteins (env protein, gp 160, core proteins).

In a study of breast-milk samples from 215 HIV-infected women in Rwanda (Van de Perre et al., 1993), the most frequently identified HIV-specific antibody in breast milk was IgG (in >95% of samples); the next was IgM (in 41–78% of samples) and the least frequent was IgA (in 23–41% of samples). Lack of persistence of HIV-specific IgM in breast milk collected at 18 months was associated with a high risk of transmission of HIV in children who survived longer than 18 months. This suggests that IgM protects against transmission of HIV during breastfeeding (Van de Perre et al., 1993). Other components of breast milk protect against viral infections. Human lactoferrin has been shown in vitro to inhibit HIV (Harmsen et al., 1995); lipid-dependent antiviral activity directed at HIV and other enveloped viruses has also been described (Orloff et al., 1993). An additional breast-milk factor, possibly a sulphated protein, glycoprotein mucin or glycosaminoglycan, appears to inhibit the binding of HIV to CD4+ receptors (Newburg et al., 1992). Preliminary findings based on 11 HIV-infected and four uninfected women in the USA and Zambia suggest that HIV-specific CD8+ cells in the breast milk of infected women can contribute to limiting transmission of infection through breastfeeding (Sabbaj et al., 2002).

In summary, anti-infective substances in the breast milk of HIV-infected women, including immunoglobulins, lactoferrin, and mucins, may target HIV, but further studies are needed to investigate the correlation between risk of transmission and the presence of these substances.

Benefits of breastfeeding for children born to HIV-infected mothers

There is little information on the benefits of breastfeeding to HIV-infected infants; further study is needed. In a randomized trial in Nairobi to evaluate the effect of mode of infant feeding on the risk of mother-to-child transmission of HIV (Nduati et al., 2000), the cumulative two-year mortality rate among infants in the formula-feeding group was 20%, not significantly different from the 24% in the breastfeeding group (hazard ratio 0.8, 95% confidence interval 0.5–1.3), even after adjusting for HIV-infection status (hazard ratio 1.1, 95% confidence interval 0.7–1.7). In addition, the rate of HIV-free survival at two years was significantly lower in the breastfed than in the formula-fed group (58% and 70% respectively, P=0.02). The incidence of diarrhoea during the first two years of life was also similar in both groups: 155 and 149 per 100 child-years of follow-up in the formula and breastfeeding groups respectively, while the incidence of pneumonia was identical at 62 per 100 child-years of follow-up (Mbori-Ngacha et al., 2001). Infants in the breastfeeding arm tended to have better nutritional status (p=0.06 overall), significantly so during the first six months of life (p=0.003). After adjusting for HIV-infection status, infants in the breastfeeding arm had significantly better nutritional status than those in the formula arm over the two-year period (p=0.04). The proportion of children with malnutrition in the study population was relatively low in the first year of life (2%), but increased to 15% during the second year.

In a recent small study in Durban, South Africa, HIV-infected infants who were never breastfed had a poorer outcome than those who were breastfed: 60% of 15 never-breastfed, infected infants had three or more morbidity episodes in the first 18 months of life compared with 32% of 47 breastfed, infected infants (Coutsoudis et al., 2003). During the first two months of life, never-breastfed infants, regardless of HIV status, were nearly twice as likely as breastfed infants to have had an illness episode (OR 1.91, p=0.006).

An earlier study from South Africa (Bobat et al., 1997) compared partly breastfed and exclusively formula-fed HIV-infected and non-infected infants: both feeding groups had a similar incidence of failure to thrive, diarrhoea, and pneumonia.

Like the study of Nduati et al., (2000) above, preliminary results from a recent meta- analysis of data from seven drug trials on prevention of transmission in sub-Saharan Africa also suggest that breastfeeding by HIV-infected mothers does not protect either infected or uninfected infants against infant mortality (Newell ML, 2003), although multivariate analysis did not reach statistical significance. The trials compared ever breastfed with never breastfed infants.

In summary, evidence of benefit, in terms of morbidity or mortality, or of nutritional status, of breastfeeding to children born to HIV-infected mothers is, so far, contradictory or inconclusive.

Mortality among HIV-infected breastfeeding mothers

Results from a secondary analysis of data collected in the randomized trial of breastfeeding compared with formula feeding, in Nairobi, Kenya, suggested a three-fold higher mortality rate in HIV-infected women in the breastfeeding arm than in those in the formula-feeding arm (Nduati et al., 2001). Overall, 24 of the 397 women died in the two years after delivery: 18 of 197 women allocated to breastfeeding and six of 200 randomized to the formula-feeding group. Since assessment of mortality was not the main aim of the trial, this unexpected observation must be interpreted with caution (Newell, 2001a). The authors suggest that the high energy-demands of breastfeeding in HIV-infected mothers may accelerate the progression to HIV-related death. If this is the case, women who exclusively breastfeed their infants would be expected to have a higher death rate than those who give their infants food supplements or avoid breastfeeding altogether.

In a study in Durban, South Africa, women made an informed choice about infant feeding, and those who chose to breastfeed were advised to do so exclusively (Coutsoudis et al., 2001b). A detailed analysis over an average follow-up period of 11 months of both breastfeeders and non-breastfeeders found no evidence of increased mortality or morbidity among exclusively breastfeeding mothers. Two of 410 exclusively breastfeeding mothers died, as did three of 156 who never breastfed. In addition, no association was found between clinical conditions in the mother and duration of breastfeeding. Though these results are reassuring, the number of women participating was small and the study had limited power to exclude any increase in mortality or morbidity in mothers who breastfed.

Neither the Nairobi nor the Durban study provided detailed information on the mode, duration or amount of breastfeeding or the associated mortality risks. In addition, the two groups of women enrolled in the trials were not directly comparable. The Durban mothers were in general healthier, as evidenced by a lower prevalence of anaemia and better immune status at enrolment, than the Nairobi group. The overall mortality rate in the Durban group was less than 1% with an average follow-up of 10.5 months compared with overall mortality rates over 4% at one year and 7% at two years in the Nairobi group. Whether or not breastfeeding HIV-infected women have higher mortality than non-breastfeeding women in some circumstances cannot be concluded on the basis of these two studies alone.

Data pooled in a large international initiative to estimate the risk of postnatal transmission through breastfeeding (Read et al., 2003) provide an opportunity to reliably estimate mortality rates in HIV-infected women over a period of 12 to 18 months after delivery. Of the 4237 women included in the pooled analysis (Newell et al., 2003), 162 (3.8%) died within 18 months of delivery (median time to death: 9.8 months). Median CD4+ count (cells/mm3) around time of delivery was 464 (11% of women had counts under 200/mm3, 45% between 200 and 499, and 44% above 500). Overall mortality was 28.7/1000 person-years at 12 months follow-up and 32.2/1000 at 18 months; 3717 (87.7%) women ever breastfed (median duration 8.8 months).

