

HIV Transmission Through Breastfeeding



A REVIEW OF AVAILABLE EVIDENCE

2007 Update



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HIV Transmission Through Breastfeeding

A Review of Available Evidence

2007 Update



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Preface

This Review was originally prepared as a background paper for the Technical Consultation on HIV and Infant Feeding that took place in Geneva in October 2006. It was updated during 2007 to include relevant new information.

As the Review was going to print at the beginning of 2008, several trials were underway to assess use of extended maternal or infant antiretrovirals to reduce transmission among HIV-exposed breastfed infants. Relevant findings were presented at the 15th Conference on Retroviruses and Opportunistic Infections (CROI) held from 3 to 5 February 2008 and are summarized here.¹

Postnatal HIV transmission, infant outcomes and infant feeding practices

In a pooled analysis of individual data from a South African and a West African cohort study (abstract #46), the overall risk of postnatal HIV infection was 3.9% among children breastfed for <6 months and 8.7% among children breastfed for >6 months (adjusted hazard ratio: 1.8). Breastfeeding duration, as well as maternal immune status, appear to be major determinants of HIV transmission. The risk did not differ between exclusively and predominantly breastfed children. Exposure to breastfeeding mixed with solids during the first 2 months increased the postnatal risk of acquisition of HIV (adjusted hazard ratio: 2.9).

In the Vertical Transmission Study in South Africa (abstract #636), 18-month HIV-free survival of children of HIV-infected women shows that breastfeeding of HIV-uninfected infants beyond 6 months of age increases the risk of HIV

acquisition without gains for survival. It remains important to identify means of making breastfeeding safer for HIV-infected women who have no choice other than to continue breastfeeding.

In a study on mastitis in Zambia (abstract #650), breast milk samples were collected from 38 women who had clinical symptoms of mastitis. The study found that during mastitis, elevations of breast milk viral load are restricted to the mastitic breast and eventually return to baseline levels, supporting current recommendations for women with mastitis to breastfeed from the unaffected breast.

Maternal outcomes and infant feeding practices

In the Ditrane-Plus cohort study in Abidjan (abstract #73), the risk of pregnancy before 12 months post-partum was comparable in replacement feeding and breastfeeding groups: 4%. Between 12 and 24 months post-partum, the risk of pregnancy was significantly lower among replacement feeders than breastfeeders. Replacement feeding was not responsible for a greater incidence of pregnancies in this West African urban context, probably due to the systematic offer and the frequent use of contraceptive services.

Antiretrovirals in breastfeeding women

The Kisumu Breastfeeding Study in Kenya (abstract #45LB) was an observational prospective cohort of children of lactating women taking antiretroviral treatment (ART) to prevent mother-to-child transmission (MTCT). Overall transmission rates were 3.9% at 6 weeks, 5% at 6 months, 5.9% at 12 months and 6.7% at 18

¹ CROI abstracts are available at <http://www.retroconference.org>, accessed February 15, 2008.

months. There was no difference in HIV transmission by baseline maternal CD4 count. For those infants who became infected during the first 6 weeks of life, resistance was initially not detected (abstract #84LB), but emerged during the breastfeeding period.

In the MASHI trial in Botswana (abstract #637), the MTCT rate at one month was 1.2% among breastfeeders and 1.1% among formula feeders. The authors concluded that breastfeeding was not a risk for MTCT within the first month of life for children exposed to maternal ART and receiving infant antiretroviral prophylaxis.

The preliminary results of the non-randomized part of the Kesho-Bora study being conducted in five African sites (abstract #638) showed that the HIV transmission rate at 12 months was 7.6% in women with <200 CD4 with no significant difference according to infant feeding pattern; the rate was 5.8% among women with >500 CD4 count, respectively 7.5% and 0% in ever and never breastfed infants.

In the Dream cohort in Mozambique (abstract #369), 341 mother-infant pairs were followed from pregnancy until 12 months post partum; mothers breastfed while receiving ART until 6 months post delivery. ART continued beyond 6 months in women who initiated it for their own health. The HIV MTCT rates were: 1.2% (4) at birth, 1.9% (6) at 6 months, and 2.8% (8) at 12 months. Four late post-natal HIV-1 infections (>1 month of age) were observed in this cohort; 15% were lost to follow-up.

The Breastfeeding, Antiretroviral and Nutrition (BAN) Study in Malawi (abstract #648) reports on antiretroviral concentrations. Infants' plasma concentrations for all antiretrovirals were

well below levels required for treatment, suggesting minimal risk for drug toxicity. Lamivudine (3TC) and nefinavir exposure in infants would suggest minimal risk for resistance in HIV-infected children; however, low-level nevirapine (NVP) exposure via breast milk may predispose HIV-infected infants to resistance.

Antiretrovirals in breastfed children

The PEPI-Malawi Study (abstract #42LB) evaluated in a randomized controlled trial if 14 weeks of extended daily infant antiretroviral prophylaxis with NVP (group 2) or NVP+ZDV (group 3) with breastfeeding cessation from age 4-6 months would reduce postnatal transmission of HIV compared to controls receiving single dose (sd) NVP and one week ZDV (group 1). At age 9 months, the risk of HIV infection was 10.6% in group 1, 5.2% in group 2 and 6.4% in group 3. However, at 18 months, the HIV rate reach 13.9% in group 1, 10.1% in group 2 and 10.2% in group 3. Postnatal transmission occurred after NVP cessation among breastfed children. Post-exposure prophylaxis in breastfed children could reduce postnatal transmission but should be maintained over the entire breastfeeding duration.

In the SWEN randomized controlled Trial conducted in Ethiopia, India and Uganda (abstract #43), an extended infant post-exposure prophylaxis with daily NVP for 6 weeks in breastfed infants of HIV-infected mothers was assessed. The 6-week HIV transmission rate in the extended-NVP arm was 2.5% versus 5.3% in the sd NVP arm ($p=0.009$), but the 6-month HIV rate was 6.9% in the extended-NVP arm versus 9.0% in the sd NVP arm ($p=0.16$). The extended-NVP arm was safe, but postnatal transmission occurred after stopping NVP in breastfed children with a reduction of long term efficacy. Occurrence of resistance to NVP in infected children was very high (11/12).

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Kai Lashley performed the final copy-edit of the text.

Acronyms

3TC	lamivudine
AIDS	acquired immunodeficiency syndrome
ANRS	Agence Nationale de Recherches sur le SIDA (France)
ARV	antiretroviral
ART	antiretroviral therapy
AZT	azidothymidine
BF	breastfeeding
CI	confidence interval
D4T	stavudine
ddI	didanosine
DNA	deoxyribonucleic acid
EBF	exclusive breastfeeding
FF	formula feeding
HIVIGLOB	HIV hyperimmune globulin
HIV	human immunodeficiency virus
HR	hazard ratio
MF	mixed feeding
MTCT	mother-to-child transmission of HIV
NVP	nevirapine
OR	odds ratio
PCR	polymerase chain reaction
PMTCT	prevention of mother-to-child transmission of HIV
RF	replacement feeding
RNA	ribonucleic acid
SLPI	secretory leukocyte protease inhibitor
SDS	sodium dodecyl sulfate
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGASS/AIDS	United Nations General Assembly Special Session on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization
ZDV	zidovudine

Glossary

ART, an abbreviation for antiretroviral therapy, is a combination of three or more different antiretroviral drugs used in the treatment of those infected with HIV to reduce viral load.

Breast-milk substitute refers to 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) are lymphocytes (a type of white blood cell), which are key in both humoral and cell-mediated immune responses. These are the main target cells for HIV. Their numbers decrease during HIV infection, and their level is used as a marker of progression of the infection. CD8 cells are a subtype of T lymphocytes, which also play an important role in fighting infections. Their numbers may be increased during HIV infection.

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

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

Cessation of breastfeeding means completely stopping breastfeeding, which includes no more suckling at the breast.

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

Commercial infant formula means 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.

Complementary food means any food, whether manufactured or locally prepared, used as a complement to breast milk or to a breast-milk substitute, when either becomes insufficient to satisfy the nutritional requirements of the infant.

DNA, an abbreviation for deoxyribonucleic acid, is the carrier of genetic information found in cell nuclei.

Exclusive breastfeeding means an infant receives no other food or drink, not even water, other than breast milk (which can include expressed breast milk), with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines.

Formula feeding involves the use of commercial infant formula that is 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.

Human immunodeficiency virus (HIV) refers to HIV-1 in this review. Cases of mother-to-child transmission of HIV-2 are rare.

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

Incidence density means the incidence rate of an event, i.e. HIV infection or death per person-time (months or years).

Infant refers to a child from birth to 12 months of age.

Intrapartum means the period during labour and delivery.

Lamivudine, or 3TC, is an antiretroviral drug often used in combination with zidovudine, ZDV, also known as azidothymidine, AZT.

Late postnatal HIV transmission means transmission that takes place after about six weeks of life, the earliest time at which it is possible to determine that transmission did not take place during delivery.

Lipid means any one of a widely varying group of fats and fat-like organic substances.

Macrophage is a large ‘wandering’ phagocytic white blood cell that ingests foreign matter, and plays an important role in resisting infection.

Mature breast milk is milk produced from about 14 days postpartum until the cessation of breastfeeding.

Mixed feeding refers to breastfeeding with the addition of fluids, solid foods and/or non-human milks such as formula.

Mother-to-child transmission (MTCT) indicates instances of transmission of HIV to a child from an HIV-infected woman during pregnancy, delivery or breastfeeding. The term is used in this document 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.

Neonatal describes the period immediately following birth through the first 28 days of life.

Nevirapine, or NVP, is an antiretroviral drug commonly used as a treatment regimen, either alone or in combination with other drugs, to prevent MTCT.

Partial breastfeeding means giving a baby some breastfeeds and some artificial feeds, either milk or cereal, or other food.

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

Peripartum transmission is mother-to-child transmission of HIV occurring around the time of delivery (i.e. late in pregnancy, during or immediately after delivery).

Postnatal transmission is mother-to-child transmission of HIV after delivery, during the breastfeeding period.

Predominant breastfeeding means breastfeeding is the main source of nourishment, but an infant is also given small amounts of non-nutritious drinks, such as tea, water and water-based drinks.

Replacement feeding means the process of feeding a child who is not receiving any breast milk with a diet that provides all the nutrients the child needs until the child is fully fed on family foods.

RNA, an abbreviation for ribonucleic acid, is a substance found in the nucleus of all living cells and in many viruses. An intermediate of DNA, it is the medium by which genetic instructions from the nucleus are transmitted to the rest of the cell. RNA viral load, expressed as copies of RNA per ml of plasma or other body fluid, reflects the amount of actively replicating virus in the body. High viral RNA levels occur (temporarily) immediately after acquisition of infection and later with progression of disease, and are associated with higher rates of transmission.

Virion refers to those parts of the virus that are able to replicate HIV.

Wet-nurse refers to the breastfeeding of an infant by someone other than the infant’s mother.

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

Executive summary

Breastfeeding is best for infants, and is an effective method of reducing the risk of common childhood morbidity, particularly gastrointestinal and respiratory infections, and of promoting child survival and maternal health through child spacing. 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. Thereafter, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues to 24 months or beyond.

While breastfeeding carries significant health benefits to infants and young children, HIV can be transmitted during breastfeeding from an HIV-infected mother to her infant. Reducing this transmission while ensuring improved HIV-free survival¹ is one of the most pressing public health dilemmas confronting researchers, health-care professionals, health policy-makers and HIV-infected women in many areas of the world, especially in developing countries.

In 2007, 2.5 million children aged less than 15 years worldwide were living with HIV and an estimated 420 000 children aged less than 15 years were newly infected with HIV in 2007 alone, nearly always through mother-to-child transmission (MTCT). HIV/AIDS is an increasingly important cause of mortality in those aged less than five years in Africa. Before the antiretroviral therapy (ART) era, child mortality due to HIV was estimated to be 35.2% by age one year and 52.5% by two years of age.

Mother-to-child transmission of HIV can occur during pregnancy, labour or delivery, or through breastfeeding. Without specific interventions, HIV-infected women will pass the virus to

their infants during pregnancy or delivery in about 15-25% of cases; and an additional 5-20% of infants may become infected postnatally during breastfeeding, for an overall risk of 30-45%. Breastfeeding may thus be responsible for one third to one half of HIV infections in infants when interventions are not available.

HIV has been detected in breast milk in cell-free and cell-associated compartments and there is now evidence that both compartments are involved in transmission of HIV through breast milk. Following ingestion of HIV infected breast milk, infant gut mucosal surfaces are the most likely site at which transmission occurs.

The rate of late postnatal transmission (that is, after six weeks of age) can be better quantified in 2007 than previously. Data from a meta-analysis show that the cumulative probability of late postnatal transmission at 18 months is 9.3% (95% confidence interval, CI, 3.8-14.8%). Late postnatal transmission, therefore, could contribute as much as 42% to the overall rate of MTCT. Analysis indicates that late postnatal transmission risk is around 1% per month of breastfeeding and is constant over time from between four and six weeks to 18 months. Transmission can take place at any point during breastfeeding, and the longer the duration of breastfeeding, the greater the cumulative risk.

The risk of postnatal transmission through breastfeeding is associated with clinical, immunological and virological maternal factors and infant feeding patterns. Maternal seroconversion during breastfeeding, low maternal CD4 cell count, increased maternal RNA viral load in plasma and breast milk and a lack of persistence of HIV-specific IgM in breast-milk at 18 months are strongly associated with increased risk of

¹ HIV-free survival refers to young children who are both alive and HIV-uninfected at a given point in time, usually 18 months.

transmission through breastfeeding. Breast pathologies such as clinical and subclinical mastitis, nipple bleeding, and abscesses, fissures or lesions are also associated with a higher risk of transmission through breastfeeding. Exclusive breastfeeding for up to six months, however, is associated with a three to fourfold decreased risk of transmission of HIV compared to non-exclusive breastfeeding; mixed feeding, therefore, appears to be a clear risk factor for postnatal transmission. One study found that about 4% of exclusively breastfed infants became infected through exclusive breastfeeding from six weeks to six months.

The incidence of HIV infection among women during the postpartum period is high in Africa. The overall risk of MTCT is increased in recently-infected lactating women and estimated to be 29% (95% CI, 16–42%), illustrating the importance of prevention of primary infection throughout the breastfeeding period.

The most appropriate infant feeding option for an HIV-infected mother depends on her individual circumstances, including her health status and the local situation. The health services available and the counselling and support she is likely to receive should be considered. The World Health Organization (WHO) recommends HIV-infected women breastfeed their infants exclusively for the first six months of life, unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time. When those conditions are met, WHO recommends avoidance of all breastfeeding by HIV-infected women.

To help HIV-positive mothers make the best choice, they should receive appropriate counselling that includes information about the risks and benefits of various infant feeding options based on local assessments, and guidance in selecting the most suitable option for their own situation. Counselling, information provision and support during the antenatal period is key for women to make informed choices. Postnatal fol-

low-up with repeated growth measurements is also crucial to this support, as is nutritional counselling, particularly around the period of breastfeeding cessation.

Early cessation of breastfeeding could also prevent a sizable proportion of postnatal HIV infections but several studies in Africa have reported that it was associated with an increased risk of infant morbidity (especially diarrhoea) and mortality in HIV-exposed children. Recent data from Zambia and Botswana show that prolonged breastfeeding of children already infected with HIV is associated with improved survival compared to early cessation of breastfeeding.

It is also important to identify approaches to treating expressed breast milk to eliminate the risk of transmission while preserving the milk's nutritional content and protective qualities. With this aim, expressed heat-treated breast milk and microbicides to treat HIV-infected breast milk may have a role to play in shortening the duration of breastfeeding and allowing for a safe transition period to other types of foods.

More research is required to provide practical tools that can be used routinely – especially around the time of early breastfeeding cessation – to contribute to the assessment of the nutritional adequacy of complementary feeding and guide efficiently the nutritional counselling of children exposed to HIV.

Other possibilities for preventing HIV from being transmitted through breast milk are emerging. These include giving ART to women during breastfeeding (whether or not necessary for the mother's health) and post-exposure prophylaxis to the infant. Recent studies have sought to determine the effects of the former, and several studies on the latter are ongoing; both are discussed in this review. Finally, passive and active immunization strategies of breastfed newborns are increasingly being studied. Further research on their potential role in reducing MTCT of HIV is needed and ongoing.

Introduction

Despite substantial progress in reducing child morbidity and mortality and promoting family health in recent decades, there are still unacceptable disparities in maternal and child health worldwide (Black et al. 2003; WHO 2005). While child mortality has declined in the past decades in many regions, progress on key indicators has begun to slow down. In parts of sub-Saharan Africa, child mortality is on the rise (Black et al. 2003). About 9.7 million children under five die each year (WHO mortality data bank, access on request), mainly from preventable causes and almost all in poor countries. In the period between 2000 and 2003, four causes accounted for over 80% of the then estimated 10.6 million yearly deaths in children aged less than five years: pneumonia (19%), diarrhoea (17%), malaria (8%), and neonatal conditions (37%). Among neonatal deaths, 36% were due to infections including sepsis, pneumonia, tetanus and diarrhoea, 28% were due to being pre-term and 23% were due to asphyxia (Bryce et al. 2005). Undernutrition is an underlying cause of more than half of all deaths in children aged less than five years, and is associated with infectious diseases (Bryce et al. 2005). It is also the leading underlying cause of disability and illness worldwide, particularly so in countries with high infant mortality, where suboptimal feeding practices are a major cause of underweight (Bryce et al. 2005). Promotion of breastfeeding has played an important role in protecting infants and young children, since breastfeeding provides optimal nutrition, protects against common childhood infections, reduces mortality significantly, and has child-spacing effects (Nicoll et al. 2000a; WHO Collaborative Study Team 2000). Exclusive breastfeeding is therefore recommended until six months of age (WHO 2001).

