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TECHNICAL REPORT

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Human Milk, Breastfeeding, and Transmission of Human Immunodeficiency Virus Type 1 in the United States

ABSTRACT. Transmission of human immunodeficiency virus type 1 (HIV-1) through breastfeeding has been conclusively demonstrated. The risk of such transmission has been quantified, the timing has been clarified, and certain risk factors for breastfeeding transmission have been identified. In areas where infant formula is accessible, affordable, safe, and sustainable, avoidance of breastfeeding has represented one of the main components of mother-to-child HIV-1 transmission prevention efforts for many years. In areas where affordable and safe alternatives to breastfeeding may not be available, interventions to prevent breastfeeding transmission are being investigated. Complete avoidance of breastfeeding by HIV-1-infected women has been recommended by the American Academy of Pediatrics and the Centers for Disease Control and Prevention and remains the only means by which prevention of breastfeeding transmission of HIV-1 can be absolutely ensured. This technical report summarizes the information available regarding breastfeeding transmission of HIV-1.

ABBREVIATIONS. HIV-1, human immunodeficiency virus type 1; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Pediatrics; CI, confidence interval; WHO, World Health Organization; UNICEF, United Nations Children's Fund; UNAIDS, the Joint United Nations Program on HIV/AIDS; OR, odds ratio; RR, relative risk; SLPI, secretory leukocyte protease inhibitor.

INTRODUCTION

The benefits of breastfeeding are well recognized and include significantly decreased infant morbidity and mortality rates by providing optimal nutrition, by protecting against common childhood infections such as gastrointestinal and respiratory tract infections, and by promoting child spacing.[1–6] Breastfeeding is particularly important in resource-poor regions of the world, where limited access to clean water increases the risk of diarrheal disease if replacement feeding is used. However, human immunodeficiency virus type 1 (HIV-1) is transmitted through human milk, leading to the dilemma that use of replacement feeding in resource-poor settings, although protecting the infant against HIV-1 infection, also could place the infant at risk of mortality from other infections. Shortly after the first report of transmission of HIV-1 through breastfeeding,[7] the Centers for Disease Control and Prevention (CDC) recommended that HIV-1-infected women in the United States avoid breastfeeding,[8] because replacement feeding is safe, affordable, and culturally acceptable. The CDC and the American Academy of Pediatrics (AAP)[9] have continued to recommend counseling HIV-1-infected women in the United States not to breastfeed or provide their milk for the nutrition of their own or other infants. Avoidance of breastfeeding remains an important component of mother-to-child HIV-1 transmission prevention efforts in the United States,[10] where perinatal transmission of HIV-1 has been substantially decreased.[11] However, in areas of the world where breastfeeding is the norm and safe replacement feeding generally is not possible, the enormous and unremitting epidemic of mother-to-child transmission of HIV-1 continues.[12] Research efforts focused on the continuing problem of breastfeeding transmission in much of the world have yielded additional information regarding mechanisms of HIV-1 transmission through breastfeeding as well as the timing of and risk factors for such transmission. This technical report summarizes the available information regarding transmission of HIV-1 through human milk. Complete avoidance of breastfeeding by HIV-1-infected women remains the only means by which prevention of breastfeeding transmission of HIV-1 can be absolutely ensured.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

EVIDENCE OF BREASTFEEDING TRANSMISSION OF HIV-1

Over nearly 2 decades, the understanding of mother-to-child HIV-1 transmission through breastfeeding has increased tremendously. Beginning with the earliest clinical evidence of breastfeeding transmission of HIV-1 (case reports), additional information regarding breastfeeding transmission has come from both other epidemiologic studies (descriptive and analytic) and laboratory studies.