Independent risk factors for mortality in multivariate analyses were:

- maternal CD4+ count (lower CD4+ increased risk of 12–month and 18–month mortality: $p<0.001$);
- mode of feeding (mothers who ever breastfed had a lower risk of mortality than mothers who never breastfed: $p=0.033$ for 12 months and 0.068 for 18 months mortality);
- geographical location (south, east and west Africa).

Further analyses are in progress, in particular to investigate the effect of breastfeeding duration on mortality in the breastfeeding woman. In this context the issue of reverse causality needs to be resolved, namely whether the outcome (mortality in breastfeeding women) is a determinant of the supposed predictor (duration of breastfeeding) and not the contrary. The lower the mortality rate in a given breastfeeding population, the longer the duration of breastfeeding. More precisely, a woman with advanced disease has little chance to breastfeed her infant.

In summary, the evidence to date suggests that mortality among infected women in the period following delivery is associated with HIV infection and not with infant feeding modality (The Breastfeeding and HIV International Transmission Study (BHITS) Group, unpublished data, 2004).

Mother-to-child transmission

HIV infection in women

HIV infection is most commonly due to unprotected sex with an infected partner, but can also occur from receiving contaminated blood, or exposure to non-sterile instruments or medical procedures (Buvé et al., 2002). As most infected children under 15 years have contracted the virus by transmission from their mothers, their number reflects the prevalence of the infection in women of childbearing age.

In Africa, HIV prevalence varies considerably. In most countries in Southern Africa more than one in five pregnant women are HIV-infected, and in a few sub-Saharan countries median HIV prevalence in antenatal clinics in 2003 exceeded 10%. In some urban settings in Southern Africa antenatal seroprevalence reaches over 40% (Buvé et al., 2002: UNAIDS, 2002). "Across most of sub-Saharan Africa, including parts of Southern Africa, HIV prevalence among pregnant women visiting antenatal clinics has been roughly level for several years – albeit at very high levels in Southern Africa." (UNAIDS, 2002). It should be noted that the apparent stabilization of prevalence rates observed in most of sub-Saharan Africa is due to the matching of the persistently high number of annual new HIV infections with the equally high number of AIDS deaths.

In West Africa HIV prevalence in pregnant women remains generally stable at low levels, though in some urban areas it exceeds 10%; in rural areas the rates are generally lower. In East Africa and parts of Central Africa prevalence among pregnant women has fallen sharply from its high levels of a decade ago. In Addis Ababa, for instance, among 15–24-year-old pregnant women, prevalence has fallen to about 11% in 2003 from around 24% in 1995 (WHO/UNAIDS, 2003).

Asia is experiencing a rapidly growing epidemic: seroprevalence rates in some cities or provinces of Indonesia, Cambodia, India and Thailand range from 1% to 5% (UNAIDS/WHO, 2002). Eastern Europe similarly is seeing an exceptionally rapid increase in prevalence, especially among injecting drug users; almost 80% of new infections occur before the age of 29 years. Women account for an increasing share of newly diagnosed HIV infections – 33% in 2002 compared with 24% a year earlier. One consequence is a sharp rise in mother-to-child transmission. In six countries in the Caribbean Basin the most recent national estimates have shown HIV prevalence among pregnant women reaching or exceeding 2%. In Central and South America, HIV-1 prevalence rates among pregnant women range from 0.1% to 5.0% (WHO/UNAIDS, 2003).

The risk of mother-to-child transmission is increased if a breastfeeding mother is newly infected, owing to the initially high levels of virus. Preliminary evidence from a study in Zimbabwe suggests that about 4% of women who were HIV-negative when giving birth become infected in the first year postpartum, and that the risk continues into the second year (J. Humphrey, personal communication, 2002). This merits attention as in this population 85% of women still breastfeed at 15 months and 30% at 21 months. Similar findings have been reported from another study in Zimbabwe, with 66 new infections among 372 women, nearly 5%, over the two years postpartum (Mbizvo et al., 2001). HIV- prevention interventions directed at pregnant and lactating women could contribute greatly to reducing mother-to-child transmission, but this possibility has so far attracted little research or programmatic effort.

Rates of mother-to-child transmission and risk factors

Mother-to-child transmission of HIV can occur before, during or after delivery, but only rarely in early pregnancy. Without specific interventions to reduce the risk of transmission, estimated rates of mother-to-child, or vertical, transmission range from 14% to 25% in Europe and America and from 13% to 42% in developing countries (Msellati et al., 1995). The difference in risk between populations is largely attributable to the characteristics of the population studied as they relate to HIV infection and to the prevalence of factors influencing the likelihood of transmission. In particular, the additional risk posed by breastfeeding explains a large part of the estimated differences (Table 1) (Newell, 2001; Dabis and Ekpini, 2002).

In developed countries the rate of mother-to-child transmission has declined substantially. With

TABLE 1

Estimated risk and timing of MTCT in the absence of interventions (Adapted from De Cock KM et al., 2000.)

Timing	Transmission rate
During pregnancy	5–10%
During labour and delivery	10–15%
During breastfeeding	5–20%
Overall without breastfeeding	15–25%
Overall with breastfeeding to six months	20–35%
Overall with breastfeeding to 18–24 months	30–45%

Note: Rates vary because of differences in population characteristics such as maternal CD4+ cell counts, RNA viral load and duration of breastfeeding.

antiretroviral prophylaxis, elective caesarean section, and refraining from breastfeeding, rates below 2% have been reported in American and European populations (Dorenbaum et al., 2002; European Collaborative Study, 2001). In developing countries, peripartum antiretroviral prophylaxis with one drug alone can decrease the rate of infection in breastfed infants assessed at two to three months of age to around 10% (Dabis and Ekpini, 2002; The Petra Study Team, 2002; Guay et al., 1999), and with two or more drugs to about 7% at six weeks (Dabis et al., 2003). Infants remain at risk of infection, however, while breastfeeding continues (Leroy et al., 2002; Leroy et al., 2003; The Petra Study Team, 2002)

The overall risk of mother-to-child transmission is associated with factors related to the virus, the mother and the infant (Newell, 2001). Maternal RNA viral load in plasma has been strongly associated with this risk (Mayaux et al, 1997; European Collaborative Study, 1999; Dabis et al., 1999; Shaffer et al., 1999; Simonds et al., 1998). Although the risk increases substantially with increasing viral load, the virus can, however, be transmitted to the fetus or infant with even very low or undetectable levels of viral load, albeit rarely. Similarly, at very high levels of HIV-RNA, transmission does not always occur. Women with a low CD4+ cell count (under 200/mm^3) near the time of delivery and those with severe clinical disease are about three times as likely to transmit as those who are less severely affected (European Collaborative Study, 2001; Leroy et al., 2002).

HIV has been recovered from vaginal and cervical secretions of pregnant women (John et al., 1997; Loussert-Ajaka et al., 1997) and from gastric secretions of infants born to HIV-seropositive women (Ait-Khaled et al., 1998; Nielsen et al., 1996). Delivery factors, such as vaginal delivery and duration of rupture of membranes, which increase contact between the infant and HIV-infected maternal body-fluids (cervico-vaginal secretions and blood), have been linked with increased risk of transmission (International Perinatal HIV group, 1999; European Mode of Delivery Collaboration, 1999). RNA levels in plasma and in vaginal and cervical secretions are correlated; HIV-RNA, however, can be detected in the secretions even when plasma RNA is undetectable (Kovacs et al., 2001).