In 2007, 2.5 million children aged less than 15 years worldwide were living with HIV. An es-

timated 420 000 children aged less than 15 years were newly infected in 2007 (UNAIDS 2006). There were also an estimated 380 000 deaths due to AIDS among children. Africa has the highest prevalence: 90% of both new infections and AIDS-related deaths among children occur there, particularly in southern Africa (UNAIDS 2007).

MTCT is the most significant source of HIV infection in young children. The virus may be transmitted during pregnancy, labour or delivery, or through breastfeeding (De Cock et al. 2000). Without specific interventions, HIV-infected women will pass the virus to their infants during pregnancy or delivery in about 15–25% of cases; and an additional 5–20% of infants may become infected post-natally during breastfeeding (De Cock et al. 2000; Nduati et al. 2000). About two thirds of infants born to HIV-infected mothers will not be infected. Breastfeeding may thus be responsible for one third to one half of HIV infections in infants and young children in African settings (De Cock et al. 2000). HIV/AIDS is an increasingly important cause of mortality in children aged less than five years in Africa (Dabis & Ekpini 2002; Walker et al. 2002). Before the antiretroviral therapy (ART) era, child mortality due to HIV was estimated to be 35.2% by age one year and 52.5% by two years of age among HIV-infected children in a meta-analysis, which pooled information from the African clinical trials that aimed to assess the efficacy of interventions to reduce MTCT. Mortality varied by geographical region, and was associated with maternal death, maternal CD4 cell counts $<200\mu\text{l}$, and infant HIV infection and its timing. In HIV-infected children, mortality was significantly lower for those with late infection than those with early infection (Newell et al. 2004). These findings highlight the need for effective prevention of MTCT, early paediatric HIV diagnosis and antiretroviral care and support for HIV-infected children and all members of affected families.

Prevention of MTCT of HIV using available antiretroviral interventions can be achieved, even in breastfeeding populations. Considerable effort is ongoing to scale-up these interventions to reach a wider population (WHO 2006). However, in settings where breastfeeding beyond one year is the norm, postnatal transmission through breastfeeding reduces the impact of perinatal antiretroviral interventions (Leroy et al. 2002). While breastfeeding carries the risk of HIV transmission, not breastfeeding carries other significant health risks to infants and young children, such as an increased risk of diarrhoea and pneumonia morbidity and mortality (Nicoll et al. 2000a; WHO Collaborative Study Team 2000; Thior et al. 2006).

The prevention of HIV transmission should be balanced against the risk of other morbidity and mortality risks, including malnutrition. The reduction of HIV transmission through the breastfeeding period is one of the most pressing public health dilemmas confronting researchers, health-care professionals, health policy-makers and HIV-infected women in many areas of the world, especially in developing countries. 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 within the general population. Countries need to develop (or revise) comprehensive national feeding policies of infants and young children to consider the risks of HIV transmission during infant feeding, while continuing to protect, promote and support breastfeeding for infants of HIV-negative women and women whose HIV infection status is unknown.

The Declaration of Commitment endorsed at the United Nations General Assembly Special Session on HIV (UNGASS) in 2001 set the goal of reducing the proportion of infants infected with HIV by 20% by 2005 and 50% by 2010 (Harwood & Planetwire.org 2001; UN 2001). A further goal was ensuring that 80% of pregnant women who receive antenatal care have access to HIV prevention services. However, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that less than 10% of HIV-infected pregnant women have access to appro-

prate care and highlights missed sexual and reproductive health opportunities (UNAIDS 2006). To meet international goals for reductions in child mortality, efforts must continue to focus on preventing MTCT, but must also prevent undernutrition and strengthen health systems and programmes that can deliver available interventions for the other major diseases killing children in the developing world (Bryce et al. 2006a). The fourth Millennium Development Goal (MDG) calls for a two thirds reduction between 1990 and 2015 in deaths of children aged less than five years (<http://www.un.org/millenniumgoals>). Achieving this goal will require widespread use of effective interventions for preventing deaths, and is also linked to MDG5 on maternal mortality, as infant health and survival is closely linked to maternal health (Bryce & Victora 2005; Costello & Osrin 2005; Mason 2005; Bryce et al. 2006b).

This report is an update of the review of current knowledge on HIV transmission through breastfeeding (WHO/UNICEF/UNFPA/UNAIDS 2004) with a focus on information made available between 2001 and 2007. It reviews recent scientific evidence on the risk of HIV transmission through breastfeeding, the impact of different feeding options on child health outcomes, and conceivable strategies to reduce HIV transmission through breastfeeding with a specific emphasis on the developing world. This review further informs guidance on HIV prevention and infant feeding strategies (WHO 2006).

To update this review, published and unpublished literature contributing to recent evidence about children affected and infected by HIV/AIDS and infant feeding patterns since 2001 was consulted. Medline, one of the main bibliographic scientific databases, was used, facilitating a wide variety of studies to be selected, ranging from randomized clinical trials to epidemiological cohort studies (investigating HIV/AIDS-related morbidity and mortality among children, MTCT and infant feeding patterns), to demographic and national surveillance surveys (infant feeding indicators). The most relevant references have been included in this review, including other systematic reviews.

Mother-to-child transmission of HIV

HIV infection in women

Sexual contact continues to be the major mode of HIV transmission, leading to high prevalence of HIV infection in women making access to sexual and reproductive health services essential (Schmid et al. 2004).

The prevalence of HIV infection varies considerably from region to region. Children in sub-Saharan Africa are disproportionately affected, with nearly nine in every 10 newly-infected children worldwide living in this region (UNAIDS 2007). In West and Central Africa, HIV prevalence in pregnant women currently reaches up to about 7% in some urban areas, with generally lower rates in rural areas. Prevalence in East Africa is up to about 9% in urban areas, while in Southern Africa antenatal seroprevalences of about 16-39% have been reported. In the Caribbean, Central America and South America, rates among pregnant women are generally below 1%. In Asia, seroprevalence rates in some cities or provinces of Cambodia, India, Indonesia and Thailand range from less than 1% up to about 5%. In Eastern Europe, where there has been an exceptionally rapid increase in the number of HIV-infections, the estimated antenatal prevalence is still less than 1% (UNAIDS 2007).

The incidence of HIV among women during the postpartum period is also high in Africa. The HIV incidence rate was 3.5/100 women-years (95% confidence interval, CI, 1.9–5.0) in early 1990 in Rwanda (Leroy et al. 1994). In Zimbabwe in late 1990, among the 9562 women who were HIV-negative at the time of giving birth, 3.4% (95% CI 3.0–3.8) and 6.5% (95% CI 5.7–7.4) acquired HIV infection over 12 and 24 months postpartum, respectively (Humphrey et al. 2006). As 85% of women still breastfeed at 15 months and 30% at 21 months in this population, new postpartum infections subsequently increase the number of children exposed to HIV.

Rates of, and risk factors for overall mother-to-child transmission of HIV

In HIV-infected pregnant women, MTCT can occur before, during or after delivery, but transmission in early pregnancy is rare (Rouzioux et al. 1993). Without specific interventions aimed at reducing the risk of transmission, estimated rates of MTCT range from 15% to 25% in Europe and the United States of America and from 25% to 45% in developing countries (The Working Group on Mother-to-Child Transmission of HIV 1995). The additional risk posed by breastfeeding as commonly practised in developing countries ranges from 5% to 20%, with an attributable risk of 40% (Table 1) (De Cock et al. 2000). These breastfeeding practices account for a large part of the estimated differences in the risks of MTCT between developing and developed countries (where breastfeeding is less common). The overall risk of MTCT is increased immediately after HIV is acquired, due to the initially high levels of maternal viral load. Therefore, when a woman contracts HIV during pregnancy or the breastfeeding period, the risk of virus transmission is increased. There is some evidence of an increased risk of acquisition of HIV during pregnancy (Gray et al. 2005).

The overall risk of MTCT 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 the risk of MTCT (European Collaborative Study 1996; European Collaborative Study 1997; Mayaux et al. 1997; Simonds et al. 1998; Shaffer et al. 1999b; Leroy et al. 2001). However, although the risk of transmission increases substantially with increasing viral load, transmission of the virus to the fetus or infant can occur, albeit rarely, even with very low, or undetectable, viral load levels. Similarly, at very high levels of HIV RNA, transmission does not always occur.

TABLE 1. Estimated absolute rates of MTCT of HIV by timing of transmission, without interventions

Timing of HIV transmission	HIV transmission rate (%)		
	No breastfeeding	Breastfeeding through six months	Breastfeeding through 18 to 24 months
During pregnancy	5 to 10	5 to 10	5 to 10
During labour	10 to 15	10 to 15	10 to 15
During breastfeeding	0	5 to 10	15 to 20
Overall	15 to 25	20 to 35	30 to 45

Nevertheless, women with a low CD4 cell count near the time of delivery (below 200 cells per mm³) and those who have been diagnosed with severe clinical disease are more likely to transmit the virus than those who are less severely affected by HIV infection (European Collaborative Study 2001; Leroy et al. 2002). HIV has been recovered from vaginal and cervical secretions of pregnant women (Nielsen et al. 1996; John et al. 1997; Kovacs et al. 2001) and from gastric secretions of infants born to HIV-seropositive women (Mandelbrot et al. 1999), constituting independent risk factors for MTCT. There is also evidence that malaria could increase the risk of MTCT (Ayoubu et al. 2003; Mwapasa et al. 2004), although the interaction between placental malaria and MTCT appears to be variable and complex (Ayisi et al. 2004). Delivery factors such as vaginal delivery and duration of delivery, which increase contact between the infant and HIV-infected maternal body fluids (cervico-vaginal secretions and blood) have been linked with increased risk of MTCT (European Collaborative Study 1996; European Collaborative Study 1997).

The increasing use of ART in pregnancy in developed countries has resulted in a growing proportion of women achieving undetectable levels of the virus by the time of delivery, which has had a substantial impact on vertical transmission. Several studies are currently under way in breastfeeding populations in resource-poor settings to evaluate the use of ART for mothers during pregnancy and postnatally, and for uninfected infants during the breastfeeding period. (Thorne & Newell 2007). Results from the DREAM study carried out in Mozambique sug-

gest that a highly-active combination antiretroviral treatment regimen, given during and after pregnancy, is able to significantly reduce HIV RNA viral load in both plasma and breast milk. This suggests there may be a role for ART prophylaxis in mothers as a means to reduce breastfeeding-associated transmission (Giuliano et al. 2007).

Prevention of mother-to-child transmission of HIV

The United Nations strategy to prevent the transmission of HIV to infants and young children involves: 1) prevention of HIV infection in general, especially in women and young people; 2) prevention of unwanted 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, their infants and family. Guidance for implementing programmes at national scale is available (WHO/UNICEF, 2007).

In developed countries, the rate of MTCT has declined substantially in the past ten years. With the use of antiretroviral combinations, elective caesarean section delivery and avoidance of breastfeeding, rates below 2% have been reported in American and European populations (European Collaborative Study 2001; Dorenbaum et al. 2002; Newell 2006). In developing countries, shorter, simpler peripartum antiretroviral prophylaxis interventions have been shown to be effective in reducing transmission risk, but their application in populations where breastfeeding is commonly practised poses considerable challenges (Dabis et al. 2000).

Early randomized clinical trials from 1998 in Africa and Thailand demonstrated the short-term efficacy of several antiretroviral regimens administered around the time of delivery (peripartum) to prevent transmission (Dabis et al. 1999; Guay et al. 1999; Saba 1999; Shaffer et al. 1999a; Wiktor 1999). This short-term efficacy was measured by comparing infant HIV infection status at six and eight weeks of age between groups receiving different antiretroviral interventions or a placebo. These regimens involved three different ARV drugs, used alone or in combination: zidovudine (ZDV), lamivudine (3TC) and nevirapine (NVP).

The NVP prophylactic regimen is particularly easy to use with one single dose given to the woman at the onset of labour, and one dose of syrup administered to the baby within 72 hours of delivery, reducing transmission by around 40%, from a rate of 20% to 12% at six to eight weeks postpartum (Guay et al. 1999). Transmission rates at six to eight weeks of 15% have been reported when ZDV is given to the mother from week 36 of gestation (Dabis et al. 1999; Wiktor 1999). Peripartum ZDV efficacy has been reported as greater in women with higher CD4 cell counts, even at six weeks postpartum (Leroy et al. 2002). In another regimen, ZDV given in combination with 3TC to the mother from weeks 28–36 of gestation until one week postpartum, while the newborn receives ZDV prophylaxis during one week, reduced transmission to between 6% and 9% (Saba et al. 2002).

The respective efficacy of these different antiretroviral regimens was compared in a recent pooled analysis using a standardized definition of peripartum HIV infection (Leroy et al. 2005). This study included 4125 singleton live births from six African trials, which adjusted MTCT rates at six to eight weeks for other maternal and child determinants. In comparison with placebo, the adjusted relative reduction in MTCT reached 77% for the combination of ZDV and 3TC administered antepartum, intrapartum and seven days postpartum; 51% for the combination of ZDV and 3TC during the intrapartum and postpartum periods only; 45% for ZDV only, administered antepartum, intrapartum and postpartum; and 40% for single-dose NVP. Thus, at

six to eight weeks, in comparison with NVP, only the longest combination of ZDV and 3TC is significantly more effective, leading to a 61% adjusted reduction ($p < 0.0005$). These results suggest that there exists an equivalence of choice between single-dose NVP and short-course ZDV. They confirm that a combination of ZDV and 3TC from 36 weeks of gestation has a greater efficacy in reducing early transmission than the same combination starting during labour and delivery or than any single antiretroviral prophylaxis (short-course ZDV or single-dose NVP).

There is no doubt that even lower peripartum transmission rates, comparable to those obtained in developed countries, could be achieved through enhanced short-course antiretroviral regimens. In the ANRS 1201/1202 Ditrane Plus cohort in Abidjan, Côte d'Ivoire, transmission rates at six to eight weeks postpartum were 6.5% (95% CI 3.9–9.1%) with ZDV plus single-dose NVP, a relative 72% reduction compared with ZDV alone (95% CI 52–88%, $p = 0.0002$ adjusted on maternal CD4 cell count, clinical stage of infection and breastfeeding status) (Dabis et al. 2005). The overall rate was 4.7% (95% CI 2.4–7.0%) when mothers were given both ZDV and 3TC from week 32 of gestation, continued for one week postpartum (for both mother and child), in addition to single-dose NVP to mother and infant. Despite these considerable advances, several problems remain to be addressed, which are detailed elsewhere (WHO 2006).

Single-dose NVP given to women and infants reduces mother-to-child HIV transmission and is easy to use, but NVP resistance develops in a large percentage of women, raising concerns for future maternal treatment (Eshleman et al. 2004a; Eshleman et al. 2004b; Jourdain et al. 2004; Eshleman et al. 2005). Alternatives to NVP are being considered, but this problem can be avoided to a considerable extent by a postpartum three-day to one week regimen of AZT and 3TC.

Residual MTCT rates remain high in mothers who have advanced HIV disease (Leroy et al. 2002). Antiretroviral therapy is now recommended for these women (WHO 2006). More recent cohort studies in Côte d'Ivoire and Mozambique indicate that when three-drug combi-

nation antiretroviral therapy (i.e. ART) is given to HIV-infected pregnant women either universally – irrespective of CD4 cell count (Giuliano et al. 2007) – or only to those who require it for their own health (Tonwe-Gold 2007), MTCT rates below 5% can be achieved at four weeks postpartum.

Women presenting late for delivery without knowing their HIV status, which frequently happens in resource-constrained settings, do not receive the ante and intrapartum components of these regimens. In this context, the efficacy of a simple neonatal-only antiretroviral post-exposure prophylactic regimen has been demonstrated in Malawi. The overall MTCT rate at six to eight weeks was 15.3% in 484 babies who received NVP and ZDV and 20.9% in 468 babies who received NVP only in the NVAZ trial conducted in Malawi ($p=0.03$) (Taha et al. 2003). In South Africa, single-dose NVP given to newborns exposed to HIV tended to reduce MTCT. The rate at 12 weeks was 14.3% in 518 babies who received NVP, and 18.1% in 533 babies who received ZDV during six weeks postnatally ($p=0.4$). Among newborns who were not infected at birth, the 12-week MTCT rate was 7.9% in the NVP arm and 13.1% in the ZDV arm ($p=0.06$) (Gray et al. 2005).