Evidence From Epidemiologic Studies

Descriptive Studies

In 1985, Ziegler and colleagues[7] in Australia described the case of an HIV-1-infected infant who apparently acquired the infection after being breastfed by his previously healthy mother, who received a postpartum transfusion of HIV-1-contaminated blood. Over the next several years, this report was confirmed by other case reports from around the world.[13–26] In general, these case reports described acquisition of HIV-1 infection by children of breastfeeding mothers, with the mothers being at low risk of HIV-1 infection and presumed HIV-1-seronegative until acquisition of infection after delivery, usually through HIV-1-contaminated blood transfusions. On the basis of a case series of 10 breastfeeding women, the estimated risk of breastfeeding transmission among women with acquisition of HIV-1 infection after delivery was 27% (95% confidence interval [CI]: 6%–61%).[27] Because of viremia associated with primary infection with HIV-1 and the presumably high viral load concomitantly in human milk, women who breastfeed during primary infection with HIV-1 could represent a particularly high-risk group. Therefore, the generalizability of the implications of these case reports to breastfeeding women with HIV-1 infection acquired before delivery, who represent most HIV-1-infected breastfeeding women, was not clear. However, on the basis of these case reports and because of concern that women with chronic HIV-1 infection also could be at risk of transmitting HIV-1 to their infants through breastfeeding, in 1985 the CDC issued the recommendation that HIV-1-infected women avoid breastfeeding.[8]

Studies of mother-to-child transmission of HIV-1 in different countries around the world yielded transmission rates, in the absence of interventions to decrease transmission, ranging from 13% to 42%.[28] The finding that transmission rates were generally higher in countries where virtually all mothers breastfeed compared with countries such as the United States, where breastfeeding by HIV-1-infected women is unusual,[29,30] suggested the possibility that breastfeeding transmission accounted for some of the discrepancy in rates between different settings.

Observational, Analytic Studies

Higher rates of HIV-1 infection among breastfed children compared with formula-fed children were reported in several studies.[31–35] On the basis of a systematic review of published studies meeting criteria allowing the determination of the quantitative risk of breastfeeding transmission of HIV-1,[36] the estimated risk of transmission of HIV-1 through breastfeeding by mothers who acquired HIV-1 infection postnatally was 29% (95% CI: 16%–42%). Similar analysis of published studies with mothers who had chronic HIV-1 infection resulted in an estimated further risk of transmission through breastfeeding (in addition to in utero and/or intrapartum transmission) of 14% (95% CI: 7%–22%).

On the basis of the information available at the time, consensus statements from the World Health Organization (WHO) in 1987[37] and 1992[38] included recommendations that were intended to result in the greatest likelihood of prevention of infant mortality and of mother-to-child transmission of HIV-1 through breastfeeding in different regions of the world. These recommendations were that breastfeeding should be advised for women, including HIV-1-infected women, in areas of the world where most infant deaths were attributable to infections and malnutrition. In addition, it was recommended that in other areas of the world where infectious diseases were not the main causes of infant death, HIV-1-infected women be advised not to breastfeed but instead to use safe feeding alternative(s) for their infants.

Prospective cohort studies published in the mid-1990s[39–42] provided estimates of the excess risk of HIV-1 transmission attributable to breastfeeding ranging from 4% to 22%. In 1997[43] and 1998,[44–46] the WHO along with the United Nations Children's Fund (UNICEF) and the Joint United Nations Program on HIV/AIDS (UNAIDS) issued revised recommendations regarding breastfeeding and HIV-1 transmission. These recommendations called for giving women access to HIV-1 counseling and testing as well as information that would allow them to make fully informed decisions regarding infant feeding.

Interventional, Analytic Study

A randomized clinical trial of breastfeeding versus formula feeding among HIV-1-infected women in Kenya demonstrated HIV-1 transmission through breastfeeding.[47] This trial enrolled 425 HIV-1-infected pregnant women. Compliance was higher in the breastfeeding arm (any use of human milk, 96%) compared with the formula-feeding arm (complete avoidance of human milk, 70%). The median duration of breastfeeding was 17 months. The cumulative probability of HIV-1 infection in the children at 24 months of age was significantly higher in the breastfed children (36.7% [95% CI: 29.4%–44.0%] in the breastfeeding arm vs 20.5% [95% CI: 14.0%–27.0%] in the formula-feeding arm [$P = .001$]). Most breastfeeding transmission occurred early (75% by 6 months of age), but transmission continued throughout the duration of human milk exposure.

Individual Patient Data Meta-analysis

The objectives of the Breastfeeding and HIV-1 International Transmission Study, a meta-analysis of individual patient data from randomized, placebo-controlled clinical trials conducted in Africa, are to estimate the contribution of breastfeeding to the overall risk of mother-to-child transmission of HIV-1, to clarify the timing of breastfeeding transmission, and to identify determinants of late postnatal transmission through breastfeeding.[48] The large sample size and the application of uniform definitions across trials in this meta-analysis should provide more reliable and precise estimates than have previous studies of the risk and timing of late postnatal transmission of HIV-1 through breastfeeding.