Prevention of mother-to-child transmission

The United Nations strategic approach to the prevention of transmission of HIV to infants and young children has four areas:

1. Prevention of HIV infection in general, especially in young women and pregnant women;
2. Prevention of unintended pregnancies among HIV-infected women;
3. Prevention of HIV transmission from HIV-infected women to their infants; and
4. Provision of care, treatment and support to HIV-infected women, and their infants and families.

A significant and sustainable impact will be achieved only when all four areas are in place and functioning. The present paper is concerned particularly with area 3, prevention of mother-to-child transmission.

Current approaches to prevention of mother-to-child transmission (area 3) target the late intrauterine and intrapartum period. For one reason, this period is a relatively short interval of relatively high risk: an estimated 40% of overall transmission occurs in late pregnancy and during labour and delivery. Peripartum antiretroviral prophylaxis reduces transmission risk in the period around delivery (Dabis et al., 2000).

Caesarean section before onset of labour and rupture of membranes approximately halves the risk of mother-to-child transmission (European Mode of Delivery Collaboration, 1999; International Perinatal HIV group, 1999), even a risk already reduced by antiretroviral prophylaxis (European Collaborative Study, 2001; Ioannidis et al., 2001). Elective caesarean section, however, may not be a safe option in the parts of the world where HIV prevalence is highest, because of an increased risk of infectious complications. The use of antiseptic or antiviral agents to cleanse the birth canal during labour and delivery has been suggested as a possible means of reducing intrapartum transmission of HIV-1. Although two randomized trials in sub-Saharan Africa showed that cleansing with

TABLE 2

Rates of mother-to-child transmission (MTCT) assessed at 4–8 weeks after delivery (reflecting intrauterine, intrapartum and early postpartum infection), by peripartum antiretroviral therapy used

Trial	MTCT rate as %	Age at assessment (weeks)	Antiretroviral drug(s) used in the peripartum period	Median CD4+cell count per mm^3 plasma near delivery
ANRS049 + Retro-Ci (Dabis et al, 1999, Wiktor et al. 1999)	14.7	6	ZDV	545
HIVNET012 (Guay et al, 1999)	11.9	6	NVP	461
SAINT (Moodley et al, 2003)	10.7	4	NVP	405
SAINT (Moodley et al, 2003)	8.1	4	ZDV+3TC	385
Petra medium (The Petra Study Team, 2002)	8.9	6	ZDV+3TC	475
Petra long (The Petra Study Team, 2002)	5.7	6	ZDV+3TC	445
ANRS1201 V1.0 (Dabis et al, 2003)	6.4	4	ZDV+NVP	370
ANRS 1201 V1.1 (Dabis et al, 2003)	4.5	4	ZDV+3TC+NVP	439

chlorhexidine did not reduce the risk of mother-to-child transmission overall, it may benefit a subgroup of women with prolonged duration of ruptured membranes (Biggar et al., 1996; Gaillard et al., 2001).

Zidovudine monotherapy during the second and third trimesters of pregnancy, intravenously during delivery, and to the infant for six weeks (a regimen known as ACTG 076) substantially reduces the risk in a non-breastfeeding population (Connor et al., 1994; European Collaborative Study, 2001; Dorenbaum et al., 2002). Shorter, more practical, regimens beginning later in pregnancy have also been shown to reduce peripartum transmission in non-breastfeeding (Shaffer et al., 1999; Lallemant et al., 2001) and breastfeeding populations (Dabis et al., 1999; Wiktor et al., 1999; The Petra Study Team, 2002; Guay et al., 1999). Peripartum antiretroviral therapy can reduce the overall risk of HIV infection, even in breastfeeding populations (Leroy et al., 2002).

Combination therapy with two or more antiretroviral drugs is likely to be more effective than monotherapy in reducing the risk of vertical transmission (European Collaborative Study, 2001; Dorenbaum et al., 2002, The Petra Study Team, 2002). Dabis et al. (2003) studied two cohorts in the same setting: one consisted of women on zidovudine during pregnancy and nevirapine during labour, and whose neonates were given zidovudine; the other was a historical control cohort who received only zidovudine. The addition of nevirapine in the former cohort resulted in a 49% lower overall rate of transmission than with zidovudine alone, but the rate of transmission in infants of women with a CD4+ cell count lower than 200/mm3 was high and similar in both cohorts (18.6% and 21.2%).

With the short peripartum regimen of antiretroviral drugs as monotherapy or combination therapy, transmission rates assessed at four to eight weeks of age are in the range of 4.5–15% (Table 2); the lowest rates observed have been with triple combination of zidovudine and lamivudine (ZDV+3TC) during the last eight weeks of pregnancy, with additional nevirapine during labour and delivery and to the neonate (Dabis et al., 2003).

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 (Palasanthiran et al., 1993; Van de Perre et al., 1991; Stiehm and Vink, 1991; Hira et al., 1990; Lepage et al., 1987; Ziegler et al., 1985). Other reports related to infants with no other known exposure to HIV, whose source of infection was wet-nursing or pooled breast milk (Nduati et al., 1994).

Rates of breastfeeding transmission

According to the limited data available in the early 1990s, the estimated additional risk of transmission from breast milk, above that of transmission during pregnancy and delivery, among women with established HIV infection, was approximately 15% when breastfeeding continued for two years or more (Dunn et al., 1992). The risk of transmission through breastfeeding among women with recent infection (acquired postpartum) was nearly twice as high. More recent and more reliable data, including the results of a randomized clinical trial in Nairobi, confirm these initial findings: HIV-infected pregnant women were randomly allocated to either breastfeeding (n=212) or artificial feeding (n=213) (Nduati et al., 2000). Compliance with the assigned feeding modality was 96% in the breastfeeding arm and 70% in the formula arm. Median duration of breastfeeding was 17 months. The cumulative probability of HIV infection at 24 months of age in the breastfeeding and formula-feeding arms was, respectively, 36.7% and 20.5%. The estimated absolute rate of transmission through breastfeeding was therefore 16.2% at two years follow-up; in the breastfeeding arm 44.1% of all transmission was attributable to breastfeeding. Although exclusive breastfeeding in the early months was recommended in this trial, information on intensity of breastfeeding was not collected and breastfeeding was probably not totally exclusive in this population.

Further confirmation of the rate of transmission through breastfeeding can be inferred from the results of trials of a peripartum intervention to reduce the risk of transmission. The rates seen in these trials are broadly in line with the results from the randomized trial, with an estimated increase in infection rates of 10–14% between the ages of 4 to 6 weeks and 18 to 24 months (Leroy et al., 2002; Owor et al., 2000; The Petra Study Team, 2002). Differences between trial findings could be explained by the different methods used to assess rate of transmission (The Ghent Group, 2003), variation in the duration of breastfeeding between populations, or differences in maternal or other factors possibly associated with increased risk. Further standardized analytical evaluations are under way across the West African short-course zidovudine trials, the Nairobi breastfeeding trial, the HIVNET 012 SAINT nevirapine trial, and the PETRA trials (The Ghent Group, 2003).