All these short-course peripartum antiretroviral regimens have lower field efficacy when taking into account the subsequent risk of postnatal transmission of HIV in African populations

where prolonged breastfeeding is the norm (Leroy et al. 2003). In the West African trials, the 24-month efficacy of short-course ZDV to mothers was still significant, giving a 26% reduction, with a residual MTCT rate of 22.5% in the ZDV arm compared to 30.2% in the placebo arm (Leroy et al. 2002). In the NVP trial, the 18-month efficacy was sustained with a residual MTCT rate of 15.7% in the NVP arm, a 41% significant reduction (Jackson et al. 2003). In the PETRA trial, although the six-week efficacy of the combined ZDV+3TC long-course (ante, intra and postpartum/postnatal) regimen and the ZDV+3TC medium-course (intra- and postpartum/postnatal) regimen was significantly effective, the 18-month long-term efficacy was lost mainly because of postnatal transmission (Saba et al. 2002). However, this trial lacked statistical power to address differences at 18 months.

Given the considerable advances that have been made in the past ten years, peripartum HIV transmission rates below 5% can be achieved, even in African breastfeeding populations, with relatively inexpensive, easy-to-use and feasible short-term antiretroviral combinations (WHO 2006). The introduction of short-course antiretroviral regimens to prevent MTCT in less-developed countries should be accompanied by interventions to minimize the risk of subsequent transmission through breastfeeding (Leroy et al. 2003). Postnatal transmission will be detailed in the next section.

HIV transmission through breastfeeding

Transmission of HIV through breastfeeding has been well documented since 1985. The first reports indicating the possibility of HIV transmission through breast milk were in breastfed infants of women who had acquired infection postnatally through blood transfusions or through heterosexual exposure (Ziegler et al. 1985; Hira et al. 1990; Van de Perre et al. 1991; Palasanthiran et al. 1993). There were also reports of infants – with no other known exposure to HIV – who were infected through being wet-nursed and through pooled breast milk (Nduati et al. 1994). There is a theoretical risk of oral transmission from infant to wet-nurse, with cases having been reported (Visco-Comandini et al. 2005).

Pathogenesis and mechanisms of breastfeeding transmission

HIV has been detected in breast milk in cell-free and cell-associated compartments. To date most studies have used DNA or RNA polymerase chain reaction assays to evaluate breast milk for HIV. In an early study from Kenya, breast milk HIV RNA was detected in 39% of 75 specimens (Lewis et al. 1998). In this study viral levels in breast milk were about one log lower than in plasma. However, there were some cases that suggested compartmentalization of virus to breast milk with higher levels in breast milk than plasma. Viral variants in blood and breast milk were found to be distinct, with some major variants in breast milk not detected in blood. This finding would suggest that some virus in breast milk replicates independently, in the mammary compartment. The observation of a compartmentalization of HIV between peripheral blood and breast milk highlights that postnatal transmission of HIV can occur with variants that may

not be predicted from the analysis of circulating viral populations (Becquart et al. 2002).

The origin of HIV in breast milk is still not well understood. There is now evidence that both cell-free and cell-associated HIV in breast milk are responsible for breast-milk transmission (Kouliniska et al. 2006). Studies have demonstrated the presence of cell-free virus and latent (non-productive) infected cells, but not productive HIV infective cells. Cells, including macrophages and lymphocytes, and cell-free virus may migrate from the systemic compartment to breast milk. Recently, it has been reported that infected CD4 cells demonstrate a greater capacity to enter into a viral replication cycle in the breast-milk compartment compared with blood (Petitjean et al. 2006).

Following ingestion of HIV infected breast milk, infant gut mucosal surfaces are the most likely site at which transmission occurs. Cell-free or cellular HIV may penetrate to the submucosa through mucosal breaches or lesions, via transcytosis through M cells or enterocytes expressing galactosyl ceramide (Gal Cer) or Fc receptors. In vitro models suggest that secretory IgA or IgM may inhibit transcytosis of HIV across enterocytes (Bomsel 1997; Bomsel et al. 1998). Breast-milk HIV immunoglobins may play a role in protection from transmission by coating infant mucosal surfaces: in a cohort of lactating women infected with HIV in Rwanda, anti-HIV antibodies of the IgG isotype were more frequently detected in breast milk followed by secretory IgM (Van de Perre et al. 1993). Tonsils may also be a portal of entry for HIV in breast-milk transmission. Tonsils include M cells in close proximity to lymphocytes and dendritic cells, and tonsillar M cells are capable of HIV replication (Frankel et al. 1997).

Risk of postnatal transmission through breastfeeding

The risk attributable to transmission of HIV through breastfeeding has been difficult to measure because of the difficulty in distinguishing intrapartum transmission from early transmission through breastfeeding.

Based on an assessment of the limited data available in the early 1990s, the additional risk of transmission from breast milk – above that occurring during pregnancy and delivery – among women with established HIV infection was estimated to be approximately 15% when breastfeeding continued for two years or more. When the mother acquires HIV postnatally, the estimated risk of transmission is estimated to be 29% (95% CI: 16–42%) (Dunn et al. 1992).

Subsequent data, including the results of a randomized clinical trial, confirm these initial findings in HIV-infected pregnant women. In the clinical trial in Nairobi, HIV-infected pregnant women were randomly allocated to either breast (n=212) or formula (n=213) feeding groups in the absence of any preventive antiretroviral intervention (Nduati et al. 2000). Compliance with 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 was 36.7% in the breastfeeding arm and 20.5% in the formula-feeding arm, with 44% of HIV infection in the breastfeeding arm attributable to breastfeeding. Most breastfeeding transmission occurred early, although transmission continued throughout the duration of exposure (Nduati et al. 2000). Although exclusive breastfeeding was recommended in this trial it was likely not always exclusive in this population. Furthermore, information on the mode of breastfeeding was not collected.

Other estimations of the rate of transmission through breastfeeding can be inferred from the results of trials in which a peripartum intervention to reduce MTCT risk was evaluated both in the short-term (four to six weeks) and in the long-term, after the end of breastfeeding exposure at 18–24 months. Additional postnatal transmis-

sion beyond four to six weeks ranging from 4% to 12% was reported from these trials (Ekpini et al. 1997; Saba et al. 2002; Jackson et al. 2003; Leroy et al. 2003). Differences need to be interpreted according to the risk factors for postnatal transmission. However, there is strong evidence of a continued increase in cumulative transmission risk as long as the child is breastfed (Leroy et al. 1998; Miotti et al. 1999; Leroy et al. 2003; The Breastfeeding and HIV International Transmission Study Group (BHITS) 2004; Iliff et al. 2005).

Timing of postnatal transmission through breastfeeding

Transmission of HIV through breastfeeding can take place at any time during lactation. There is insufficient information available to estimate the exact association between duration of breastfeeding and the timing of transmission. However, there is some evidence that there is an increased early postnatal risk within the first six to eight weeks. This still remains uncertain, however; a late postnatal risk beyond six to eight weeks has been better characterized recently (The Breastfeeding and HIV International Transmission Study Group (BHITS) 2004).

Early postnatal transmission through breastfeeding

Data suggest that the first six to eight weeks of breastfeeding could be a high risk period for transmission of HIV. However, it is difficult to investigate for technical reasons, and thus difficult to draw any conclusions about the relative risk of transmission through colostrum and mature breast milk (Van de Perre et al. 1993; Ruff et al. 1994; Lewis et al. 1998). First, colostrum and mature breast milk contain different types of cells and varying levels of immune-modulating components (e.g. vitamin A, immunoglobulins and lactoferrin). Second, the total volume of colostrum ingested by the infant is much smaller than that of mature breast milk. Third, the infant's immune system is less well-developed during the first few days of lactation than in later lactation, while younger infants have an increased blood concentration of maternal anti-

bodies. There is no evidence to suggest that avoidance of colostrum would reduce the risk of breastfeeding transmission to the infant.

Based on statistical modelling using data from studies with a limited duration of breastfeeding, it appears that the highest risk period for transmission is within the first four to eight weeks of life, and that infectivity may vary in populations at different stages of the disease (Dunn 1998). Evidence remains weak to detail the percentage of transmission occurring early. In the randomized clinical trial of breast milk versus formula carried out in Nairobi, Kenya, 10% of the total 16% cumulative difference in infection rates between infants in the breastfed and formula-fed arms apparently occurred by week six of age. The cumulative rate of HIV infection in the formula-feeding arm was approximately half that of the breastfeeding arm at birth (3.1% versus 7.0%, $p=0.35$). Although not statistically significant, this differential between arms raised concern about the true comparability of the two arms at birth, with women in the breastfeeding arm having more advanced disease than in the formula-feeding arm (Bulterys 2000).

Additionally, the breastfeeding women were likely more ill as evidenced by the much higher than expected mortality in this group compared to the women giving formula to their children (Nduati et al. 2001). In the Kenya trial, the proportion of new HIV infections between birth and six to eight weeks was 6.3% (from 3.1% to 9.7% in formula-fed versus 7.0% vs 19.9% in breastfed babies, $p=0.005$) (Nduati et al. 2000). Seventy-five per cent of the risk difference between the two arms occurred by six months of age, although transmission continued throughout the duration of exposure (Nduati et al. 2000). In a subsequent analysis of this data, 75% of the risk difference between the two arms occurred by six months of age, although transmission continued throughout the duration of exposure (Nduati et al. 2000). In a subsequent analysis of this trial 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 higher for mothers with low CD4 cell counts and high RNA viral

load in plasma. Of note, the probability of infection through breastfeeding per day of exposure was not significantly different for children aged less than four months versus those older than this (0.00015 versus 0.00031, $p=0.4$).

In the SAINT trial in South Africa, although not randomized on infant feeding modalities, the proportion of new infections having occurred between birth and six to eight weeks increased to 5.6% when comparing breastfed infants to formula-fed infants (Moodley et al. 2003).

Late postnatal transmission through breastfeeding

Late postnatal risk of HIV transmission through breastfeeding can be reliably estimated among children born to infected mothers who tested negative at four to six weeks postpartum. These children are followed until after they cease breastfeeding to determine their rate of acquisition of HIV infection through breastfeeding. The time at which the exposure starts is determined by the age at which infants are tested. This is now usually around four to six weeks of age, but in earlier studies was between three and six months of age. These different 'starting points' may explain different estimates of rates of late postnatal transmission between studies (Table 2).

The best evidence on the risk of late postnatal transmission comes from a meta-analysis of a large number of data relating to breastfeeding and postnatal transmission of HIV from randomized controlled trials of peripartum interventions conducted in sub-Saharan Africa. Early transmission was defined as a positive HIV test before four weeks, and late postnatal transmission as a negative diagnostic test at or after four weeks of age, followed by a subsequent positive test result (The Breastfeeding and HIV International Transmission Study Group (BHITS) 2004). Of 4085 children (breastfed singletons for whom HIV testing was performed) from nine eligible trials, 993 (24%) were definitively infected (placebo arms, 25.9%; treatment arms, 23.4%, $p=0.08$). The time of infection was unknown for 454 children. Of 539 children where the time of infection was known, 225 (42%) were infected during the late postnatal period. Late

TABLE 2. Estimated rates of late postnatal transmission of HIV in African cohorts

Study location (citation)	Age at negative test (determining denominator)	Median duration of breastfeeding	Infection incidence per 100 child-years of breastfeeding (%)	Cumulative percentage of infants infected by 12 months	Cumulative percentage of infants infected at last follow-up
Malawi (Miotti et al. 1999)	1 month	>12 months	6.9	8.9	10.3 (18 months)
Africa (Leroy et al. 1998)	3 months	16 months	3	2.5	9.2 (36 months)
West Africa(Leroy et al. 2003)	4 weeks	12 months	8.6	9.5	13.1 (18 months); 13.1 (24 months)
Africa BHITS (The Breastfeeding and HIV International Transmission Study Group (BHITS) 2004)	4 weeks	10 months	8.9	7	9.3 (18 months)
Zvitambo, Zimbabwe (Iliff et al. 2005)	6 weeks	>18 months	9.2	7.7 EBF: 3.42 PBF: 7.29 MF: 8.41	12.1 (18 months) EBF: 6.94 PBF: 8.56 MF: 13.92
South Africa, the Vertical Transmission Study (Coovadia et al. 2007)	4-8 weeks	6 months	10.7 (EBF only)	NA	EBF: 4.04 (6 months)
Côte d'Ivoire, the ANRS 1201/1202 Ditrane Plus study (Leroy et al. 2004)	4 weeks	5 months	3.8 EBF: 5.9 PBF: 11.3 MF: 31.6	NA	NA

NA, not available; EBF, exclusive breastfeeding; PBF, predominant breastfeeding; MF, mixed feeding (breast milk and other fluids, foods and/or formula).

postnatal transmission occurred throughout breastfeeding. The cumulative probability of late postnatal transmission at 18 months was 9.3% (95% CI 3.8-14.8%). The overall risk of late postnatal transmission was 8.9 transmissions per 100 child-years of breastfeeding (95% CI 7.8-10.2 per 100 child-years) follow-up (Table 2). Late postnatal transmission could contribute as much as 42% to the overall rate of MTCT (The Breastfeeding and HIV International Transmis-

sion Study Group (BHITS) 2004). Analysis of how transmission rates vary with time from birth indicated that late postnatal transmission risk is around 1% per month of breastfeeding and is constant over time from four to six weeks and 18 months, i.e. between 0.8 and 1.2 per 100 child-months of breastfeeding. The longer the duration of breastfeeding, the higher the cumulative risk of postnatal transmission of HIV.

In conclusion, the rate of late postnatal transmission is now better characterized than previously and is estimated to be around 1% per month of breastfeeding and constant over time. When breastfeeding is prolonged to 18-24 months or beyond, the additional cumulative postnatal risk of transmission through breastfeeding varies from 4% to 16% according to the study (Miotti et al. 1999; Nduati et al. 2000; Jackson et al. 2003; Leroy et al. 2003).

Factors associated with risk of transmission of HIV through breastfeeding

There is reliable quantification of the effect of risk factors associated with an increased or decreased likelihood of transmission of the virus through breastfeeding. Clinical, immunological and virological factors in mothers, as well as infant feeding patterns, affect postnatal transmission (Table 3).

Maternal factors

Maternal seroconversion during breastfeeding

HIV maternal seroconversion during breastfeeding constitutes a high risk factor for postnatal HIV transmission; it is higher than among women who have been infected previous to breastfeeding (Van de Perre et al. 1991; Dunn et al. 1992). High levels of virus in plasma, and probably also in breast milk, are seen in primary

HIV infection, when the rate of postnatal transmission has been estimated to be nearly 30% (Dunn et al. 1992). In a study in Kenya, the relative risk of MTCT was increased about six-fold during primary infection of the mother (Embree et al. 2000).

HIV-related immune status

More data are now available on the association between maternal immune status (CD4 cell counts) and MTCT through breastfeeding. Maternal immunosuppression defined by low CD4 cell count, although strongly correlated with plasma RNA viral load, is an independent risk factor for breastfeeding transmission in all studies with available information. In an analysis of pooled data from two West African ZDV trials (Leroy et al. 2002; Leroy et al. 2003), maternal CD4 cell counts below 500 cells per mm³ in plasma close to time of delivery was associated with a threefold increase in risk of late postnatal transmission compared to women with CD4 cell counts equal to or greater than 500 per mm³ (Leroy et al. 2003). In the BHITS meta-analysis of data from nine intervention trials in sub-Saharan Africa, the risk of late postnatal acquisition of infection after four weeks of age was strongly associated with maternal CD4 cell count. Transmission increased eightfold when CD4 cell counts were below 200 per ml, and 3.7-fold where CD4 cell counts were between 200 and 500 per ml, compared to the reference group

Table 3. Factors associated with transmission of HIV through breastfeeding

Maternal

- Younger maternal age, lower parity
- Maternal seroconversion during lactation
- Clinical and/or immunological (CD4 cell count) disease progression
- RNA viral load in plasma
- RNA viral load in breast milk
- Local immune factors in breast milk
- Breast health (subclinical or clinical mastitis, abscess, cracked nipples) (indirect factor)
- Maternal nutritional status
- Duration of breastfeeding

Infant

- Factors associated with the immune system
- Pattern of infant feeding (exclusive breastfeeding versus mixed)
- Morbidity leading to less vigorous suckling, milk stasis and increased leakage of virus across milk ducts (oral thrush)

Source: Adapted from John-Stewart et al. (2004).

of CD4 cell count above 500 per ml (The Breastfeeding and HIV International Transmission Study Group (BHITS) 2004). In the Vertical Transmission Study in South Africa, infants born to mothers with CD4 cell counts less than 200 cells per mm³ were almost four times more likely to acquire HIV or die than were those born to mothers with CD4 cell counts greater than 500 cells per mm³; and those born to mothers with CD4 cell counts between 200 and 500 cells per mm³ were 2.2 times more likely to acquire HIV or die (Coovadia et al. 2007).

RNA viral load in plasma and breast milk

Increased maternal RNA viral load in plasma and breast milk are both strongly associated with increased risk of transmission through breastfeeding. In West Africa, the rate of late postnatal transmission increased 2.6-fold for every one log₁₀ increase in plasma RNA viral load (measured in late pregnancy) (Leroy et al. 2001; Leroy et al. 2003). Breast-milk HIV RNA levels correlate with systemic viral load (Willumsen 2003), and are likely to be associated with risk of breast-milk HIV transmission (Semba et al. 1999a; Willumsen 2003). In Malawi, the risk of transmission increased fivefold when RNA virus had been detected in breast-milk samples taken at six weeks postpartum (Semba et al. 1999a). In Nairobi, breast-milk RNA levels were assessed in serial samples up to two years after delivery (John et al. 2001). In analyses comparing 92 infected infants with 187 infants who were uninfected at two years, maternal plasma RNA, mastitis and breast abscess were associated with late transmission (occurring after two months postpartum). Median RNA load in colostrum and early milk was higher than in mature milk collected more than 14 days after delivery. Breast-milk RNA load was significantly associated with transmission through breastfeeding. In a study conducted in Durban, South African women with detectable RNA viral load in breast milk at any time during the first six months postpartum were more likely to transmit than those with undetectable RNA viral load (Pillay et al. 2000).