Laboratory Studies

Early reports indicated HIV-1 could be detected in human milk from HIV-1-infected women.[49–52] Subsequent studies confirmed the detection of HIV-1 in human milk as both cell-free virus and cell-associated virus.[53–56] HIV-1 proviral DNA has been detected in human milk cells in 44% to 58% of samples in different studies,[53,55–58] with detection of HIV-1 DNA associated with lower maternal $CD4^+$ cell counts and severe deficiency of vitamin A (a micronutrient deficiency associated with diminished epithelial integrity and systemic immunity).[59] In a study in Kenya, cell-free virus (HIV-1 RNA) was detectable in 39% of human milk samples,[60] with the prevalence being higher in mature milk (47%) than in colostrum (27%). A higher human milk viral load is associated with a higher risk of mother-to-child transmission.[61,62] In South Africa, HIV-1 RNA was detectable in 63% of samples, with higher human milk viral load being associated with a greater risk of transmission of HIV-1 to the infant (odds ratio [OR] = 2.82 [95% CI = 1.22%–6.51%] for each log increase in viral load).[63] Similarly, a higher plasma viral load is associated with higher probability of breastfeeding transmission per liter of milk ingested by the infant.[62] The viral load in different body fluids (plasma, human milk, and genital secretions) is correlated.[64]

RISK FACTORS FOR BREASTFEEDING TRANSMISSION OF HIV-1

Because breastfeeding transmission of HIV-1 does occur, and because avoidance of breastfeeding is impossible in many settings, identification of risk factors for transmission of HIV-1 through breastfeeding is important to design interventions to prevent such transmission. Potential risk factors for breastfeeding transmission of HIV-1 include duration of breastfeeding as well as characteristics of the mother, the infant, and the human milk or type of breastfeeding (Table 1).

Duration of Breastfeeding

The cumulative risk of breastfeeding transmission of HIV-1 has been estimated. In a study conducted in Malawi, the cumulative risk of infection for infants of HIV-1-infected mothers continuing to breastfeed after 1 month of age was 3.5% at the end of 5 months, 7.0% at the end of 11 months, 8.9% at the end of 17 months, and 10.3% at the end of 23 months.[65] A pooled analysis of individual data from prospective cohort studies of HIV-1-infected women and their children[66] incorporated data from studies in Rwanda, the Ivory Coast, and Kenya, where breastfeeding is the norm. Late postnatal transmission (defined as acquisition of HIV-1 infection after 2.5 months of age) occurred among 49 of 902 children (5%). The overall estimated risk of breastfeeding transmission was 3.2% per 100 child-years of breastfeeding (95% CI: 3.1%–3.8%). With information regarding the timing of breastfeeding transmission available for 20 of the 49 children, the cumulative probability of acquisition of late postnatal transmission was 0.6% (95% CI: 0.2%–2.2%) at 6 months of age, 0.95% (95% CI: 0.4%–2.5%) at 9 months of age, 2.5% (95% CI: 1.3%–4.7%) at 12 months of age, 6.3% (95% CI: 3.9%–9.95%) at 18 months of age, 7.4% (95% CI: 4.5%–12.1%) at 24 months of age, and 9.2% (95% CI: 5.3%–15.5%) at 36 months of age. Differences in the cumulative risk of transmission between these 2 studies could be related to different definitions of late postnatal transmission (acquisition after 1 month of age in the Malawi study and after 2.5 months of age in the pooled analysis).

Longer durations of breastfeeding by mothers infected with HIV-1 are associated with an increased risk of HIV-1 transmission to their infants. In Italy,[35] univariate analyses suggested a higher likelihood of HIV-1 infection among breastfed children (compared with bottle-fed children), with an increasing likelihood of HIV-1 infection with increasing duration of breastfeeding (OR = 2.16 [95% CI: 1.17%–4.00%] for children breastfed for 20 days or less, increasing to OR = 6.41 [95% CI: 2.98%–13.79%] for children breastfed more than 92 days). In a small study in South Africa, a 15% increased risk of HIV-1 transmission was observed with breastfeeding compared with formula feeding, and the data suggested higher transmission rates with longer durations of breast-