Mechanisms of breastfeeding transmission

Although HIV has been detected in breast milk (Nduati et al., 1995; Ruff et al., 1994; Van de Perre et al., 1993), mechanisms of transmission through breastfeeding remain incompletely understood. Not yet reliably quantified are the respective roles of cell-free and cell-associated virus in transmission through breastfeeding or the association between virus levels in plasma and milk. The portal of entry for the virus via the infant mucosa also merits further investigation; animal models have shed some light on this issue (Featherstone, 1997; Amerongen et al., 1991; Bomsel, 1997).

After ingestion of HIV-1-infected breast milk, infant gut mucosal surfaces are the most likely site of transmission. Cell-free or cellular HIV-1 may penetrate to the submucosa in the presence of mucosal breaches or lesions, or via transcytosis through M cells or enterocytes expressing specific receptors; and laboratory studies suggest that secretory IgA or IgM may inhibit transcytosis of HIV-1 across enterocytes. Thus, breast-milk HIV-1 immunoglobins may contribute to protection from transmission. Tonsils may also be a portal of entry for HIV-1 in breast-milk transmission. Tonsils include M cells close to lymphocytes and dendritic cells, and tonsillar M cells are capable of HIV-1 replication; oral transmission has been demonstrated in a macaque SIV model (Baba et al., 1994).

Subclinical mastitis in the mother is hypothesized to increase 'leakiness' in the cell lining of the breast duct and therefore to increase the amount of virus to which an infant is exposed (Semba et al., 1999; Willumsen et al., 2003).

Intestinal permeability of the young infant has been suggested as a possible means of entry for the virus, but evidence is limited (Rollins et al., 2001); it seems biologically plausible that mixed feeding increases the risk of HIV transmission, by making the gut more susceptible through mechanical or inflammatory mechanisms.

Timing of postnatal transmission through breastfeeding

HIV can be transmitted through breast milk at any point during lactation, and thus the rate of infection in breastfed infants increases with duration of breastfeeding. The persistence of maternal antibodies and the presence of a "window period" during which infection is undetectable by current technology make it difficult to determine whether an infant has been infected during delivery (intrapartum) or – through breastfeeding – immediately after birth. There is too little information to estimate the exact association between duration of breastfeeding and risk of transmission. There is strong evidence, however, that the longer the duration of breastfeeding the greater the risk of transmission – in other words, the risk is cumulative (Miotti et al., 1999; Leroy et al., 1998; Read et al., 2003; Leroy et al., 2002; The Petra Study Team, 2002).

It is difficult to draw any conclusions about the relative risk of transmission by colostrum and mature breast milk (Ruff et al., 1994; Van de Perre et al., 1993; Nduati et al., 1995; Lewis et al., 1998). First, colostrum and mature breast milk contain different types of cells and different levels of immune modulating components (e.g., vitamin A, immunoglobulins and lactoferrin). Second, the infant ingests much less colostrum than mature breast milk. Third, the infant's immune system is less well developed in the first few days of lactation than later, and younger infants have an increased blood concentration of maternal antibodies. There is no evidence to suggest that avoidance of colostrum would reduce the risk of breastfeeding transmission to the infant.

Statistical modelling, with data from studies in which breastfeeding was of limited duration, has suggested that the highest-risk period for transmission is the first several weeks of life, and that infectivity may vary in populations at different stages of the epidemic (Dunn et al., 1998). The randomized trial in Nairobi, Kenya, comparing breast milk with formula, suggested that 10% of the cumulative difference in infection rates between infants in the breastfed and formula-fed arms had occurred by six weeks of age, compared with the total cumulative difference of 16%. Also, 75% of all breastfeeding transmission had occurred by six months of age (Nduati et al., 2000).

In a subsequent analysis of those data, the probability of transmission through breastfeeding was estimated to be 0.00064 per litre of breast milk ingested and 0.00028 per day of breastfeeding (Richardson et al., 2003). Breast-milk infectivity was significantly and substantially higher in mothers with low CD4+ cell counts and high RNA viral load in plasma. It should be noted that the probability of infection through breastfeeding per day of exposure was not statistically significantly different for infants of less than four months than for older infants (0.00015 vs 0.00031, p=0.4). The SAINT trial (Moodley et al., 2003) found that breastfed infants were at twice the risk of infection of non-breastfed infants during the first four weeks of life and at seven times the risk between the fourth and eighth weeks. This is because few replacement-fed children become HIV-infected after four weeks.

Late postnatal transmission

Another way of estimating the risk associated with breastfeeding is to start with infants who had been born to infected mothers and had tested negative for HIV early in life, and to follow them until after they ceased being breastfed, to determine the rate at which they become HIV-infected through breastfeeding. If infants with evidence of not being infected at an early age are taken as the denominator, the rate is estimated from the number of breastfed children who have subsequent positive virological tests or persistent antibodies beyond 15–18 months or after cessation of breastfeeding. The time at which the exposure begins is determined by the age at which infants are tested. This is now usually around four to six weeks, but in earlier studies was between three and six months; different 'start' times may explain why different studies gave different estimates of rates of late postnatal transmission (LPT) (Table 3). Estimated rates of LPT range from about 9% to 13% at 18 months.

In about 700 infants with prolonged duration of breastfeeding in African studies, the risk of postnatal transmission after three to six months of age was estimated to be 4% (95% CI 2–5%) (John et al., 2001). In a recent meta-analysis in sub-Saharan Africa of a large number of individual data on breastfeeding and postnatal transmission of HIV from randomized control-

TABLE 3
Estimated rates of late postnatal transmission

Study	Age at negative test determining denominator	Incidence per 100 child-years of breastfeeding	Cumulative percentage infected by 12 months	Cumulative percentage infected at last follow-up (months)
Malawi (Miotti et al, 1999)	1 month	6.9		8.9 (18 months) 10.3 (24 months)
Africa (Leroy et al, 1998)	3 months	3	2.5	9.2 (36 months)
West Africa (Leroy et al, 2003)	4 weeks	8.6	9.5	13.1 (18 months) 13.1 (24 months)
Africa BHITS (Read et al, 2003)	4 weeks		7	9.3 (18 months)

led trials of peripartum interventions, early transmission was defined by a positive HIV-test before four weeks, and late postnatal transmission by a negative diagnostic test at or after four weeks of age, followed by a subsequent positive test result. In all, 4343 children were breastfed and HIV-tested. A child was presumed to be no longer at risk of infection once breastfeeding had ceased, and the method used dealt adequately with such censoring. The overall rate of transmission was 24%; of the 993 infected children, the infection had occurred early in 314 (31.4%), late in 225 (23.1%), and at an unknown time in 454 (45.4%). The mean duration of breastfeeding was nearly seven months, and the median, four months. The risk of late postnatal transmission continued throughout the breastfeeding period and was more or less constant over time (The Breastfeeding and HIV International Transmission Study [BHITS] Group, in press). The cumulative probability of becoming HIV-infected after age four weeks was 1.6 % at three months, 4.2 % at six months, 7.0 % at 12 months, and 9.3 % (95% CI 3.8–14.8) at 18 months. The contribution of late postnatal transmission (after four weeks) to overall transmission was estimated to be at least 23%, but possibly as much as 42% (The Breastfeeding and HIV International Transmission Study [BHITS] Group, in press).