The evolution of HIV RNA in breast milk after peripartum antiretrovirals needs to be better

understood. In particular, viral load rebound (i.e. increased levels of the virus after cessation of antiretrovirals) in breast milk after discontinuation of peripartum antiretrovirals is of concern (Van de Perre et al. 1997). An increase in the levels of HIV RNA in breast milk from day eight to day 45 after delivery was associated with maternal short-course ZDV prophylaxis compared to the placebo group in the Ditrane Plus ANRS 049a trial (Manigart et al. 2004). In this West African trial, breast-milk HIV-RNA from 28 women who transmitted HIV postnatally and from 130 women who did not transmit HIV was compared. Levels of HIV RNA in breast milk at day eight after delivery and its increase from day eight to days 45-90 postpartum were both independently associated with postnatal transmission (Manigart et al. 2004). Although HIV transmission continues after cessation of peripartum antiretroviral therapy, there is no clinical evidence to suggest that stopping antiretroviral therapy in this early period is associated with an increased rate of breastfeeding transmission due to viral rebound after cessation of antiretrovirals. Indeed, in the pooled analysis of the West African trials using short-course perinatal ZDV prophylaxis, the cumulative postnatal transmission risks were similar in the ZDV (9.8%, n=254) and placebo groups (9.1%, n=225) at age 24 months (Leroy et al. 2003). The long-term overall efficacy of this peripartum ZDV regimen was reduced in both groups. Global recommendations on antiretrovirals during pregnancy are available (WHO, 2006).

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

Breast milk contains maternal antibodies, with all basic forms of immunoglobulins IgG, IgM, IgA, IgD, and IgE present. The most abundant is usually secretory IgA (Lawrence & Lawrence 2004). The role of breast-milk HIV-specific antibodies in inhibiting HIV transmission through breastfeeding has been investigated (Van de Perre et al. 1993, Kuhn et al. 2006). The breast milk of women with established HIV infection has been found to have HIV-specific IgG, with its wide spectrum of activity against HIV proteins, comparable to HIV-specific IgG in serum. The

spectrum of activity of serum IgA against HIV has been found to be similar to that of serum IgG, but the spectrum of activity of HIV-specific secretory IgA (sIgA) in breast milk is directed against only a limited number of viral proteins (envelope protein, glycoprotein 160, core proteins). In Zambia, HIV-specific sIgA was detected more often in breast milk of transmitting mothers (76.9%) than in breast milk of non-transmitting mothers (46.9%, $p=.009$). The authors concluded that HIV-specific sIgA in breast milk did not appear to be a protective factor against HIV transmission among breastfed infants (Kuhn et al. 2006).

In another study in Zambia, the concentration of alpha-defensins in breast milk was significantly associated with reduced transmission through breastfeeding (Kuhn et al. 2005). This is consistent with earlier work in Rwanda (Van de Perre et al. 1993), where 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). Low levels of HIV-specific IgM in breast milk collected at 18 months were associated with a high risk of transmission of HIV.

Other components of breast milk are protective against viral infections. Human lactoferrin has been shown *in vitro* to have an inhibitory activity against HIV (Van de Perre 1999), and lipid-dependent antiviral activity, specifically directed at HIV. Data suggest the presence of HIV-specific major HIV CD8(+) cytotoxic T lymphocytes in breast milk of HIV-infected women could play a role in limiting transmission and provide a rationale for vaccine strategies to enhance these responses (Sabbaj et al. 2002).

Breast health

Breast health has also been associated with the risk of transmission through breastfeeding, with breast pathologies such as clinical and subclinical mastitis, nipple bleeding, abscess or fissures relatively common in HIV-infected populations. In Kenya, clinical mastitis was detected in 7-11% of HIV infected mothers (John et al. 2001), while the estimated prevalence of subclinical mastitis

elsewhere, defined as having elevated levels of sodium and/or potassium in breast milk, in studies of HIV-infected mothers six to 14 weeks after delivery ranged from 11 to 16% (Semba et al. 1999b; Willumsen 2001; Willumsen 2003). Nipple lesions have been detected in 10-13% of HIV-infected mothers in several cohort studies (Embree et al. 2000; John et al. 2001; Ekpini et al. 2002). Breast abscess on clinical exam was detected at least once in 12% of breastfeeding mothers over a two-year follow-up period in one study and in 3% of mothers in another study with a shorter follow-up period. Mastitis, abscess, and nipple lesions have all been associated with a relative increase in the risk of transmission through breastfeeding (Semba et al. 1999a; Embree et al. 2000; Willumsen 2000; John et al. 2001; Willumsen 2003).

Nutritional status

Maternal nutritional status may influence risk of transmission overall, as well as breastfeeding transmission. In a randomized trial investigating the effect of multivitamins and vitamin A on the risk of transmission, multivitamins (excluding A) given to the mother had no effect on the overall risk of transmission. However, vitamin A alone was associated with a slight increase in MTCT, and an increased risk of transmission during breastfeeding (Fawzi et al. 2002b). Multivitamins were associated with a non-significant reduction in breastfeeding transmission and mortality of the infant in the first two years of life. In a further analysis of these data, children of women who were randomized to receive multivitamins during pregnancy and lactation had a significantly lower risk of diarrhoea ($p=0.03$) and a substantially higher mean CD4 cell count ($p=0.006$) than those in the arm with no multivitamins. The benefit for HIV-infected children was similar to that for uninfected children.

Vitamin A supplementation given to mothers reduced the risk of respiratory infections in the child ($p=0.03$) but was not associated with a reduction in diarrhoea. It has been speculated that antioxidant micronutrient (e.g. vitamin E, selenium, vitamin A and B-carotene) deficiencies may increase the risk of mastitis and there-

fore the risk of MTCT (Semba et al. 1994; Semba & Neville 1999). Finally, in Zimbabwe, the Zvitambo trial did not report a significant role of vitamin A supplementation on the risk of postnatal transmission (Iliff et al. 2005). However, the investigators reported that severe anaemia (<70g/l) and low maternal arm circumference related to nutritional maternal health, were independent risk factors for HIV transmission postnatally (Iliff et al. 2005). These findings highlight the importance of nutritional support for HIV-infected breastfeeding women, but more clarity is needed about which interventions would best decrease postnatal transmission of HIV.

Infant factors

Integrity of mucous membranes

Factors resulting in disruption of the integrity of infants' mucous membranes, such as oral thrush, may be associated with an increased risk of transmission through breastfeeding. However, the direction of any causality is difficult to establish since early HIV infection may also be associated with thrush (Ekpini et al. 1997; Embree et al. 2000). Infant oral thrush can also lead to maternal nipple thrush and fissures. Feeding with cow's milk, allergic reactions to complementary foods and infectious illness can all result in intestinal damage, which could also be a risk factor for transmission. It has also been hypothesized that the intestinal permeability of the young infant may be affected by mode of feeding, with infants who receive only breast milk having a less permeable and therefore healthier lining of the gut than those who also receive other foods. However, in the one study carried out to investigate this further, feeding mode was not associated with infant intestinal permeability (measured with lactulose-mannitol ratios, i.e. dual sugars), although infants who had been diagnosed with HIV infection at 14 weeks had higher permeability at six and 14 weeks than did uninfected children (Rollins et al. 2001).

Immune factors

A well-characterized innate factor that has been considered for protection against mucosal transmission of HIV, including by breast milk, is se-

cretory leukocyte protease inhibitor (SLPI). Infant salivary SLPI has been associated with decreased risk of late breast-milk HIV transmission (Farquhar & John-Stewart 2003). However, in a study of 43 unselected HIV-infected breastfeeding mothers in Bangui, with breast-milk samples obtained at one week, four weeks and six months after delivery, the mean levels of SLPI in breast milk of mothers who transmitted HIV did not significantly differ from those of mothers who did not transmit HIV (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. In addition, HIV-specific cellular immune responses to HIV envelope peptides detected in HIV-exposed infants are associated with reduced transmission through breastfeeding (Kuhn et al. 2001).

Patterns of infant feeding: mode and duration

Of greater importance than other factors, the mode of infant feeding is now clearly associated with HIV transmission through breast milk. In most populations worldwide, breastfeeding is usually initiated, but supplemented with water, other drinks or foods at an early age (Nicoll et al. 2000a). Exclusive breastfeeding for the recommended six months is uncommon, although globally rates are increasing (UNICEF 2005). There is observational evidence from three large studies that exclusive breastfeeding is associated with a lower risk of postnatal transmission of HIV compared to non-exclusive breastfeeding, that is, breastfeeding with formula, other fluids (water, fruit juice) or solids (Table 2). In a study in Durban, South Africa, 551 HIV-infected women self-selected to breastfeed or formula feed after being counselled (Coutsoudis et al. 2001). Breastfeeding women were encouraged to practise exclusive breastfeeding for three to six months. A total of 157 women formula-fed their infants from birth and never breastfed, 118 exclusively breastfed for three months or more and 276 women mixed fed. The three feeding groups did not differ in any of the significant risk factors for transmission, and at birth the rate of

infection in their infants was similar at about 7%. Children who received both breast milk and other foods before three months were significantly more likely to be infected by 15 months of age (36%) than those who were exclusively breastfed until at least three months (25%) or those who had been formula-fed (19%). Exclusive breastfeeding was associated with a significantly lower risk of HIV infection than mixed breastfeeding (hazard ratio, HR, 0.56, 95% CI 0.32-0.98) and had a similar risk to children who were never breastfed (HR 1.19, 95% CI 0.63-2.22).

In the Vertical Transmission Study in South Africa, 1132 of 1372 (83%) infants born to HIV-infected mothers initiated exclusive breastfeeding from birth. Of 1276 infants with complete feeding data, median duration of cumulative exclusive breastfeeding was 159 days (first quartile to third quartile, 122-174 days). Further, 14.1% (95% CI 12.0-16.4) of exclusively breastfed infants were infected with HIV by age six weeks and 19.5% (95% CI 17.0-22.4) by six months; risk was significantly associated with maternal CD4 cell counts below 200 per mm³ (adjusted HR 3.79, 95% CI 2.35-6.12), and birth weight less than 2500 g (adjusted HR 1.81, 95% CI 1.07-3.06). Kaplan-Meier estimated risk of acquisition of infection at age six months was 4.04% (95% CI 2.29-5.76) (Coovadia et al. 2007). Breastfed infants who also received solids were significantly more likely to acquire infection than were exclusively breastfed children (HR 10.87, 95% CI 1.51-78.00, $p=0.018$), as were infants who at 12 weeks received both breast milk and formula milk (HR 1.82, 95% CI 0.98-3.36, $p=0.057$). Cumulative three-month mortality in exclusively breastfed infants was 6.1% (95% CI 4.74-7.92) versus 15.1% (95% CI 7.63-28.73) in infants given replacement foods (HR 2.06, 95% CI 1.00-4.27, $p=0.051$) (Coovadia et al. 2007).

In Zimbabwe, children who received both breast milk and other foods or were predominantly breastfed during the first three months of life were significantly more likely to be infected by 18 months of age (13.9% and 8.6% respectively) than those who were exclusively breastfed

(6.9%) (Iliff et al. 2005). In Côte d'Ivoire, mixed breastfed children tended to have a higher post-natal transmission risk than exclusively breastfed children, although the difference was not significant (Leroy et al. 2004). These data support the hypothesis that exclusive breastfeeding carries a lower risk than mixed feeding. This phenomenon could be explained by the effect of enteric infection caused by the early introduction of foods on the integrity of the infant intestinal gut (Goto et al. 1999). It has been hypothesized that increased risk of transmission with mixed feeding early in life could be associated with increased gut permeability or levels of local inflammation. Another potential mechanism is that mixed feeding may be associated with suboptimal breastfeeding practices and with subclinical mastitis, or it could be due to confounding between mixed feeding and susceptibility to infection.

Duration of breastfeeding is confirmed to be one of the main risk factors for HIV transmission through breastfeeding. In Zimbabwe, among the 2060 children exposed to breastfeeding, the risk of postnatal transmission was 12%; 68% of transmission events occurred after six months (Iliff et al. 2005). This is consistent with studies in West Africa (Leroy et al. 2003), South Africa (Coutsoudis et al. 2001) and the United Republic of Tanzania (Fawzi et al. 2002a). The authors in Zimbabwe concluded that early cessation of breastfeeding could prevent a sizable proportion of postnatal HIV infections, but that this can only be done when women are socially supported to do so, and when safe, nutritionally adequate alternatives are available.

Sex

In the international meta-analysis of late post-natal transmission (The Breastfeeding and HIV International Transmission Study Group (BHITS) 2004), covariates potentially affecting the relationship between breastfeeding and late postnatal transmission of HIV were evaluated, including both maternal variables (age, parity, CD4 cell count) and child variables (birth weight, sex). Neither maternal age, parity nor birth weight were significantly associated with late postnatal transmission, but maternal CD4 cell

count and child's sex were, with girls being 40% less likely to become infected after four weeks of age during breastfeeding than boys (HR 0.6, 95% CI 0.4-0.9, $p=0.014$). The risk of late postnatal transmission was highest for boys breastfed by mothers with CD4 cell counts below 200 per mm^3 , followed by boys breastfed by mothers with CD4 cell counts between 200 and 499 per mm^3 and then girls breastfed by mothers with CD4 cell counts below 200 per mm^3 . It was previously reported in the European Collaborative Study, which studied the effect of sex among newborns delivered by elective caesarean section, that girls were more at risk of antepartum and peripartum

infection than boys were (Thorne & Newell 2004). Duration of breastfeeding was similar among boys and girls, but no information was available on the age at which, and what type of other foods were introduced. This difference may be due to boys receiving complementary foods at an earlier age, which thus put them at higher risk of becoming infected. Further research is ongoing to confirm this finding, although a recent study did not confirm these differences in transmission rates between boys and girls during exclusive breastfeeding (Coovadia et al. 2007).

Benefits of breastfeeding

Health benefits of breastfeeding in the general population

Maternal health benefits

Exclusive breastfeeding helps a mother space her pregnancies. Healthy birth spacing is associated with improved birth outcomes and maternal recovery following birth. A woman who exclusively, or almost exclusively, breastfeeds her infant during the first six months of life, and has not resumed menstruation, has a less than 2% risk of becoming pregnant during that time (WHO et al. 1995).

Child health benefits

Current evidence that breastfeeding is beneficial for infant health is mainly based on observational studies. Potential sources of bias in such studies have led to doubts about the magnitude of these health benefits in developed countries. However, several randomized clinical trials show that breastfeeding is the best nutrition during the first months of life (Nicoll & Williams 2002).

One of the most important benefits of breast milk is its ability to protect against common childhood infections such as diarrhoea, pneumonia, neonatal sepsis and acute otitis media. In a recent outbreak of diarrhoea in Botswana, not being breastfed was the most significant risk factor for diarrhoea and death among children (Creek 2006). Following a period of unusually heavy rainfall cases of diarrhoea quadrupled, from about 8500 in 2004 to more than 35 000, while deaths increased more than 20-fold, from 24 to about 530. An epidemiological investigation of the outbreak revealed that a large proportion of the infants who experienced diarrhoea were not breastfed. In a multivariate analysis, lack of breastfeeding was the strongest predictor of infant diarrhoea, increasing the risk 50-fold. In one village, one third of formula-fed babies

died of diarrhoea, while none that were breastfed did. Details are provided in section 5.3.5.

In a substudy of the Botswana outbreak, 93% of 153 babies with diarrhoea were not breastfed (about 75% were fed infant formula and the remainder were fed cow's milk). Sixty-five per cent of their mothers were HIV-positive, and among the infants, 18% were HIV-infected at the time of the study. Kwashiorkor was the only significant predictor of death, not maternal or infant HIV status. In the United States of America, a nationally representative cross-sectional home survey conducted from 1988 to 1994 documented an increased risk of respiratory tract infections, including pneumonia and recurrent otitis media, in children who were fully breastfed for four versus six months (Chantry et al. 2006). There are earlier studies showing the benefits of breastfeeding (Habicht et al. 1986; Victora et al. 1987; Victora et al. 2000; WHO Collaborative Study Team 2000). In a study in Brazil, the risk of hospital admissions for pneumonia was increased 17-fold in infants who were not being breastfed (odds ratio, OR, 16.7, 95% CI 7.7–36.0) compared to those being breastfed (Cesar et al. 1999).

Results from a pooled analysis of six case-control studies carried out from 1983 to 1991 confirm that breastfed infants have a reduced mortality risk compared to non-breastfed children (WHO Collaborative Study Team 2000). In the three studies in non-African settings where outcomes for breastfed infants could be compared to that of non-breastfed infants, mortality rates were significantly higher for non-breastfed infants through the first eight months of life. This finding was particularly striking in the first few 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. The protective effect of breastfeeding is most marked in the first six months of life and gradually diminishes as the infant grows older.