TABLE 1. Potential Risk Factors for Human Milk Transmission of HIV-1

Category	Risk Factor
Duration of breastfeeding	Longer duration
Maternal characteristics	Younger age
	Higher parity
	Lower $CD4^+$ count
	Higher peripheral blood viral load
	Breast abnormalities
	Breast abscess
	Mastitis
	Nipple lesions
Infant characteristics	Oral candidiasis
Human milk characteristics	Higher viral load
	Lower concentrations of antiviral substances (eg, lactoferrin, lysozyme, SLPI, epidermal growth factor)
	Lower concentration of virus-specific cytotoxic T-lymphocytes
	Lower secretory IgA
	Lower IgM
Exclusivity of breastfeeding	Mixed breastfeeding

IgA indicates immunoglobulin A, IgM, immunoglobulin M.

feeding.[67] In a meta-analysis of published data from prospective cohort studies of HIV-1-infected women and their children,[68] 499 HIV-1-infected women who breastfed their children were identified. The estimated risk of breastfeeding transmission of HIV-1 was 16% (95% CI: 9%–22%). Among breastfed infants, 47% of HIV-1 infections were attributable to breastfeeding. Breastfeeding transmission occurred in 21% (10%–22%) of those who breastfed for a median length of 3 or more months and 13% (95% CI: 4%–21%) among infants who breastfed for a median of less than 2 months.

Characteristics of the Mother and Infant

Characteristics of the mother and infant have been associated with increased risk of breastfeeding transmission of HIV-1. Maternal factors associated with breastfeeding transmission of HIV-1 include younger maternal age and higher parity,[65] maternal HIV-1 disease stage, and breast abnormalities. More advanced maternal disease stage, as manifested by low $CD4^+$ cell counts, is a risk factor for postnatal transmission of HIV-1,[61,63,69] along with higher maternal peripheral blood or human milk viral load.[61–63] An early case report of the temporal association of acquisition of HIV-1 infection by the child of an HIV-1-infected woman with a breast abscess suggested the ingestion of inflammatory cells related to the bacterial infection of the breast contributes to breastfeeding transmission of HIV-1.[70] Later studies confirmed the association of transmission of HIV-1 through breastfeeding with maternal breast abnormalities, such as breast abscesses, mastitis, and nipple lesions. In Kenya, mastitis and breast abscesses were associated with late postnatal transmission of HIV-1 (relative risk [RR] = 21.8 [95% CI: 2.3%–211.0%] and RR = 51.6 [95% CI: 4.7%–571.0%], respectively).[68] In Malawi, women with increased human milk sodium concentrations consistent with subclinical mastitis had higher human milk viral loads than did women without increased human milk sodium concentrations.[61] In another study in Kenya, maternal nipple lesions (OR = 2.3 [95% CI: 1.1%–5.0%]) and mastitis (OR = 2.7 [95% CI: 1.1%–6.7%]) were each associated with an increased risk of postnatal transmission.[69] Oral candidiasis before 6 months of age is associated with late postnatal transmission (OR = 2.8 [95% CI: 1.3%–6.2%]).[69] Results of a study in the Ivory Coast suggested maternal breast abscesses and cracked nipples, as well as oral candidiasis in infants, were risk factors for late postnatal transmission of HIV-1 through breastfeeding.[42]

Characteristics of Human Milk or Type of Breastfeeding

In addition to higher human milk viral load, characteristics of human milk possibly associated with a higher risk of breastfeeding transmission of HIV-1 include lower concentrations of antiviral substances, such as lactoferrin,[71,72] lysozyme, secretory leukocyte protease inhibitor (SLPI),[73] and epidermal growth factor,[74] as well as lesser specific, local immune responses to HIV-1. Interestingly, HIV-1-infected women with subclinical mastitis, higher human milk viral loads, and higher rates of mother-to-child transmission had higher human milk concentrations of lysozyme and SLPI than did HIV-1-infected women without subclinical mastitis.[75] However, SLPI concentrations in human milk have not been found by other investigators to be associated with HIV-1 transmission through breastfeeding.[76] It has been suggested that epidermal growth factor in colostrum helps to make the gastrointestinal tract less permeable to viral infection.[74] Higher mother-to-child transmission of HIV-1 has been associated with lower human milk concentrations of secretory immunoglobulin A and immunoglobulin M during the first several weeks of life in some[55] but not all studies.[77]