Factors associated with risk of transmission through breastfeeding

There is limited, though gradually increasing, reliable quantification of the effect of risk factors associated with an increased or decreased likelihood of breastfeeding transmission. 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 mother; mode of infant feeding; infant factors (such as oral ulcers); and, possibly, protective elements in the milk.

Maternal factors

RNA viral load in plasma and breast milk

The risk of transmission through breastfeeding is probably strongly related to RNA levels in the milk, but the degree of risk has not yet been adequately determined. Limited evidence suggests that RNA viral load in blood is only partly correlated with that in breast milk; and RNA load in breast milk is highly variable between breasts and over time (Willumsen, 2001, 2003). In a study in Durban, South African women in whom RNA viral load in breast milk was detectable at any time during the first six months postpartum were more likely to transmit than those in whom it was undetectable (Pillay et al., 2000). A study in Malawi found that the risk of transmission was increased fivefold if RNA virus had been detected in breast-milk samples taken at six weeks postpartum (Semba et al., 1999). In West Africa, the rate of late postnatal transmission increased 2.6 times for every one log10 increase in plasma RNA viral load measured in late pregnancy (Leroy et al., 2003).

The level of HIV-RNA in milk has been studied on only a limited number of samples from HIV-infected mothers. According to studies by Willumsen et al. (2001, 2003) in South Africa, RNA viral load in milk, in general, appears to be lower than in plasma, and levels are often below that which currently used assays can detect. The authors quantified RNA viral load three times in the first three months after delivery, in samples taken from both breasts of 145 lactating women. RNA shedding varied between breasts and over time. Milk viral load was below the limit of detection of the HIV-RNA PCR assay (<200 copies/ml) in a substantial proportion of samples, and in the first 14 weeks was highly variable and difficult to pre-

dict by maternal or infant factors. Low blood CD4+ cell count (<200/mm3) during pregnancy and a raised Na+/K+ ratio (a marker of subclinical mastitis) were significantly associated with increased milk RNA viral load at all times, but there were no consistent associations between mode (exclusive or mixed) of infant feeding and RNA viral load in milk. Together the results of these studies indicate the random nature of virus shedding into breast milk.

HIV-related immune status

More data are available on the association between maternal immune status (CD4+ cell counts) and transmission of HIV through breastfeeding than on that between RNA viral load and transmission. The recent analysis of pooled data from the two West African zidovudine trials (Leroy et al., 2003) found that a maternal CD4+ cell count lower than 500/mm^3 in plasma close to time of delivery was associated with an increase in risk of late postnatal transmission three times that of women with CD4+ cell counts equal to or greater than 500/mm^3 (Leroy et al., 2003). In the Ugandan trial comparing nevirapine with zidovudine (Nakabiito et al., 2002), children whose mothers had a low CD4+ cell count around the time of delivery were especially liable to become infected. Low CD4+ counts in plasma have also been associated with detection of HIV-DNA in breast milk (Nduati et al., 1995). In the meta-analysis of data from nine intervention trials in sub- Saharan Africa, the risk of postnatal occurrence of infection after four weeks of age was strongly associated with maternal CD4+ cell count: transmission increased eightfold at CD4+ cell counts lower than 200/mm^3, and 3.5 times at CD4+ cell counts between 200 and 500/mm^3, compared with the reference group of CD4+ cell count above 500/mm3 (Read et al., 2003).

Breast conditions

Clinical or subclinical mastitis has been associated with transmission risk (Semba et al., 1999; John et al., 2001). Subclinical mastitis, which is likely to be more common than clinical mastitis, is not necessarily an infective process and may occur with milk stasis and engorgement of the breast. In the study by Willumsen et al. (2003), subclinical mastitis was associated with RNA load in the milk but, probably because of small sample size, not with late postnatal transmission. Subclinical mastitis is more likely to occur when the milk first comes in after birth, when there is inadequate milk drainage (as would occur during mixed feeding), or when there is poor attachment, or less vigorous suckling by an ill infant, or during rapid weaning. In a cohort study in Nairobi, transmission was independently associated with nipple lesions, maternal CD4+ cell count lower than 400 /mm3, infant oral thrush under the age of six months, and prolonged duration of breastfeeding (Embree et al., 2000; John-Stewart et al., 2004; Rollins et al., 2004). Whether, at a population level, treatment of breast lesions results in a reduction of the rate of transmission through breastfeeding is not clear, and further studies are in progress.

Nutritional status

Maternal nutritional status may influence risk of transmission overall, as well as breastfeeding transmission. A recent paper presented results from an additional analysis of data from a randomized trial investigating the effect of micronutrients and vitamin A on risk of transmission (Fawzi et al., 2002, 2003). Micronutrients excluding vitamin A, given to the mother during pregnancy and breastfeeding, had no effect on the overall risk of transmission, but vitamin A alone was associated with a slight increase of mother-to-child-transmission rates overall, and an increased risk of transmission during breastfeeding. Micronutrients were associated with a non-significant reduction in breastfeeding transmission and mortality in the first two years of life. Further analysis of these data showed that children of women who had been randomized to receive micronutrients 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 in the non-micronutrient arm. The benefit to HIV-infected children was similar to that for uninfected children. Vitamin A given to the mother reduced the risk of respiratory manifestations in the child (p=0.03) but not the risk of diarrhoea. These findings confirm the importance of nutritional support for HIV-infected breastfeeding women. Other studies (Coutsoudis et al., 1999; Kumwenda et al., 2002) showed no impact of vitamin A supplementation during pregnancy on risk of transmission during breastfeeding.

Infant factors

Integrity of mucous membranes

Conditions that damage the mucous membrane of infants, such as oral thrush (*Candida* infection), may be associated with an increased risk of transmission through breastfeeding. It is difficult, however, to determine which is cause and which effect, since thrush may be a feature of early HIV-1 infection (Ekpini et al., 1997; Embree et al., 2000). Infant oral thrush can also cause nipple thrush and fissures. Damage to the

intestinal mucous membrane can result from feeding with cow's milk, allergic reactions to complementary foods, and infections. Mode of feeding may affect the intestinal permeability of the young infant: infants who receive only breast milk may have a less permeable and therefore healthier lining of the gut than those who also receive other feeds. In the one study carried out to investigate this further, however, feeding mode was not associated with intestinal permeability in infants (measured with lactulose-mannitol ratios, i.e., dual sugars). Infants who had been diagnosed with HIV infection at 14 weeks, however, had higher permeability at six and 14 weeks than uninfected infants (Rollins et al., 2001).