More recently, the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster-randomized trial, has produced convincing evidence of benefit for term infants (Kramer et al. 2001). Maternity hospitals were randomly allocated to receive an evidence-based intervention designed to increase the uptake and duration of breastfeeding according to the principles of the Baby-friendly Hospital Initiative sponsored by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). Among the 16 491 mother-baby pairs followed for 12 months, those born in intervention hospitals were significantly more likely to be exclusively breastfed at three and six months of age. Moreover these children had approximately half the risk of experiencing gastrointestinal infection (OR 0.60, 95% CI 0.40–0.91) and atopic eczema (OR 0.54, 95% CI 0.31–0.95).

The optimum duration of exclusive breastfeeding in terms of health benefit has long been a subject of debate. In the PROBIT trial, the effects on infant growth and health comparing 2862 infants exclusively breastfed for three months with 621 infants who were exclusively breastfed at least six months were reported (Kramer et al. 2003). Weight and length gain were slightly greater in the three-month group but the six-month group had a faster length gain from nine to 12 months and a larger head circumference at 12 months. A significant reduction in the incidence of gastrointestinal infections was observed during the period from three to six months in the six-month group (adjusted incidence density ratio: 0.35 [0.13, 0.96]), but there were no significant differences in risk of respiratory infectious outcomes or atopic eczema. Exclusive breastfeeding for six months was associated with a lower risk of gastrointestinal infection and no demonstrable adverse health effects in the first year of life in a general population with low HIV prevalence (Kramer et al. 2003). This trial shows both that exclusive breastfeeding prevalence can be increased by a hospital intervention promoting breastfeeding,

and that this is accompanied by significant health gains during an infant's first year of life. It also demonstrates that implementing exclusive breastfeeding on a population basis is feasible with adequate support and training of health-care professionals (Kramer et al. 2001).

In a secondary analysis of a large randomized clinical trial on immunization and Vitamin A, infant feeding patterns (exclusive breastfeeding, predominant breastfeeding, partial breastfeeding and no breastfeeding) were studied in relation to mortality and hospital admissions over six months. Altogether, 9424 infants and their mothers in Ghana, India and Peru were enrolled when infants were in the neonatal period. The main outcome measures were all-cause mortality, diarrhoea-specific mortality, mortality caused by acute lower respiratory infections and hospital admissions. There was no significant difference in the risk of death between children who were exclusively breastfed and those who were predominantly breastfed (adjusted HR 1.46, 95% CI 0.75–2.86). Non-breastfed infants had a higher risk of dying when compared with those who had been predominantly breastfed (adjusted HR 10.5, 95% CI 5.0–22.0, $p < 0.001$) as did partially breastfed infants (adjusted HR 2.46, 95% CI 1.44–4.18, $p = 0.001$). These findings highlight that the risks of death are high in non-breastfed children, but are significantly lower and similar for infants who are predominantly breastfed and those who are exclusively breastfed. The authors suggested that in settings where rates of predominant breastfeeding are already high, promotion efforts should focus on sustaining these high rates rather than on attempting to achieve a shift from predominant breastfeeding to exclusive breastfeeding (Bahl et al. 2005).

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. Thereafter, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues to 24 months or beyond (WHO 2001). This recommendation has considered the benefits of breastfeeding, as well as the adverse effects associated with formula feeding at an early age in the general population

with low HIV-prevalence (Kramer & Kakuma 2004).

Health benefits of breastfeeding in children born to HIV-infected mothers

There is little information regarding whether the breast milk from HIV-infected women confers immune properties for both their uninfected and infected children. HIV-infected women may have immune dysfunction and produce lower levels of protective antibody and cell-associated immunity against diarrhoeal and respiratory infections; hence their milk would have lower levels of protective antibodies, than women without HIV infection. The findings from these two studies indicate that breastfeeding does confer protective benefits on HIV-exposed infants.

HIV-exposed children, regardless of HIV status

Only two trials randomized on infant feeding practices have been conducted among HIV-infected pregnant women and these have provided information on the health benefits of breastfeeding among HIV-exposed children.

In a secondary analysis from a randomized trial aimed at evaluating mode of infant feeding on the risk of MTCT of HIV in Nairobi, Kenya (Nduati et al. 2000), the two-year mortality rate among infants in the formula-feeding group was 20%, not significantly different from the 24% figure in the breastfeeding group (HR 0.8, 95% CI 0.5–1.3), even after adjusting for HIV infection status (HR 1.1, 95% CI: 0.7–1.7). 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 than those in the formula arm ($p=0.06$ 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 ($p=0.04$). In this trial, there was substantial

movement between arms, and many in the formula arm left the study before follow-up.

On the other hand, in the Mashi trial in Botswana, results were slightly different from the Kenya trial (Thior et al. 2006). The Mashi trial evaluated the efficacy and safety of breastfeeding and ZDV prophylaxis in infants for six months compared to formula feeding from birth and one month of ZDV prophylaxis of the infant for reducing postnatal transmission of HIV. There were significantly higher rates of mortality (mainly related to diarrhoeal disease and pneumonia) in formula-fed than in breastfed children in the first six months of life. The cumulative incidence of infant death was significantly higher in the formula-fed group than in the breastfed plus ZDV group at age seven months (9.3% versus 4.9%, $p=0.003$); however, this difference diminished beyond seven months, such that the mortality through 18 months of age was not significantly different (10.7% in the formula-fed arm versus 8.5% in the breastfed arm, $p=0.21$).

HIV-infected children

There is more reliable information relating to the benefits of breastfeeding for HIV-infected children issued from observational cohort studies (with available data from highly selective samples). In a small study from Durban, South Africa, HIV-infected infants who were never breastfed had a poorer outcome than breastfed HIV-infected children: 60% of 15 never-breastfed infants had three or more morbidity episodes in the first 18 months of life compared to 32% of 47 breastfed HIV-infected infants (Coutsoudis et al. 2003). During the first two months of life, never-breastfed infants, regardless of their HIV status, were nearly twice as likely to have had an illness episode as compared to breastfed infants (OR 1.91, $p=0.006$). Two earlier studies from South Africa compared 90 partially breastfed and exclusively formula-fed HIV-infected infants (Bobat et al. 1997); both groups had similar frequencies of failure to thrive, episodes of diarrhoea and pneumonia, as did 43 uninfected infants born to HIV-positive mothers.

More recently, preliminary data presented from Zambia in the ZEBS trial (Thea et al.

2004), showed that breastfeeding of HIV-infected infants beyond four months was associated with improved survival compared to stopping breastfeeding at four months (Kuhn et al. 2007). These studies indicate that HIV-infected infants fare better when breastfed rather than formula fed.

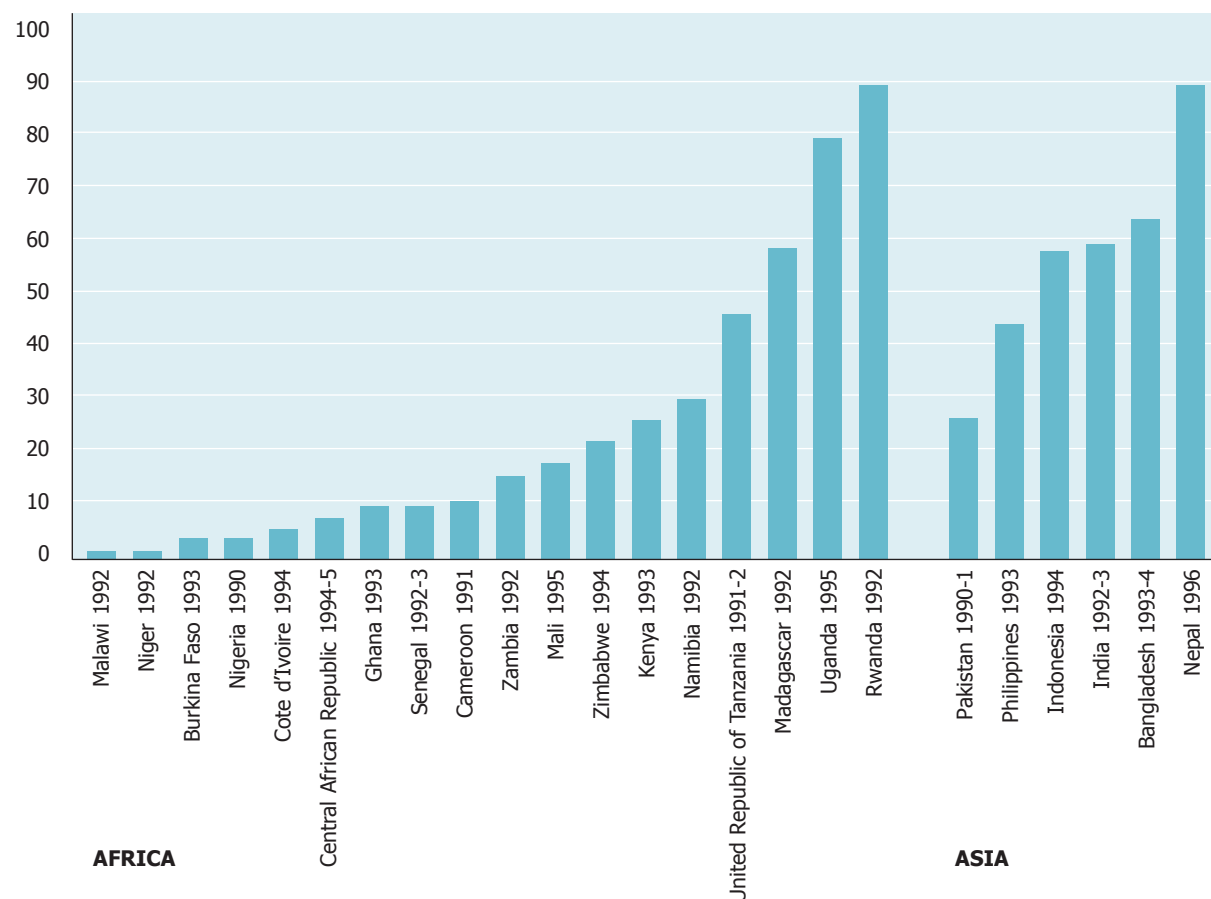
Global breastfeeding practices

Nearly all infants in developing countries are initially breastfed from the first week of life (WHO Global Databank on Breastfeeding and Complementary Feeding 2006), and most children continue to be breastfed until at least six months of age, frequently into the second year of life (Nicoll et al. 2000a; WHO Collaborative Study Team 2000). Continued breastfeeding (beyond 12 months) is common in sub-Saharan Africa and Asia, but less so elsewhere (Nicoll & Williams 2002). In 2005, it was estimated that

94% of infants in the world were breastfed for some time, 79% of infants continued breastfeeding at age one year and 52% at two years of age (WHO Global Databank on Breastfeeding and Complementary Feeding 2006).

Non-exclusive breastfeeding is common, and giving fluids and foods in addition to breast milk is frequent (Becquet et al. 2005a). The practice of exclusive breastfeeding at age one month varies according to geographic region and is mainly observed in East Africa and Nepal, while it remains low (less than 30%) in other regions (Figure 1) (Nicoll et al. 2000b). Between 1990 and 2000, the data suggest that exclusive breastfeeding levels in the developing world increased 15% overall among infants aged less than four months (from 46% to 53%) and aged less than six months (from 34% to 39%) (Labbok et al. 2006; UNICEF Global Breastfeeding Databank 2005).

FIGURE 1. Prevalence of exclusive breastfeeding at four weeks of age in African and Asian children



Source: Adapted from Nicoll et al. (2000b)

Strategies to reduce HIV transmission through breastfeeding

Because guidance on prevention of HIV transmission in the peripartum period is relatively non-controversial, research on the prevention of mother-to-child transmission of HIV now concentrates mostly on the breastfeeding period, including the primary prevention of HIV in lactating women, antiretroviral prophylaxis to mothers or their infants and other interventions relating to infant feeding practices (Dabis et al. 2004; Kourtis et al. 2006). These interventions need to be tailored according to different contexts.

Primary prevention of HIV in women of childbearing age

The best approach to preventing HIV infection in infants and young children, including transmission through breast milk, is to prevent HIV infection of young girls and women of childbearing age (De Cock et al. 2002). In sub-Saharan Africa, Asia and the Caribbean, the main mode of HIV transmission is heterosexual contact (Buve et al. 2002). In developed countries, although most women with HIV have a history of injecting drug use, or sexual partners with a history of injecting drug use or bi-sexuality, heterosexual transmission has become an increasingly important 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 infections and poor nutritional status (Mostad et al. 1999). Cultural, social and economic factors also contribute to HIV transmission by increasing the vulnerability of girls and women (Buve et al. 2002; De Cock et al. 2002).

Strategies to prevent all MTCT should be linked to primary prevention programmes that

provide education about safer sex, condoms, 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 considerable percentage of whom may acquire infection in the two years after delivery while still breastfeeding) because of the particularly high risk of MTCT if mothers are infected with HIV during breastfeeding. In poorer settings, some of the benefits of breastfeeding result from its physiological contraceptive effect, which helps to maintain an advantageous birth interval; lactational amenorrhoea is 98% effective as a contraceptive method (Vekemans 1997). Additionally, in some cultures there is a reduction in coitus associated with breastfeeding, which may enhance this effect. Hence, the issue of contraception should be addressed, given that interventions for the prevention of MTCT include replacement feeding and may include modifications to breastfeeding, such as early cessation as an option. Antenatal testing and counselling (including infant feeding options) for HIV-infected pregnant women are part of the strategy to reduce HIV transmission during breastfeeding. Such strategies must include high rates of antenatal testing and use of interventions to reduce HIV transmission; ensuring continued contact between health-care professionals and mothers and infants from 18 to 24 months postpartum is also vital (Temmerman et al. 2003).

HIV prevention interventions directed at pregnant and lactating women could contribute to reducing MTCT in several settings, but this currently does not attract much research or programmatic effort (Rollins et al. 2007).

Framework to assess interventions to prevent postnatal transmission

There are several conceivable interventions to prevent mother-to-child transmission of HIV that are applicable to different settings. These interventions need to be assessed as complex public health interventions using several evaluation criteria. The basic principle is to provide decision-makers (including women) with all relevant information needed to make interventions available to solve this public health issue in their specific context. Safety is a key issue which addresses negative adverse effects of interventions aimed at preventing postnatal transmission. It could be assessed in various groups using different criteria: for the infant (morbidity, mortality, growth), for the woman (mortality, fertility), for the general population (the spillover effect).¹

Acceptability is a key issue in assessing interventions aimed at reducing postnatal transmission of HIV. It should be assessed at three different population levels: the target population (in terms of social acceptability), the health system and decision-makers. Alternatives to prolonged breastfeeding are often considered as unusual infant feeding practices in some parts of the world. It is therefore essential to evaluate mothers' acceptance and use of these interventions, and their compliance with them in the long term.

Effectiveness is the level to which the intervention meets its objectives when used in real-life conditions after the evidence of its efficacy is assessed in ideal conditions. Documentation of effectiveness in preventing postnatal transmission could be assessed using both the residual overall MTCT rate after the complete cessation of breastfeeding and the postnatal rate of transmission in conditions close to those of the context where implementation of the intervention is considered.

The full assessment of strategies aimed at preventing postnatal transmission of HIV through breastfeeding should balance benefits and risks of each infant feeding option in its specific context. An intervention should be recommended only if its positive effects outweigh its negative effects after balancing benefit and risk. The negative effects of the intervention, therefore, must always be judged on whether risks can be minimized to an acceptable level, given the effectiveness. With this aim, HIV-free survival² is a useful index with which to assess both effectiveness and safety; indeed, it is now the most reliable and easy measurement to assess the long-term effect of postnatal interventions (Alioum et al. 2001).

Modifying infant feeding options for HIV-infected women: replacement feeding

Modifying infant feeding practices could play an important role in preventing postnatal risk and needs to be assessed according to the local context. The first alternative to prolonged breastfeeding consists of the complete avoidance of breastfeeding, which is then usually replaced by commercial infant formula. 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.

Table 4 presents data on replacement feeding options from various recent studies. The studies include the Kenya trial conducted in an urban site and published in early 2000 (Nduati et al. 2000; Mbori-Ngacha et al. 2001); the MASHI randomized clinical trial conducted in a semi-rural setting in Botswana (Thior et al. 2006); and the ANRS 1201/1202 Ditrane Plus cohort study conducted in an urban setting in Abidjan, Côte d'Ivoire (Becquet et al. 2007; Leroy et al. 2007).

¹ Spillover is a term used to designate the feeding behaviour of new mothers who either know that they are HIV-negative or are unaware of their HIV status – they do not breastfeed, or they breastfeed for a short time only, or they mix-feed, because of unfounded fears about HIV or of misinformation or of the ready availability of breast-milk substitutes.

² HIV-free survival refers to young children who are both alive and HIV-uninfected at a given point in time, usually 18 months.

Adverse outcomes of alternatives to breastfeeding practices

Compared to unrestricted breastfeeding, replacement feeding was shown to be safe in the clinical trial in Kenya, which allocated infant feeding practices at random: morbidity and mortality rates were similar over two years in breastfed and formula-fed children (Mbori-Ngacha et al. 2001). The incidence of diarrhoea and pneumonia during the two years of follow-up was similar in the formula and breastfeeding arms, and there were no significant differences in incidence of other recorded illnesses. Infants in the breastfeeding arm tended to have better nutritional status, significantly so during the first six months of life. However, the population studied in this trial was urban with access to a relatively good water supply, and it is crucial to determine whether formula feeding could be a safe intervention in a more resource-poor population (Table 4).

In the Mashi trial in Botswana, all of the mothers received ZDV from week 34 of gestation and during labour. Mothers and infants were first randomized to receive single-dose NVP or a placebo. Infants were then randomized to groups provided with six months of breastfeeding and prophylactic ZDV (breastfed plus ZDV), or six months of formula feeding and one month of ZDV prophylaxis (Shapiro et al. 2005b; Thior et al. 2006). The median duration of breastfeeding was six months, and self-reported compliance with formula feeding high (93%). However, compliance with exclusive breastfeeding was poor. The cumulative incidence of infant death by month seven was significantly higher in the formula-fed group than in the breastfed plus ZDV group (9.3% versus 4.9%, $p=0.003$), but this difference diminished beyond month seven, such that the time-to-mortality distributions through 18 months of age were not significantly different (10.7% versus 8.5%, $p=0.21$). Formula feeding was more commonly associated with severe diarrhoea and pneumonia (17.6%), which were also the leading causes of death in this group, compared to breastfed children (13.1%, $p=.03$). These results highlight

the relatively high morbidity and mortality rates associated with the feeding of formula, and the need to carefully assess the local management of childhood illnesses before the implementation of a formula-feeding strategy in a given context.

In the ANRS 1201/1202 Ditrane Plus study conducted in Côte d'Ivoire, the two-year occurrence of adverse health events defined as hospitalization or death was similar among early-weaned breastfed and formula-fed children (15% and 14%, respectively) (Becquet et al. 2007). To assess whether these two modified infant-feeding practices were safe as opposed to a longer breastfeeding period, the 18-month mortality among these children was compared with the mortality observed in long-term breastfed children within an historical cohort followed in the same population. No differences in mortality were observed in the children given alternative foods over the same period as those breastfed, when taking into account HIV status: an overall 18-month probability of survival of 96% was observed among HIV-uninfected early weaned infants and formula-fed children, which was similar to the 95% probability observed in the long-term breastfed children. Given appropriate nutritional counselling and care, access to clean water and a supply of breast-milk substitutes, replacement feeding could be a safe intervention to prevent MTCT of HIV in urban African settings.

Social acceptability of feeding practices

As the infant feeding option was allocated at random in the Kenyan and the Botswana trials, the social acceptability of the intervention cannot be fully studied. In the Kenya trial, compliance for women in the formula-feeding group was estimated to be 70%, compared to 96% in the breastfeeding group (Nduati et al. 2000). In Mashi, full adherence to formula feeding was self-reported as 93% (Thior et al. 2006). However, three infants of 245 in the formula-fed group were infected between four weeks and seven months, presumably because they were exposed to breast milk.

The ANRS 1201/1202 Ditrane Plus cohort study of women attending community-run health facilities was conducted in poor areas in Abidjan, Côte d'Ivoire (Becquet et al. 2005c; Leroy et al. 2007). Two nutritional interventions were systematically proposed to the women during antenatal visits, and the staff was trained to support individual women's choices (Table 4). The first option consisted of the complete avoidance of breastfeeding: replacement feeding from birth to nine months of age with free provision of infant formula, facilitated by the use of a single oral dose of cabergoline for inhibiting lactation. The second option consisted of practising exclusive breastfeeding for the first few months with the aim of stopping after a short period (not exceeding two weeks) and obtaining complete cessation of breastfeeding by four months of age. Replacement feeding from cessation of breastfeeding until nine months of age as well as the materials needed were provided free of charge, while cup feeding was encouraged from three months of age. Overall, 53% of women initiated formula feeding. Of those, only 15% were non-compliant to this intervention at age one year (i.e. they had breastfed their child at least once), of whom 41% mixed-breastfed temporarily at day two, mainly because of the pressure of their environment or because of low birth-weight (Leroy et al. 2007).

Among the breastfeeding mothers, the probability of practising exclusive breastfeeding from birth was extremely low: only 10% at three months of age (Becquet et al. 2005c). The duration of breastfeeding was considerably reduced in this population: breastfeeding cessation occurred at approximately four months of age, after a short (median: nine days) transition period of mixed feeding when breast milk and infant formula were given simultaneously to the infant. Provided with the necessary support, women's acceptance of, and compliance with, formula feeding and early cessation of breastfeeding were high. Exclusive breastfeeding was not practised despite regular nutritional counselling given during antenatal and postnatal counselling to promote it. In this setting, formula feeding was more

socially acceptable than breastfeeding. This social acceptability must be balanced with long-term health outcomes of the mother and child in order to guide safe recommendations on infant feeding among HIV-infected women in urban African settings.

In contrast, Bland and colleagues (2007) found that exclusive breastfeeding was more socially acceptable than replacement feeding in a study near Durban, South Africa. The purpose of the study was to examine the intentions of HIV-infected and uninfected women with regard to feeding their infants. This involved assessing the appropriateness of their choices according to their local resources, as well as determining the mothers' adherence to those choices during the first week postpartum. The intentions of pregnant women were studied within the context of four resources that facilitate replacement feeding: clean water, adequate fuel, access to a refrigerator and regular maternal income. First-week feeding practices were documented. The antenatal feeding intentions of 1253 HIV-infected women were: exclusive breastfeeding 73%; replacement feeding 9%; undecided 18%. Significantly more HIV-infected women intending to exclusively breastfeed adhered to their intention in week one (exclusive breastfeeding 78%; replacement feeding 42%; $p < 0.001$). Of 1238 HIV-negative women, 82% intended to exclusively breastfeed; 2% to replacement feed; and 16% were undecided. Seventy-five per cent who intended to exclusively breastfeed adhered to this intention postnatally, and only 11 infants (<1%) received no breast milk. The number of antenatal home visits during the study significantly influenced adherence to feeding intention. The authors concluded that adherence to intention among HIV-infected women was higher in those who chose to exclusively breastfeed than to replacement feed, and that with appropriate counselling and support, spillover of suboptimal feeding practices to HIV-negative women was minimal.

Table 4. Assessment of various intervention strategies to prevent postnatal transmission of HIV through breastfeeding in studies conducted in Africa

Study location and name (citation)	Study design	Peripartum ARV regimen	Postpartum ARV regimen	Sample size	Infant feeding options	Choice of feeding method, and adherence to it	Safety: morbidity and mortality	Effectiveness: HIV transmission rate and HIV-free survival
Nairobi, Kenya (Nduati et al. 2000; Mbori-Ngacha et al. 2001)	Randomized clinical trial.	None.	None.	425	Randomization of infant feeding option: exclusive FF or BF.	Self-reported compliance: 71% in FF arm. Median duration of BF: 17 months.	24 month mortality: 20.0% in the FF arm vs. 24.4% in the BF arm (HR 0.8, 95% CI 0.5-1.3).	HIV: 20% in the FF arm vs. 36.7% in the BF arm (p=.001). HIV-free survival: 58% in the FF arm vs. 70% in the BF arm (p=.02).
Botswana, the MASHI trial (Shapiro et al. 2005a; Shapiro et al. 2005b; Thea et al. 2006; et al. 2006)	Randomized clinical trial Initial design: short-course ZDV with/without maternal and infant NVP and BF/FF.Revised: short-course ZDV and infant NVP with/without maternal NVP and BF/FF; if CD4 count <200: ART given to mothers.	1st randomization: ZDV from 34 weeks of gestation + oral ZDV intrapartum and either single-dose NVP at onset of labour or placebo.	2nd randomization: BF + ZDV for 6 months + single-dose NVP (infant) vs. FF + ZDV (infant) for 4 weeks + single-dose NVP (infant).	1179	Randomization of infant feeding option: FF or short-term EBF recommended; then early cessation between months 5 and 6. (Infant formula provided at no cost for 12 months.)	Self-reported compliance of BF arm (50%): adherence to EBF: 57% at 4 weeks and 18% at 5 months; compliance in FF arm (50%): 93% reported full adherence.	Death: at 7 months 9.3% in the FF arm vs. 4.9% in the BF arm (p=.003); at 18 months 10.7% in the FF arm vs. 8.5% in the BF arm (p=.21).	HIV: at 7 months 5.6% in the FF arm vs. 9.0% in the BF arm (p=.04); at 18 months 6.0% in the FF arm vs. 9.5% in the BF arm (p=.02). HIV-free survival: at 7 months 12.5% in the FF arm vs. 12.9% in the BF arm (p=.86); at 18 months 13.9% in the FF arm vs. 15.1% in the BF arm (p=.60).

ARV, antiretroviral; ART, high activity antiretroviral therapy; BF, breastfeeding; EBF, exclusive breastfeeding; FF, formula feeding; RF, replacement feeding; NA, not available; HR, hazard ratio; CI, confidence interval; MF, mixed feeding (breast milk and other fluids, foods or formula); ddl, didanosine; D4T, stavudine

Study location and name (citation)	Study design	Peripartum ARV regimen	Postpartum ARV regimen	Sample size	Infant feeding options	Choice of feeding method, and adherence to it	Safety: morbidity and mortality	Effectiveness: HIV transmission rate and HIV-free survival
Abidjan, Côte d'Ivoire, ANRS 1201/1202 Ditrame Plus study, (Becquet et al. 2005c; Dabis et al. 2005; Becquet et al. 2006; Leroy et al. 2008; Becquet et al. 2007; Leroy et al. 2007)	Open label cohort: ZDV + single-dose NVP.	ZDV from 36 weeks of gestation; intrapartum oral ZDV + single-dose NVP at onset of labour.	Mother: none; infant: single-dose NVP, and ZDV for seven days.	373	Antenatal choice: RF or short-term EBF then cessation between months 4 and 5. (Infant formula provided at no cost for 9 months.)	53% of mothers chose FF, of whom 15% breastfed at least once; 47% chose short-term EBF. EBF at 3 months: 10%; median duration: 4 months. Complete cessation of any BF: in 45% and 63% of BF women.] by 4 and 6 months, respectively.	Probability of a severe event (morbidity) in 2 years: FF infants: 14%; short-term BF children: 15% (adjusted HR 1.19, 95% CI 0.75-1.91, p=0.44). 18-month probability of survival of FF : 15.8% 96% for both FF and short-term BF infants. (Similar to the 95% probability observed in the long-term BF children of the historical ANRS Ditrame trial.)	At 6 weeks: 6.5%; at 18 months: FF: 9%; short-term BF: 16%. Historical control group given short-course ZDV only, and were breastfed: 6 weeks: 12.8%; 18 months: 22%. 18 month HIV-free survival: FF : 15.8% short-term BF: 18.4% long-term BF: 24.5%
Abidjan, Côte d'Ivoire, ANRS 1201/1202 Ditrame Plus study (Becquet et al. 2005c; Dabis et al. 2005; Becquet et al. 2006; Leroy et al. 2008; Becquet et al. 2007; Leroy et al. 2007)	Open label cohort: ZDV + 3TC + single-dose NVP.	ZDV + 3TC from 32 weeks of gestation; intrapartum oral ZDV + 3TC + single-dose NVP at onset of labour.	Mother: ZDV + 3TC for 3 days; infant: single-dose NVP, and ZDV for seven days.	420	Antenatal choice: RF or short-term EBF (4 months).			At 6 weeks: 4.7%; at 18 months: FF: 6%; short-term BF: 7%. Historical control group exposed to short-course ZDV only, and were breastfed: 6 weeks: 12.8%; 18 months: 22%. 18 month HIV-free survival: FF : 12.3% short-term BF: 10.4% long-term BF: 24.5%

Study location and name (citation)	Study design	Peripartum ARV regimen	Postpartum ARV regimen	Sample size	Infant feeding options	Choice of feeding method, and adherence to it	Safety: morbidity and mortality	Effectiveness: HIV transmission rate and HIV-free survival
South Africa, the Vertical Transmission Study (Coovadia et al. 2007)	Open label cohort.	Single-dose NVP.	None.	1372	Promotion of EBF.	82.5% of mothers initiated EBF; median duration of EBF: 159 days; 40% of women continued BF to 6 months. Mothers with CD4 count <200 were more likely to use RF.	RF was associated with an increased mortality compared with EBF (15.12% vs. 6.13% at 3 months).	Overall contraction of HIV: at 4-8 weeks: 15%; at 6 months: 21.6%. HIV-free survival: at 6 months: 75%; among infants EBF: at 4-8 weeks: 15%; at 6 months: 16%. (Early mixed feeding was a risk factor.)
Zwitambo, Zimbabwe (Piwoz et al. 2004; Iliff et al. 2005; Piwoz et al. 2005)	Open label cohort.	None.	None.	14 110	Promotion of EBF.	100% of mothers initiated EBF. EBF at 3 months: 7.6%.	NA	Overall postnatal HIV transmission: at 18 months: 12.1%, 68% occurring after 6 months. (Early mixed feeding was a risk factor.) HIV-free survival: NA
Rwanda and Uganda, the SIMBA trials (Vyankandondera et al. 2003)	Randomized clinical trial: NVP vs. 3TC postnatally in breastfeeding infants born to women who received ZDV + ddI antenatally and 7 days postpartum.	ZDV + ddI from 36 weeks of gestation; intrapartum oral ZDV + ddI.	ZDV + ddI for 7 days (mother); NVP once daily for 14 days then twice daily vs. 3TC twice daily while breastfeeding (infant).	358	Short-term EBF.	Median duration of BF: 3.5 months (interquartile range 2.9-5.1 months).	NA	HIV infection at 4 weeks: 6.9%; 7.8% at 6 months (difference not statistically significant); transmission rate 2.4% between day 3 and 6 months. HIV-free survival: NA

Study location and name (citation)	Study design	Peripartum ARV regimen	Postpartum ARV regimen	Sample size	Infant feeding options	Choice of feeding method, and adherence to it	Safety: morbidity and mortality	Effectiveness: HIV transmission rate and HIV-free survival
United Republic of Tanzania, the Mitra trial (Kilewo 2005)	Open label cohort: ZDV + 3TC (mothers), and 3TC (infants).	ZDV + 3TC from 36 weeks of gestation; intrapartum oral ZDV + 3TC.	ZDV + 3TC (mother and infant, seven days); 3TC for 6 months (infant only).	NA	BF.	Median duration of BF: 20 weeks.	NA	3.4% infection at 6 weeks and 5.1% at 3 months, among infants who were HIV-uninfected at birth. HIV-free survival: NA
Nairobi and Mombasa, Kenya; Bobo-Dioulasso, Burkina Faso, the Kesho Bora Trial (Farley & Kesho Bora Study Group 2006)	Open label cohort and randomized clinical trial: If CD4 count <200/mm ³ : ART given to mothers (ZDV + 3TC + NVP); if CD4 count >500/mm ³ : ARV prophylaxis (ZDV from 34–36 weeks of gestation until delivery, and intrapartum dose of NVP; if CD4 count 200–500/mm ³ : ZDV + 3TC + lopinavir & ritonavir regimen, beginning at 34–36 weeks of gestation until 6 months postpartum vs. no regimen.	Mother CD4 count: 200–500/mm ³ : ZDV + 3TC + lopinavir & ritonavir regimen beginning at 34–36 weeks of gestation until 6 months postpartum vs. no regimen.	NA	Promotion of EBF.	Trial ongoing.	NA	NA	
Kenya, the Kisumu Study (KIBS) (van't Hoog et al. 2005; Thomas 2007)	Phase II, open label cohort.	ART for mothers from 34 weeks of gestation.	6 months of ZDV + 3TC and NVP for women with CD4 counts <250/mm ³ ; ZDV + 3TC and nefinavir for women with CD4 counts above 250.	NA	Early weaning from 5.5 months, with BF cessation at 6 months.	Study ongoing.	Peak of severe event: diarrhoea after weaning.	NA

Study location and name (citation)	Study design	Peripartum ARV regimen	Postpartum ARV regimen	Sample size	Infant feeding options	Choice of feeding method, and adherence to it	Safety: morbidity and mortality	Effectiveness: HIV transmission rate and HIV-free survival
Rwanda, the AMATA study (Peltier, 2007, personal communication)	Open label cohort.	AZT or D4T + 3TC and NVP.	Breastfeeding with ART or FF (formula given at no cost).	425	Early weaning at 6 months.	61% of mothers chose RF; 39% chose EBF with ART.	Study ongoing.	HIV transmission at birth: 1.1%.
Malawi, the Breastfeeding Antiretroviral Nutrition Study (BAN) (Bramson et al. 2006; Corneli et al. 2007; Kourtis 2007)	Open label cohort: 1) three-drug ART for 28 weeks (mothers) or 2) daily infant NVP for 28 weeks, or 3) PMTCT only. Women are counseled to breastfeed exclusively for 28weeks, followed by rapid weaning.	Single-dose NVP + 7 days ZDV and 7 days 3TC.	Mother: 3-drug ARV for 28 weeks; infant: daily NVP for 28 weeks.	827	BF	NA	Peak of severe event: diarrhoea after weaning (mainly during rainy season).	NA
Mozambique, the DREAM cohort (Giuliano et al. 2007)	Open label cohort: NVP-based ART, irrespective of CD4 count.	D4T or ZDV + 3TC and NVP from 24 weeks of gestation; continued orally intrapartum.	Breastfeeding women: continued D4T or ZDV + 3TC & NVP regimen until infant weaned, then stopped ART; single-dose NVP + 7 days of ZDV (infant).	NA	Primarily RF.	NA	NA	HIV transmission rate 2.7% at 6 months.
Zambia, the ZEBs trial (Thea et al. 2004; Thea et al. 2006; Kuhn et al. 2007)	Randomized clinical trial.	Single-dose NVP.	None.	958	Early weaning at 4 months vs. prolonged breastfeeding	NA	Significantly lower survival among HIV-infected children weaned at 4 months.	NA

HIV-infection

The clinical trial randomized on infant feeding practices in Kenya showed that the cumulative probability of HIV infection at age two years was 37% in breastfed children and 21% among the formula-fed arm ($p=0.001$) (Nduati et al. 2000). In the Mashi trial, HIV infection at age 18 months was higher in breastfed children than in formula-fed children despite six months of ZDV prophylaxis, 9.5% and 6.0%, respectively ($p=0.02$) (Thior et al. 2006).