Human secretory leukocyte protease inhibitor

Perhaps the best-characterized innate factor considered as protective against mucosal transmission of HIV-1 is secretory leukocyte protease inhibitor (SLPI). Infant salivary SLPI has also been associated with lower risk of late transmission of HIV-1 through breast milk (Farquhar et al, 2003). However, in a study of 43 unselected HIV-infected breastfeeding mothers in Bangui, with breast-milk samples obtained at one week and one and six months after delivery, the mean levels of SLPI in breast milk of mothers of infants who became infected did not differ significantly from those in the case of infants who remained uninfected (Becquart et al., 1999). Further controlled studies are needed to confirm the role of maternal and infant SLPI in transmission, either alone or in combination with other innate and specific immune factors.

Mode of infant feeding

A factor of particular relevance at population level as regards rates of breastfeeding transmission is mode of infant feeding. In most populations worldwide, breastfeeding is usually initiated, but at an early age is supplemented with water or other drinks or feeds (Nicoll et al., 2000); exclusive breastfeeding for the recommended six months is rare. In a study in Durban, South Africa, 551 HIV-infected women, after counselling, chose whether to breastfeed or formula-feed (Coutsoudis et al., 2001a). Those who chose to breastfeed were encouraged to do so exclusively for three to six months. A total of 157 formula-fed from birth and never breastfed, 118 breastfed exclusively for three months or more, and 276 practised mixed breastfeeding. The three groups did not differ in any of the significant risk factors for transmission, and at birth the rate of infection in their infants had been similar at about 7%. 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 (25%) or formula-fed (19%). Exclusive breastfeeding carried a significantly lower risk of HIV infection than mixed breastfeeding (Hazard ratio 0.56, 95% CI 0.32–0.98) and was similar in this respect to never breastfeeding (Hazard ratio 1.19, 95% CI 0.63–2.22). Further studies are under way to confirm this finding, which has obvious implications for infant-feeding recommendations and for advice to HIV-infected women in settings where it is not acceptable, feasible, affordable, sustainable or safe to refrain from breastfeeding. In particular, results from the Zvitambo study in Harare, Zimbabwe, which are imminent, will be of much interest (J. Humphrey, personal communication, 2003). Assessment of exclusive breastfeeding is complex, and the results of current studies in Hlabisa, in which mode of feeding is assessed daily for nine months, will shed light on the impact of divergence from exclusive breastfeeding on rate of transmission (Rollins et al. 2004).

Sex of infant

In the recent meta-analysis of late postnatal transmission (LPT) (Read et al., 2003) covariates that could affect the relationship between breastfeeding and LPT of HIV-1 were evaluated, including maternal variables (age, parity, CD4+ count) and child variables (birth weight, sex). Maternal age, parity or birth weight was not significantly associated with LPT, but maternal CD4+ cell counts and sex of child were; females were 40% less likely than males to become infected through breastfeeding after four weeks of age (Hazard ratio 0.6, 95% CI 0.4–0.9, p=0.014). The risk of LPT was highest for males breastfed by mothers with CD4+ cell counts lower than 200/mm^3, followed by males breastfed by mothers with counts of 200–499 cells/mm^3, and then females breastfed by mothers with counts lower than 200 cells/mm^3. Duration of breastfeeding was similar for both sexes, but no information was available on the age at which other foods were introduced or on type of food. The sex difference in risk of LPT may be due to males receiving complementary feeds at an earlier age, thus making them mixed feeders, which may have put them at higher risk of becoming infected. Further research is testing this hypothesis.

Preventing transmission from breastfeeding

The prevention of HIV transmission from HIV-infected women to their infants is the third of the four areas that constitute the United Nations strategic approach to the prevention of transmission of HIV to infants and young children. The present paper is concerned primarily with this area.

Primary prevention

The best means of preventing HIV infection in infants and young children, including transmission through breast milk, is to prevent HIV infection of female adolescents and women of childbearing age (De Cock et al., 2002) (Area 1 of the United Nations strategic approach). In sub-Saharan Africa, Asia and the Caribbean the main mode of HIV transmission is heterosexual contact (Buvé et al., 2002). In industrialized countries, although most HIV-infected women have a history of injecting drug use or sexual partners who have such a history or are bisexual, heterosexual transmission has become an increasingly common route of infection (European Collaborative Study, 2001). The risk of HIV infection in women is increased by such factors as immaturity of the genital tract, cervical ectopy, sexually transmitted diseases, and poor nutritional status (Mostad and Kreiss, 1996). Cultural, social and economic factors also contribute to HIV trans-mission by increasing the vulnerability of female adolescents and women (Buvé et al., 2002; De Cock et al., 2002).

The prevention of all HIV transmission to infants and young children should be linked to programmes that provide education to young people on safer sex, and diagnosis and treatment of sexually transmitted infections, and that ensure the safety of medical procedures. HIV prevention should be emphasized for women who test seronegative in pregnancy (a high percentage of whom may become infected in the two years after delivery, while breastfeeding) because of the particularly high risk of mother-to-child transmission if mothers become HIV-infected during breastfeeding.

To implement the recommended preventive measures it is obviously important, though difficult, to achieve high rates of HIV testing and counselling during pregnancy as well as high rates of uptake of interventions, and ensure continued contact with mothers and infants during the 18–24 months postpartum (Temmerman et al., 2003).

Infant feeding options designed to prevent mother-to-child transmission

The infant feeding options designed to prevent mother-to-child transmission are described in detail in other documents (WHO/UNICEF/UNFPA/UNAIDS, 2003a and b). 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 (Nagelkerke et al., 1995; Nicoll et al., 2000). These models are limited by the scarcity of data on the risks associated with various methods of infant feeding and by the inability of such data to take account of all the factors that influence individual decisions about infant feeding.

According to current WHO recommendations, infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health. After six months, they should receive nutritionally adequate and safe complementary foods while breastfeeding continues up to 24 months or beyond. Given the need, however, to reduce the risk of HIV transmission to infants while minimizing also the risk of other causes of morbidity and mortality, HIV-positive mothers are recommended to avoid all breastfeeding and use replacement feeding when it is acceptable, feasible, affordable, sustainable and safe to do so. All HIV-infected mothers should receive counselling that includes 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 (WHO, 2001b). A woman's choice should always be respected and supported. Mixed feeding with both breast milk and other feeds has been associated with a higher risk of HIV infection for the infant than exclusive breastfeeding (Coutsoudis et al., 2001a) and in any case should be avoided because it brings both the risks of HIV infection and the risks of

diarrhoea and other infectious disease.

One benefit of breastfeeding to be considered, especially in poorer settings, is its physiological contraceptive effect, which helps to maintain an advantageous birth interval; lactational amenorrhoea has a 98% contraceptive effect – a level which is effective as commonly used and very effective when used correctly and consistently (WHO, 2000). In addition, in some cultures, coitus is reduced during the period of breastfeeding, which may enhance the contraceptive effect. Hence, when women at risk of mother-to-child transmission are considering the use of replacement feeding and stopping breastfeeding, the issue of replacement contraception must always receive attention.