In the ANRS 1201/1202 Ditrane Plus study in Côte d'Ivoire, the provision of peripartum antiretroviral prophylaxis combined with the promotion of alternatives to prolonged breastfeeding considerably reduced MTCT rates with a long-term benefit sustained until age 18 months (Becquet et al. 2007). HIV transmission rates as low as 6.8% and 5.6% at 18 months were found in short-term breastfed and formula-fed children, respectively, whose mothers had received a peripartum short-course regimen of ZDV, in addition to a single-dose of NVP.

In Kampala, Uganda, 306 children were enrolled in a programme to prevent MTCT providing short-course ZDV prophylaxis and replacement feeding to mothers (Magoni et al. 2005). Transmission rates were 12.0% at month six (3.7% in the exclusively formula-fed group, 16.0% in the exclusively breastfed group, and 20.4% in the mixed-fed group). No significant risk difference was observed between the exclusive breastfed and the mixed-fed groups. However, there are no follow-up data to further measure the long-term outcome of this intervention within this context, and there have been some methodological concerns.

HIV-free survival

HIV-free survival at two years was significantly higher in the formula arm compared to the breastfeeding arm in the Kenya trial and in the ANRS 1201/1202 Ditrane Plus study compared to the ANRS Ditrane historical cohort (Valérie Leroy, personal communication, 25 October 2006). In the Mashi trial, transmission rates were significantly lower among formula-fed children, but infant mortality was also higher in this group compared to breastfed children, re-

sulting in similar HIV-free survival in these two groups by age 18 months (Thior et al. 2006).

Discussion

Available findings in 2006 on replacement feeding options show that formula feeding is highly effective in reducing postnatal transmission, but its safety depends greatly on the local context in which it is implemented. In the Kenya trial and the ANRS 1201/1202 Ditrane Plus study, reduction of postnatal transmission outweighed the risks of adverse events. In Mashi, benefits and risks are balanced between infant feeding options with a comparable HIV-free survival at 18 months.

In these studies, infant formula was provided at no cost for up to 12 months with demonstration of its safe preparation. The differences between the findings of the Kenya and the Botswana trials have been explained by the fact that the Kenyan women were urban and had better access to clean municipal water and probably a higher socioeconomic status. Other differences in these contexts could explain these discrepancies and need to be further explored: access to, and the content and quality of postnatal follow-up, including nutritional counselling; and the characteristics of formula delivery. Finally, the fact that in both these trials, the infant feeding choice was allocated by randomization is informative in terms of causality analysis, but this methodological choice raises other problems that could interfere with infant health if women's choices are not assessed based on acceptability, feasibility, affordability, sustainability and safety.

An outbreak of diarrhoeal disease in Botswana showed that replacement feeding is of concern in such instances: a recent study of infant feeding practices showed that early weaning was frequent even in HIV-negative women and this practice predisposed children to greater morbidity in this outbreak (Creek 2006). Government policy in Botswana is to provide free formula for the infants of all HIV-infected women who choose that option, and about 63% of these women formula feed. During the outbreak, the number of reported cases of diarrhoea in children aged less than five years increased fourfold

from between 2004 and 2005 to 2006; and deaths from diarrhoeal illnesses of those aged less than five years increased from 24 and 21 reported in 2004 and 2005, respectively, to at least 532 in 2006. These deaths were associated with diarrhoea and malnutrition and followed unusually heavy rains, in which 25% of patients' families had overflowing latrines. Among children hospitalized for diarrhoea, 96% were aged less than two years and 93% were not breastfeeding. When reviewing the records of 20 infants who died after being fed with formula, it was found that their mothers reported receiving only 51% of the formula they should have received before their infant's illness. In such conditions, formula feeding may not save lives.

This highlights the need to ensure that minimal conditions are in place for safe replacement feeding practices: inter alia, access to clean water; counselling and information on which women can base sound choices during the antenatal period; regular postnatal follow-up (with repeated growth measurements) and nutritional counselling; an uninterrupted supply of formula (whether formula is given at no cost or subsidized) as well as the materials to dispense it. Thus, programmes that provide infant formula on a large scale need to review management difficulties. Further, health staff should be taught that formula-fed infants are at high risk of morbidity. They should be shown the clinical signs of diseases and how to intervene in such cases to aid the child. Formula feeding should be proposed only alongside regular postnatal follow-up to adapt the formula to the nutritional requirements of the growing child. In settings where infant formula is used widely by HIV-negative women, the promotion of breastfeeding needs strengthening in the general population.

These restrictive and selective conditions serve to remind that formula feeding could be an option to replace breastfeeding but is far from being applicable in all settings; thus, the need for more studies on alternative strategies for breastfeeding (e.g. antiretroviral prophylaxis).

Strategies for HIV-infected women who breastfeed

Several options could be considered to reduce postnatal transmission in breastfeeding populations. A potential intervention would be the promotion of exclusive breastfeeding during the first six months of life. Another alternative to prolonged breastfeeding consists of shortening the duration of breastfeeding. These two interventions can be combined and constitute an alternative to prolonged breastfeeding: exclusive breastfeeding with early cessation, which is expected to reduce the cumulative risk of postnatal transmission of HIV while retaining the benefits of exclusive breastfeeding during the first months of life.

Exclusive breastfeeding

Improving breastfeeding practices by promoting exclusive breastfeeding and breastfeeding cessation as soon as it is acceptable, feasible, affordable, sustainable and safe, in conjunction with lactation management to reduce (sub)clinical mastitis could be effective in reducing postnatal transmission of HIV (Piwoz et al. 2005).

Several studies are completed or currently ongoing in Africa (Côte d'Ivoire, South Africa, Zambia and Zimbabwe) to evaluate the feasibility and acceptability of exclusive breastfeeding for up to six months in HIV-infected women, and its efficacy to decrease postnatal transmission of HIV through breastfeeding. There is consistent evidence from four different studies showing a lower postnatal risk in exclusively breastfed children and those predominantly breastfed, compared to those who were mixed fed (Tables 2 and 4).

In Zimbabwe, the Zvitambo trial assessed the effect of postpartum vitamin A supplementation, and provided education and counselling about infant feeding practices and HIV (Ilf et al. 2005). Information on infant feeding practices and associated infant infections and deaths were prospectively collected. A total of 14 110 mother-newborn pairs were enrolled, randomly assigned to a vitamin A-treatment group after delivery, and followed for two years. At baseline, six weeks and three months, mothers were asked

whether they were still breastfeeding, and whether any of 22 liquids or foods offered in the study had been given to the infant. Breastfed infants were classified as exclusively or predominantly breastfed, or mixed fed. However, one lapse in the exclusivity of breastfeeding at one of the three time points was allowed if the non-breast-milk item consumed was not a milk-based liquid (e.g. fruit juice). One lapse in predominant breastfeeding was allowed only if the mother reported exclusive breastfeeding for the time period. A total of 4495 mothers tested HIV-positive at baseline, and 2060 HIV-exposed infants tested negative through polymerase chain reaction (PCR) at age six weeks. All infants initiated breastfeeding: 156 were exclusively breastfed, 490 predominantly breastfed and 1414 received mixed feeding. Overall postnatal transmission (defined by a positive HIV test after a negative test at six weeks) was 12.1%, with 68.2% of these transmissions occurring after six months of age. Compared with exclusive breastfeeding, early mixed feeding was associated with a 4.03 (95% CI 0.98–16.61), 3.79 (95% CI 1.40–10.29) and 2.60 (95% CI 1.21–5.55) greater risk of postnatal transmission at six, 12 and 18 months, respectively. Predominant breastfeeding was associated with a 2.63 (95% CI 0.59–11.67), 2.69 (95% CI 0.95–7.63) and 1.61 (95% CI 0.72–3.64) trend towards greater postnatal transmission risk at six, 12, and 18 months, respectively, compared with exclusive breastfeeding.

In the Vertical Transmission Study, high rates of exclusive breastfeeding were obtained in rural South Africa (Bland et al. 2006). Women willing to practise exclusive breastfeeding were supported at home by people trained in breastfeeding counselling, but with no previous health background. In this context, the median duration of exclusive breastfeeding from birth was five months, which is elevated in the African context, and adherence to exclusive breastfeeding was higher than for formula feeding (Bland et al. 2007). Replacement feeding was practised by 8% of the Vertical Transmission Study cohort and was associated with increased mortality compared with exclusive breastfeeding (15.12% versus 6.13% at three months). The risk of postnatal

transmission by age six months in exclusively breastfed infants who were HIV-negative at four to eight weeks of age was about 4% (Coovadia et al. 2007). This risk was about 11 times higher with the introduction of solids and two times higher with mixed feeding. Similarly, in the ANRS 1201/1202 Ditrane Plus cohort, a trend for a higher postnatal risk in mixed-fed children compared to exclusively breastfed infants was reported (Leroy et al. 2004).

These data support the recommendation, originally based on other considerations, that mixed feeding should be avoided to decrease the risk of HIV transmission. They also show that exclusive breastfeeding is possible and acceptable among both HIV-infected and uninfected women. However, frequent, good-quality counselling and support is necessary to achieve high rates of exclusive breastfeeding. Among women who decide to breastfeed, exclusive breastfeeding should be promoted until six months of age.

Early cessation of breastfeeding

Following the period of exclusive breastfeeding, it has been suggested that HIV-infected women should cease breastfeeding completely. Early cessation could substantially prevent breastfeeding-associated HIV transmission, while still providing the many benefits of breastfeeding in terms of morbidity and mortality prevention during the early months of an infant's life. However, there is little experience on how this early cessation can be achieved with a minimum of adverse effects for the infant. There is also no evidence yet to inform the timing of this cessation. Nevertheless it would be appropriate for many women to do this as soon as replacement feeding becomes acceptable, feasible, affordable, sustainable and safe, or at six months of age, when exclusive breastfeeding is no longer adequate to meet an infant's nutritional needs. As stated above, continued support is needed beyond the first six months to ensure adequate nutrition for the young child throughout the first years of life.

A clinical trial was conducted in Zambia to test the safety and efficacy of exclusive breastfeeding to four months of age to reduce HIV transmission and child mortality (the ZEBS trial): half of the women were randomly selected

to cease breastfeeding at age four months (Thea et al. 2004), although many women found it difficult to stop and continued for longer. This study was expected to assess the magnitude of reduction of postnatal transmission associated with early cessation at four months compared to prolonged breastfeeding. Early results showed that breast-milk viral load increased after early weaning in this trial. Breast milk was obtained at 22 weeks from 222 women who had either stopped or continued to breastfeed past four months. Breast-milk viral load was measured at 20 and 22 weeks in 71 randomly selected women from both groups: breast-milk viral load was detectable in 68% of those who stopped breastfeeding at four months vs. 42% of those who continued beyond, $p=0.03$); median breast-milk viral load (448 copies versus <50 copies HIV-RNA/ml, $p=0.005$) was significantly higher among those who had stopped in comparison with those who were still breastfeeding and was significantly higher in the same women after stopping compared with two weeks earlier ($p=0.001$). It is unclear whether this increase was temporary. Breast-milk viral load is substantially higher after rapid cessation, and this may pose an increased risk of HIV transmission if children resume breastfeeding after a period of cessation. Increases in breast-milk viral load with differing degrees of mixed feeding needs to be assessed (Thea et al. 2006), together with the long-term efficacy of such an intervention.

To be assessed fully, the benefits of early cessation in terms of reduction of postnatal HIV transmission have to be balanced with their potential risks for infant health. Complementary feeding practices are often inadequate in developing countries, resulting in a significant nutritional decline between six and 18 months of age (Bhandari et al. 2004). One of the potential adverse effects is that if complementary foods were to displace breast milk it would not be nutritionally appropriate. International guidelines stress that from six months breastfeeding should be coupled with the introduction of nutritionally adequate and safe complementary foods (WHO 1998; WHO 2001). Early cessation of breastfeeding may induce undernutrition if another milk source is not available, which in turn

could enhance morbidity compared to those children who are breastfed for a longer period.

Indeed, early cessation of breastfeeding before six months was associated with an increased risk of infant morbidity (especially diarrhoea) and mortality in HIV-exposed children in preliminary results from three studies in Kenya, Malawi and Uganda. These studies included the phase III infant prophylaxis Post-Exposure Prophylaxis for Infant (PEPI) trial in Blantyre, Malawi (Kafulafula 2007); the Kisumu Kenya KIBS study (van't Hoog et al. 2005) in which mothers received ART in the last month of pregnancy and for six months postpartum; and the HIVIGLOB trial in Kampala, Uganda, a phase II/III study, which compared either an infusion of HIV hyperimmune globulin (HIVIGLOB) to the mother and newborn or six weeks of NVP daily to the infant compared to the HIVNET 012 single-dose NVP regimen¹ (Onyango 2007). In the Kenya and Malawi studies there was a significantly increased risk of diarrhoea-related hospitalizations for the infants whose mothers stopped breastfeeding by six months compared to historical data where mothers breastfed into the second year of life (Kafulafula 2007; Thomas 2007). In addition, in the Malawi PEPI study there was a significantly increased risk of both overall and diarrhoea-related mortality compared to historical data. In the HIVIGLOB study, among 579 uninfected infants there was a doubling of gastroenteritis hospitalizations in the three months following cessation of breastfeeding when compared to the three months before breastfeeding stopped; and of the 15 infant deaths that occurred among uninfected infants, all occurred after cessation of breastfeeding (Onyango 2007). Early breastfeeding cessation at four months was associated with reduced HIV transmission but also with increased child mortality from four to 24 months in preliminary data presented from the randomized ZEBS trial in Zambia. Consequently, in this trial, early cessation of breastfeeding did not improve HIV-free survival (Kuhn et al. 2007).

¹ One dose of NVP given to the mother at the onset of labour and one dose of NVP given to the neonate <72 hours postpartum.

The nutritional adequacy of complementary feeding was recently assessed in Côte d'Ivoire among breastfed children exposed to breastfeeding for a median of four months (Becquet et al. 2006). After early cessation, breastfeeding was replaced by food which met nutritional requirements in terms of source of milk (e.g. infant formula, baby food), but the diversity of diet was not appropriate for the nutritional needs of babies aged six months (e.g. lacking sufficient protein). Inadequate complementary feeding at age six months was associated with impaired growth during at least the next 12 months. However, in this cohort study, where regular nutritional counselling was provided, the nutritional adequacy of complementary feeding was then improved to cover the nutritional needs of most of the children at ages nine and 12 months. As a result, two-year morbidity was not different in short-term breastfed infants compared to long-term breastfed children (Becquet et al. 2007).

More research is needed in this area to provide practical tools that can be used routinely, especially around the period of cessation, to contribute to the assessment of the nutritional adequacy of complementary feeding. Such tools could help detect children who are at risk for malnutrition and whose mothers need to receive appropriate and reinforced nutritional counselling.

In Burkina Faso, an ongoing study is assessing a locally-produced fortified flour formulation designed to meet nutrient and energy needs of infants among women practising early breastfeeding cessation in the Kesho Bora study (Cames et al. 2006). It is provided free of cost, while mothers have to pay for cow milk. The first results suggest high acceptability among mothers who choose either breastfeeding with early cessation or replacement feeding. The study on mothers' perceptions of the product, and the infants' food consumption, growth and morbidity is ongoing.

In addition, a randomized clinical trial in India showed that improving complementary feeding practices through an educational programme is feasible, but the effect on physical growth is limited (Bhandari et al. 2004). Factors that limit

physical growth must be better understood to plan more effective nutrition programmes.

Heat treatment or pasteurization of expressed breast milk

Heat-treated expressed breast milk is a method endorsed by WHO to reduce postnatal transmission of HIV. Initial results show that methods such as Pretoria Pasteurization or Flash Heat Treatment can effectively inactivate the virus in breast milk from HIV-infected mothers (Jeffery & Mercer 2000; Israel-Ballard et al. 2006b; Israel-Ballard et al. 2007). These methods can also eliminate potential contaminants and adequately inhibit bacterial growth while retaining nutrients contained in breast milk (Jeffery et al. 2003; Israel-Ballard et al. 2006a). It was recently reported that heat-treated human milk may be a feasible infant-feeding option for HIV-positive mothers in Zimbabwe. Yet, its field feasibility now needs to be assessed among HIV-infected women (Israel-Ballard et al. 2006b). It could be useful after a period of exclusive breastfeeding in children older than six months. Expressed heat-treated breast milk may also have a valuable role as an alternative to breastfeeding during periods of increased risk, such as mastitis and cracked or bleeding nipples. Pasteurization of breast milk seems difficult to implement on a large scale, however, and shares some of the same obstacles as replacement feeding – it requires mothers have access to a developed infrastructure and safe practices (such as sterilization of materials used in the process), which can be difficult to achieve in resource-poor settings.