The questions to be addressed here relate to how to make feeding safer for infants of HIV-positive women; and how to support infant feeding choice among these women, whether breastfeeding or replacement feeding. Counselling an HIV-positive woman on infant feeding may need to take into account her disease progression. Recent evidence suggests a very high rate of postnatal transmission in women with advanced disease (Leroy et al., 2003).

The infant feeding options available to HIV-positive mothers are replacement feeding with commercial infant formula or home-modified animal milk; exclusive breastfeeding with early cessation; and the breast-milk options of wet-nursing, expressing and heat-treating breast milk, and breast-milk banks.

Replacement feeding

Replacement feeding means feeding an infant who is receiving no breast milk with a diet that provides all the necessary nutrients. An HIV-infected woman who decides to eliminate the risk of HIV transmission through breastfeeding needs to avoid breastfeeding from birth and to use replacement feeding with suitable breast-milk substitutes. A suitable substitute is commercial infant formula or home-modified animal-milk.

There is so far little information about the effect of replacement feeding on infant morbidity or mortality. Recent preliminary evidence suggests, however, that mortality is high for both uninfected and infected infants born to HIV-infected mothers and may not be associated with mode of feeding (ML Newell, personal communication, 2003; Becquet et al., 2003).

Support for adequate replacement feeding is needed throughout the period for which breast milk is normally recommended and during which the child is at greatest risk of malnutrition – that is, the first two years of life. From birth to six months of age, milk only in some form is generally considered essential; after six months several additional options of replacement feeding may be used and should include complementary foods but preferably still accompanied by milk in one form or other.

Exclusive breastfeeding with early cessation

An HIV-infected mother for whom replacement feeding is not acceptable, feasible, affordable, sustainable or safe, as in many places with high HIV-prevalence, is recommended to practise exclusive breastfeeding for the first few months; this confers protection for the infant against common childhood infections and possibly also reduces the risk of HIV transmission (WHO, 2001b).

Early evidence from the pilot programmes of prevention of mother-to-child transmission in Botswana indicates that about 90% of HIV-infected women at the programme sites were exclusively formula-feeding. Of the remaining 10%, who breastfed, only 20% breastfed exclusively. At the programme sites, uninfected mothers had significantly lower rates of exclusive breastfeeding than mothers of unknown HIV-status at non-programme sites, which suggests some 'spillover' (Mompati et al., 2002). This study, however, included only women still attending the programme at the clinic and could not capture the experience of women who were non-compliant or had dropped out. This may have biased the results in favour of formula-feeding. In Mombasa, Kenya, adherence to exclusive breastfeeding was found to be improved if the partner was aware of the HIV status of the mother and involved in the decision whether to breastfeed or formula-feed (Mwanyumba et al., 2002). Similar findings have been reported from India, where mixed feeding is less likely if in-laws or husbands are consulted (Jonnalagadda et al., 2002).

In many countries rates of exclusive breastfeeding up to six months in the general population are low. Longitudinal and randomized controlled studies in different settings have shown that breastfeeding counselling increases the rates of exclusive breastfeeding. (Pérez-Escamilla R, 2002). Some countries have successfully increased the rates of exclusive breastfeeding with combined action at different levels.

After the cessation of exclusive breastfeeding, HIV-infected women are recommended to avoid breastfeeding completely. No study has so far assessed the mortality and morbidity risks of early cessation, but early and complete cessation reduces exposure and hence the risk of transmission through breastfeeding; it does not eliminate it, as the infant has been exposed for the first few months. To date, however,

there is no evidence and little experience as to how early cessation can be achieved with the minimum adverse effects for mother and infant. Nor is there evidence yet to inform the exact timing of cessation. It is advisable, however, to cease breastfeeding as soon as replacement feeding becomes acceptable, feasible, affordable, sustainable and safe, and in any case by six months of age, when exclusive breastfeeding can no longer meet an infant's nutritional needs and its anti-infective protective effect is rapidly decreasing. It should be recognized that, as stated above, continued support is still needed beyond the six months to ensure adequate nutrition for the young child throughout the first years of life.

Early cessation reduces the risk of transmission by limiting the time that an infant is exposed to HIV infection through breast milk (Read et al., 2003). Some mothers, however, may still not be able to provide replacement feeding for an infant from six months onwards; among other factors, suitable replacement foods may not be available in a practical sense. In such circumstances, early cessation may increase malnutrition among infants and young children. It is also not known how long the process of cessation should take; the current studies in sub-Saharan Africa will provide much-needed data to inform the practical recommendations relating to all aspects of early cessation. Limited experience in one study (Ndagire et al., 2000) suggests that the availability of alternative local feeds contributes to early cessation of breastfeeding.

The other breast-milk options

The other breast-milk options to reduce HIV infectivity are wet-nursing by a tested, HIV-negative woman; treating breast milk to render it non-infectious; and using milk from breast-milk banks

Wet-nursing by a tested, HIV-negative woman

Wet-nursing can be considered in communities where this option is practised. The wet- nurse must agree to, and understand the implications of, HIV testing and counselling. As she would have to be HIV-tested regularly, she would also have to be counselled about HIV and avoid becoming infected during breastfeeding. There is anecdotal evidence of infected infants transmitting the virus to their non-infected breastfeeding mothers (Bobkov et al., 1994; Pokrovski et al., 1990).

Treatment of breast milk

All means of modifying or treating breast milk to render it non-infectious involve expressing milk, and women have to be taught and supported to sustain this process for long periods, to avoid such problems as mastitis. This should not prevent the option being offered; infant feeding counselling should be provided when women choose this option, and issues of hygiene and stigma should be addressed. Expression and heat treatment could be a temporary solution during periods of increased risk of transmission as in cases of cracked nipples or breast abscess, and for low-birthweight or sick infants for whom the risk of replacement feeding is greater, and during transition from exclusive breastfeeding to replacement feeding (Rollins et al., 2004).

In vitro studies have demonstrated that when breast milk to which a known quantity of HIV has been added is subjected to heat treatment, by the Holder pasteurization method (at 62.5 °C for 30 minutes), the infectious titre of cell-free and cell-associated virus is substantially reduced (Orloff et al., 1993). This effect can also be achieved by alternative methods of heat treatment suitable for the home setting (Jeffery et al., 2000 and 2001).

Heat treatment, however, also reduces much of the immune and protective components of breast milk. Breast milk contains substances that inhibit infectious agents (Goldman, 1993). Several studies have reported that HIV is inactivated when milk is left to stand at room temperature for half an hour (Orloff et al., 1993; Newburg et al., 1992). In these studies the inhibitory effects of breast milk were attributed to a milk-lipase-activated factor that released fatty acids which were thought to dissolve or disrupt the viral envelope. Newburg et al. 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 to 10 minutes. Evaluation is needed of breast-milk treatment alternatives that utilize or enhance the action of naturally occurring anti-HIV factors to prevent HIV-transmission through breastfeeding.

Breast-milk banks

Experience with breast-milk banks in Latin America, especially in Brazil (http://www.redeblh.fiocruz.br/index_i.htm) has been positive though limited in relation to HIV infection. Breast-milk banks may be very useful in relation to HIV infection. Heat treatment of breast milk is recommended for all milk banks. Whether milk banks should systematically screen donors for HIV remains to be explored.

Current or planned research

The main public-health research question currently is whether breastfeeding by HIV-infected mothers can be made safer as to transmission risk, given the potential adverse effects of refraining from breastfeeding (for an update on ongoing research see www.Ghentgroup.org). Various ongoing or planned trials and studies concern either mode of infant feeding (exclusive or mixed) or antiretroviral therapy to either the mother or the infant over the breastfeeding period.

Results from an analysis of data on nearly 4500 infants born to HIV-positive mothers in the Zvitambo study in Zimbabwe will help to confirm or disprove the association between infant feeding modality and risk of transmission through breastfeeding. Studies in South Africa, Zambia and West Africa are assessing whether a recommendation of exclusive breastfeeding is acceptable, feasible and safe, and how the risk of infection to the infants concerned compares with that of infants who are mixed-fed. In these studies women are advised to exclusively breastfeed their infants for up to six months of age, and then to cease breastfeeding over a short period. The studies will estimate rates of transmission by mode of feeding and assess the feasibility of exclusive breastfeeding and the feasibility, safety and necessity of cessation at around six months. They will also provide information on the morbidity of infants by mode of feeding, and will inform future guidelines on infant feeding by HIV-infected mothers.

A further object of research is to determine the risk of breastfeeding women becoming infected in the two-year period after delivery.

A community-based trial is planned in Malawi to evaluate the effect of community involvement and awareness of health-related issues in decision-making relating to HIV testing and infant feeding.

Research is indicated also to assess morbidity and mortality among infected and uninfected breastfed and non-breastfed infants of HIV-infected mothers to further inform the debate about how best to counsel HIV-infected women about infant feeding.

A study in South Africa on maternal nutrition is comparing breastfeeding HIV-infected and uninfected women for weight, height, body composition and other variables.

In Malawi a randomized trial is evaluating nutritional support for breastfeeding women and for infants over six months of age receiving replacement feeding.

Another public-health research question is whether, or the extent to which, the different breast-milk options result in increased or reduced overall child survival at the age of two years.

Antiretroviral prophylaxis

Prevention of mother-to-child transmission has been confined largely to antiretroviral prophylaxis to women towards the end of pregnancy and avoidance of breastfeeding. Markers of HIV progression such as low maternal CD4+ cell counts indicate that at least some women in resource-poor countries need highly active antiretroviral therapy (HAART) to delay progression of their own disease. The "Treat 3 Million by 2005" (3 by 5) Initiative launched by WHO and its partners, designed to make antiretroviral treatment available to 3 million people living with AIDS in poor countries by the end of 2005, is likely to increase substantially the numbers of HIV-infected pregnant women with access to antiretroviral treatment, 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. Whether 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 (De Vincenzi et al., 2002).

There is little information as to the safety for the breastfed infant of treating the mother or the breastfed infant with antiretroviral drugs (Gaillard et al., 2004). The provision of antiretroviral drugs as a prophylaxis to breastfed infants or as a continued viral-load suppressant to breastfeeding women is beginning to be evaluated (see below). Trials are being planned or under way of three regimens to reduce transmission to breastfed infants: the administration to them for up to six months of nevirapine alone, of nevirapine plus zidovudine, or of lamivudine. 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 infants (Shetty et al., 2001). Further studies are indicated, therefore, to evaluate its effectiveness in reducing the rate of postnatal transmission if given to the breastfed infant for six months. This should include a careful assessment of its safety for the infant and its acceptability to the family. Preliminary findings from the first of the infant prophylaxis trials suggest low rates of transmission of about 1% in the first three months of life in infants who receive either nevirapine or lamivudine (3TC) (Vyankandondera et al., 2003). Further research is needed to confirm these low rates, which compare to a 1.6% (95% CI 0.3–2.9%) rate of late postnatal transmission between four weeks and three months without intervention (Read et al., 2003).

Current trials are evaluating the prophylactic use of antiretroviral drugs to breastfed infants whose mothers are HIV-infected. Antiretroviral prophylaxis for the infant varies in duration from one week to six months, and the regimens being used consist of one or more commonly used drugs, such as zidovudine, lamivudine or nevirapine. Such prophylaxis is designed to protect the uninfected infant while exposed to infection through breastfeeding.

An alternative approach being evaluated in several trials is to offer treatment during and after breastfeeding. In these trials, women who need HAART for their own health will be offered long-term HAART treatment, including during breastfeeding; these are mothers with evidence of advanced disease, such as CD4+ cell counts below 200/mm3. This is in line with current WHO recommendations, although its impact on rates of mother-to-child transmission is as yet unknown. HAART during breastfeeding for other categories of women, not yet in need of treatment for their own health, is also being assessed in the same trials. These trials are evaluating also the safety of the antiretroviral intervention.

Widespread use of short-term dual therapy or monotherapy in infected women may induce antiretroviral resistance mutations in populations with programmes for the prevention of mother-to-child transmission. No conclusive data support the hypothesis that such resistance is associated with increased transmission risk among women receiving zidovudine to prevent transmission. HAART regimens capable of achieving non-detectable viral loads are expected to carry a much reduced risk of resistance to individual drugs. To further understand, and to prevent, HIV transmission through breastfeeding, it is necessary to determine the potential mechanisms of viral resistance in breast milk and whether such resistance develops differently from resistance in plasma. These mechanisms may reflect separate viral origin or inadequate drug-levels, and may account for the differences.

Pharmacokinetic studies on antiretroviral diffusion in breast milk are also 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-infected mothers receive HAART while breastfeeding), infants are likely to be exposed to subtherapeutic levels of antiretrovirals through breast milk, and some will become HIV-infected. It is not known whether those who become infected will develop HIV resistance to antiretroviral drugs, or whether such resistance would affect their future HIV treatment. HIV-infected children will therefore need long-term follow-up to assess this issue.

Immunization

Active (vaccine) or passive (immunoglobulins) immunization of infants is also being considered as an approach to reducing the risk of contracting infection through breastfeeding in places where women cannot easily refrain from breastfeeding. This approach could be an addition to the use of antiretroviral prophylaxis in the peripartum or early neonatal period (Safrit et al., 2004).

Antiretroviral prophylaxis combined with vaccination

The ultimate goal of research is to prevent mother-to-child transmission by a combination of short courses of antiretroviral prophylaxis with vaccination. Further research plans thus include the development of randomized-trial protocols for the testing of vaccines to prevent infection during breastfeeding. In these trials infants born to HIV-infected mothers will likely receive antiretroviral prophylaxis for perhaps three months during which three or more doses of vaccine are given.

Conclusion

In conclusion, the ongoing or planned studies should help determine whether there are options 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-infected women for whom refraining from breastfeeding is not an acceptable, feasible, affordable, sustainable or safe option.

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