Microbicide treatment of expressed breast milk

Microbicides to treat HIV-infected breast milk could present an alternative to reduce transmission of HIV through breast milk (Urdaneta et al. 2005). It has been reported that alkyl sulfates (i.e. sodium dodecyl sulfate, SDS) are microbicidal against HIV at low concentrations, are biodegradable, have little or no toxicity and are inexpensive. Therefore, they may be used for treatment of HIV-infected breast milk. Human milk was infected artificially by adding HIV (cell-free or cell-associated); it was then treated with an SDS dilution of 1% at 37 degrees Celsius or

room temperature for 10 minutes. SDS was virucidal against cell-free and cell-associated HIV in breast milk. Viral load in artificially-infected milk was reduced to undetectable levels after treatment with 0.1% SDS. SDS could be removed from breast milk if necessary, and milk was not infectious after SDS removal. The proposed treatment concentrations are within reported safe limits for ingestion of SDS by children of 1 g per kg/day. This treatment could be helpful to protect infants from postnatal transmission after six months, where heat treatment is not feasible. The feasibility, acceptability and safety of SDS have not yet been studied.

Antiretroviral therapy during breastfeeding

In addition to replacement feeding, possibilities for preventing HIV from being transmitted through breast milk include ART during breastfeeding (whether or not necessary for the mother's health) and post-exposure prophylaxis to the infant. Antiretroviral regimens were recently designed to provide either maternal treatment, reducing the maternal viral load, or post-exposure prophylaxis to the infant during the period of breastfeeding, thus maximally reducing the risk of MTCT in settings where breastfeeding is common (Gaillard et al. 2004).

Maternal antiretroviral prophylaxis

Preliminary data are available from a trial conducted in Rwanda and Uganda evaluating post-exposure antiretroviral prophylaxis in children during the breastfeeding period, combined with the promotion of early cessation of breastfeeding (Vyankandondera et al. 2003). The trial randomized newborns in Rwanda and Uganda to receive either 3TC or NVP from birth until one month after their mothers stopped breastfeeding. The duration of breastfeeding was around three months and the overall six-month transmission rate was estimated to be 7.8% and did not differ between these two groups. Long-term outcome estimates are still awaited to fully understand the effect of this intervention.

In the Mashi trial in Botswana, it was reported that antiretrovirals given to breastfeeding mothers (NVP, 3TC and ZDV) were measured in breast milk in concentrations inhibiting HIV.

With regard to NVP this exposed infants to the potential for beneficial and adverse effects (e.g. hepatotoxicity) of the drug (Shapiro et al. 2005a). These antiretrovirals suppressed cell-free HIV RNA in breast milk but had no apparent effect on cell-associated HIV DNA loads in breast milk (Shapiro et al. 2005b). These facts highlight the need for further research on this issue to fully assess the public health effectiveness and safety of antiretroviral treatment.

Maternal antiretroviral treatment during breastfeeding

ART for pregnant or lactating women is of indisputable benefit when the mother has a CD4 cell count $\leq 200/\text{mm}^3$ or HIV-related symptoms. HIV-infected women who require antiretroviral therapy for their own health and are breastfeeding should continue to receive it, as the benefit to the health of the woman outweighs potential risks to the infant, with a beneficial expected outcome for infant health (Newell et al. 2004; WHO 2006).

ART to lactating women is expected to substantially reduce the overall risk of transmission to infants by lowering viral load in plasma and breast milk. Whether it will prevent all, most or part of postnatal transmission when breastfeeding exposure cannot be avoided must be established: will breast-milk HIV viral load be lowered as it is lowered in the blood compartment? Not only is it crucial to assess the effect of these highly-active antiretroviral regimens on breast-milk HIV viral load, but also on antiviral drug diffusion and pharmacokinetics in both breast milk and in breastfed infants, as well as on transmission of resistant mutations of the virus. Additional evidence is needed on the safety of antiretroviral prophylaxis given to women or the infant for preventing HIV transmission during breastfeeding.

The optimal duration of antiretroviral prophylaxis is unknown, and there are concerns that viral rebound following cessation of prophylaxis may lead to a high risk of MTCT among infants who continue to breastfeed after prophylaxis has stopped; it may also be detrimental to the mother. There are limited data about the level of penetration of antiretroviral therapies into

breast milk; some drugs may have high levels of penetration while others may have low or undetectable levels in breast milk. Therefore the detrimental effects on mother and child cannot be established, and the link between drug penetration into breast milk and risk of HIV transmission through breastfeeding has not yet been established. Data from a study in Botswana indicated that levels of NVP in breast milk of women receiving NVP-based antiretroviral therapy were lower than their plasma, while levels of 3TC and AZT in breast milk were about threefold higher (Shapiro et al. 2005a). More research is needed, and is indeed ongoing to address these important issues and to guide the definition of comprehensive strategies for both the care of women and prevention of MTCT, which are safe and adapted to different contexts.

When a pregnant and/or lactating woman is not eligible for ART, the benefit in terms of prophylaxis for postnatal transmission has still to be demonstrated and balanced against the risk of maternal intolerance and/or emergence of antiretroviral drug resistance and safety for the baby. It is hypothesized that antiretroviral drugs given to breastfeeding women will reduce the risk of postnatal transmission of HIV. Several ongoing studies are evaluating the effect of single or combination antiretroviral regimens given to breastfeeding women and/or the infant to prevent early and/or late postnatal transmission during breastfeeding. The WHO-coordinated Kesho Bora study randomized control trial compared women with CD4 cell counts between 200–500/mm³ given a short-course ZDV/NVP regimen beginning at 34–36 weeks versus ART (regimen of ZDV and 3TC + lopinavir/ritonavir beginning at 34–36 weeks) during six months of breastfeeding (Farley & Kesho Bora Study Group 2006).

The Breastfeeding Antiretroviral Nutrition (BAN) study is a prospective randomized controlled clinical trial of antiretroviral and nutritional interventions conducted in the postpartum period in Malawi (Bramson et al. 2006). At birth, mother-infant pairs with mothers whose CD4 cell counts were greater than 200 per ml received single-dose NVP and seven days ZDV and 3TC to prevent perinatal PMTCT. Further, study par-

ticipants received either: 1) three-drug antiretroviral therapy for 28 weeks (mothers), or daily NVP for 28 weeks (infants), or 3) nothing more than the initial drugs to prevent perinatal PMTCT. Women were counseled to breastfeed exclusively for 28 weeks, followed by rapid weaning.

In the ongoing Kisumu Kenya KIBS phase II study, mothers are receiving ART in the last month of pregnancy and for six months postpartum. The DREAM study in Mozambique is also considering this.

Infant prophylaxis during breastfeeding

Post-exposure prophylaxis (PEP) to the infant is an attractive intervention in breastfeeding women which deserves attention. It has been shown to prevent HIV infection after occupational exposure of health-care workers (Panlilio et al. 2005). The use of NVP perinatally, amounting to ‘peri-exposure’ prophylaxis, approaches post-exposure prophylaxis. Post-exposure prophylaxis can offer protection against HIV infection to babies of women who missed opportunities to be tested and counselled before or during pregnancy. Recent studies in Malawi (Taha et al. 2003) showed that neonatal prophylaxis with short-course NVP and/or ZDV reduced perinatal transmission of HIV even when mothers reached the health centre after delivery. The SIMBA trial (Vyankandondera et al. 2003) tested two peri-exposure prophylaxis regimens (with no control arm) associated with a shortened duration of breastfeeding (three months). Several studies are planned or ongoing in Brazil, Ethiopia, India, South Africa and Uganda aimed at comparing single-dose NVP versus six weeks NVP as peri-exposure prophylaxis. Extending this perinatal PEP for the entire duration of breastfeeding thus seems to be an attractive option but its efficacy needs to be assessed. PEP has several advantages over ART. First, antiretroviral drug prophylaxis in an uninfected child carries no risk that the virus will develop resistance to antiretroviral drugs (although it would if the infant became infected); second, it spares the mother from treatment when she does not need it for herself, avoiding the frequent side-effects such treatment entails; third, it may be

applicable in a great deal more settings; and finally, it is cheaper.

Immunization of breastfed newborns

An infant vaccine regimen, begun at birth, would be an attractive strategy and might also provide the basis for lifetime protection. Unique features of MTCT and HIV-positive children could be helpful in understanding correlates of immune protection and could facilitate rapid assessment of vaccine efficacy (Luzuriaga et al. 2006). A study on acceptability of paediatric vaccine was performed in Kenya, which reported that concerns about side-effects of such interventions are present in the population (Farquhar et al. 2006). Research on this issue is ongoing and urgently needed. The HIVIGLOB trial in Kampala, Uganda is a phase II/III study comparing either an infusion of HIVIGLOB to the mother and newborn or six weeks of NVP daily to the infant compared to the HIVNET 012 single-dose NVP regimen.

Translating research to public health recommendations on infant feeding

A key issue concerns the translation of research findings into practical recommendations: these depend on several criteria (acceptable, feasible, affordable, sustainable and safe) that need to be carefully defined according to the context before considering interventions to prevent postnatal transmission. The consideration of these criteria needs to be adapted to each individual context. Bland and colleagues (2007) explored the relationship of some of these criteria in provision of feeding options, and adherence by mothers to that choice.

To help HIV-positive mothers make the best choice, they should receive appropriate counselling that includes information about both the risks and benefits of various infant feeding options based on local assessments, and guidance in selecting the most suitable option for their own situation. Individual women's choice about infant feeding options is highly influenced by sociodemographic factors, including both partner or family environment and access to clean water (Becquet et al. 2005c; Leroy et al. 2007). Counselling and information during the antena-

tal period are important determinants in maternal choices, and mothers' adherence to those choices; further, improved education will help them avoid risky practices of mixed feeding due to social pressure. There is a need to train health-care professionals on how to conduct timely counselling without any coercion (Becquet et al. 2005b), and how to include antenatal home visits (Bland et al. 2007).

Mother and child pairs should also have access to follow-up care and support, including family planning and nutritional support (WHO 2006). The longer-term health needs of both HIV-infected and uninfected children and their mothers, the mortality of children living in families with HIV, and the plight of increasing numbers of orphans should not be underestimated. These issues deserve further research and implementation of effective interventions, including monitoring and evaluation for better understanding the impact of those interventions (UNAIDS 2006).

National health services should make special efforts to support primary prevention for HIV seronegative women in the antenatal and breastfeeding periods. In situations where mothers are being screened and identified as HIV-infected, provision will need to be made for their subsequent care and for that of their infected and uninfected children. Counselling on infant feeding for women known to be HIV-infected needs to be appropriate to their situations. Policymakers should also consider the effect such counselling will have on uninfected women and those of unknown HIV status in the same setting; all these women should continue to be advised and supported to exclusively breastfeed for the first six months (WHO 2001; WHO 2006).

Early cessation of breastfeeding among HIV-negative women in some settings seems common, and in these settings breastfeeding promotion needs strengthening. The Vertical Transmission Study conducted in South Africa recently showed it is possible for lay counsellors, with no health background, to help both HIV-infected and uninfected women make appropriate infant feeding choices based on their socioeconomic conditions (Bland et al. 2006). The counselling approach used was based on the set of tools de-

veloped by WHO and was effective, in most cases, in matching the intention of HIV-infected women with their resources: access to water, refrigerator, fuel and regular income. Another issue concerns the effect of providing formula at no cost to HIV-infected women in areas of high HIV prevalence. This South African study showed that the 'spillover' of suboptimal feeding practices to HIV-negative women is minimal if investment is made in provision of high-quality

ity counselling. In clinics offering HIV testing and counselling to pregnant women (and where formula was furnished to HIV-infected women) most HIV-negative women opted for breastfeeding and <1% of infants born to HIV-uninfected women received no breast milk at all in their first week of life. It is therefore possible to put in practice international guidelines on infant feeding if investment is made in the training of lay counsellors involved in infant feeding counselling.

Ongoing or planned research addressing the breastfeeding period

In 2007 there were new key research priorities on HIV and infant feeding. They are listed below.

Factors affecting HIV transmission through breast milk

These include: protective and risk factors, in both the absence and presence of antiretroviral drugs; factors affecting early and late transmission; viral factors affecting transmission including subtypes; proportion of transmission occurring via cell-free versus cell-associated virus; evaluation of immunologic quality of breast milk of infected women at different disease stages and CD4 cell counts, such as antibody content against common pathogens; quantification of risk of MTCT during the transition period from breastfeeding to replacement feeding; evaluation of the risk of postnatal MTCT in women who seroconvert during lactation.

Early cessation of breastfeeding

Research is ongoing to: determine the consequences of cessation of breastfeeding the infant before six months of age in terms of morbidity and mortality; define the optimal time and duration of the transition period from breast milk to replacement formula, as well as the optimal length of breastfeeding; and determine effective interventions to optimize nutrition following breastfeeding cessation.

Transition from exclusive breastfeeding to mixed feeding

These issues include: assessing the risks of breastfeeding cessation after six months including postnatal MTCT of HIV, and infant morbidity/mortality during the transition from exclusive breastfeeding to breastfeeding with complementary foods; determining the optimal time to cease breastfeeding for HIV-exposed uninfected infants; and the feasibility and effectiveness of dif-

ferent interventions to optimize nutrition, development and survival among older infants.

Antiretroviral therapies

Research includes: determining the effects of different antiretroviral treatments on timing of HIV transmission among breastfeeding women; identifying the ways in which antiretroviral drugs affect the risk factors for HIV transmission through breast milk; determining levels of antiretroviral drugs in breast milk and in the breastfeeding infant; ensuring infant safety through the course of their exposure to antiretroviral drugs in breast milk; determining the efficacy of antiretroviral therapies in reducing postnatal MTCT, and the effects they have on cell-free and cell-associated viral load; identifying the mechanisms through which HIV develops resistance to antiretroviral treatments in breast-milk; and finally, determining how antiretroviral resistance develops among breastfeeding infants who become infected postnatally.

Efficacy and safety for mothers and infants

Research is ongoing to: ascertain the efficacy and safety of antiretroviral prophylaxis for mothers and infants during breastfeeding (currently being evaluated in clinical trials); define the efficacy and optimal regimen and duration of antiretroviral prophylaxis for mothers and infants during the postnatal period; and to determine the safety of ceasing antiretroviral treatments for the mother, when they are being used solely for prophylaxis.

Role of passive and active immunization strategies

This includes: researching the potential role of passive and active immunization strategies for HIV prevention; assessing the safety and immunogenicity of HIV vaccine candidates (in-

fants exposed to HIV, both those that remain uninfected and those who become infected despite prophylaxis); and determining the efficacy and safety of passive, active or passive/active immunization for prevention of postnatal MTCT.

Alternatives to replacement feeding

Alternatives to replacement feeding include strategies to reduce infectivity of breast milk by use of heat treatment, microbicides, etc. Further efforts are required to: study the effects of such interventions on cell-free and cell-associated virus and milk components; determine the safety, feasibility, and effectiveness of such interventions when used for prevention of postnatal MTCT,

or when used temporarily during the transition period to mixed feeding or during periods of breast pathology, such as mastitis.

Social factors

More research is required on: counselling, programme implementation and monitoring of infant feeding practices; the social factors influencing maternal decision-making with regard to infant feeding practices, including partner involvement; the optimal level of counselling, training, and the assessment of the quality of that counselling; the efficacy of community-based interventions.

Conclusion

The most appropriate infant feeding option for an HIV-infected mother depends on her individual circumstances, including her health status and the local situation, and should also consider the health services available and the counselling and support she is likely to receive. Exclusive breastfeeding is recommended for HIV-infected women for the first six months of life unless replacement feeding meets five criteria - that it is acceptable, feasible, affordable, sustainable and safe - before that time. When these conditions are met avoidance of all breastfeeding by HIV-infected women is recommended (WHO 2006).

In considering replacement feeding, the following conditions are critical: sustainable access to clean water; regular postnatal follow-up (with repeated growth monitoring); nutritional counselling; and drugs and supplies at no cost or at a subsidized price, and with a controlled distribu-

tion. The family environment in which the mother lives plays a key role in her choice of feeding option.

Early cessation of breastfeeding by HIV-infected women remains a challenge that needs to be addressed. The five criteria (acceptable, feasible, affordable, sustainable and safe) need to be reassessed at the time of early HIV diagnosis in infants and at other times when feeding practices may be changing. Evidence now clearly shows that infants who are known to be HIV-infected should continue breastfeeding.

It is anticipated that new data will be available in 2008 to help clarify the issue of infant feeding in the context of HIV. Current recommendations as contained in the Report from the 2006 technical consultation (WHO et al. 2007) provide the best guidance for preventing postnatal HIV infection and improving HIV-free survival while awaiting the new data.

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This publication is an update of the review of current knowledge on HIV transmission through breastfeeding, with a focus on information made available between 2001 and 2007. It reviews scientific evidence on the risk of HIV transmission through breastfeeding, the impact of different feeding options on child health outcomes, and conceivable strategies to reduce HIV transmission through breastfeeding with an emphasis on the developing world.

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