When feeding patterns among infants born to HIV-1-infected women in Brazil were analyzed, neither a history of colostrum intake nor a history of mixed feeding (human milk with other milk, tea, or juice) was associated with transmission.[78] However, in South Africa, data from a randomized clinical trial of vitamin A supplementation to prevent mother-to-child transmission were reanalyzed to evaluate a possible association between feeding patterns among infants of breastfeeding HIV-1-infected mothers and mother-to-child transmission.[79,80] In this study, breastfeeding was categorized as exclusive or mixed (ie, without or with water, other fluids, and food). Women who chose to breastfeed were counseled to consider exclusive breastfeeding. Follow-up visits after birth, during which an infant feeding history was obtained, occurred at 1 week, 6 weeks, and 3 months of age and every 3 months thereafter. By 15 months of age, children who ever breastfed were more likely to have become HIV-1-infected (31.6%) than were children who never breastfed (19.4% [$P = .007$]). Of children who ever breastfed, those who exclusively breastfed until at least 3 months of age but no longer than 6 months of age had a lower estimated transmission point estimate than did those with mixed feeding, but the confidence limits for these point estimates overlap (exclusive: 24.7% [95% CI: 16.0%–34.4%]; mixed: 35.9% [95% CI: 26.7%–45.1%]). The authors proposed that the mechanism of their findings was that contaminated fluids and foods given to infants with mixed breastfeeding damaged the bowel and facilitated the entry of HIV-1 into tissues. The results of this hypothesis-generating study have prompted several investigators to pursue new studies of exclusive breastfeeding to assess more carefully the risk of HIV-1 transmission according to feeding modality.

POTENTIAL INTERVENTIONS TO PREVENT BREASTFEEDING TRANSMISSION OF HIV-1

There are several potential interventions to prevent breastfeeding transmission of HIV-1 (Table 2). The first is conceptually the simplest: complete avoidance of human milk. If breastfeeding does occur, several interventions could potentially prevent transmission of HIV-1 through human milk. First, early weaning (eg, at 6 months of age) will limit the duration of exposure to human milk. Other interventions to potentially prevent breastfeeding transmis-

TABLE 2. Proven or Potential Interventions to Prevent Human Milk Transmission of HIV-1

Risk Factor for Transmission	Associated Intervention
Longer exposure to human milk from an HIV-1-infected woman	Complete avoidance of breastfeeding Early weaning
Greater maternal infectivity (eg, higher maternal viral load in peripheral blood and in human milk)	Maternal antiretroviral therapy while breastfeeding
Factors facilitating viral transfer from mother to child (eg, mixed breastfeeding)	Avoidance of mixed breastfeeding (encouragement of exclusive breastfeeding)
Infant susceptibility to infection	Improvement of infant defenses against infection (eg, with passive immunization or with antiretroviral prophylaxis to breastfeeding infants)

sion of HIV-1 can be categorized as follows: decreasing human milk viral load (eg, with maternal antiretroviral therapy or by treating human milk by pasteurization or other means), preventing or treating factors facilitating transfer of HIV-1 from mother to child (eg, preventing or treating maternal breast abnormalities and infant candidiasis, avoiding mixed breastfeeding), and improving infant defenses against HIV-1 infection (eg, by passive or active immunization or antiretroviral prophylaxis to breastfeeding infants). Recent WHO recommendations[81] reaffirm previous recommendations for all HIV-1-infected mothers to receive counseling, including provision of general information about risks and benefits of various infant feeding options and specific guidance in selecting the option most likely to be suitable for their situation, and call for mothers to be supported in the their choices regarding their infants' feeding.

Complete Avoidance of Breastfeeding

Complete avoidance of breastfeeding (eg, by using infant formula) is an intervention of obvious utility in settings where it is feasible (ie, where clean water is available), affordable, and culturally acceptable. The randomized clinical trial of breastfeeding versus formula feeding demonstrated breastfeeding by HIV-1-infected women causes more mother-to-child transmission than does formula feeding.[47] However, although transmission of HIV-1 was much higher in the children of women randomized to breastfeeding versus formula feeding (36.7% vs 20.5% at 2 years of age [$P = .001$]), the 2 groups experienced similar rates of mortality during the first 2 years of life.[82] Mortality rates at 24 months of age were 24.4% (95% CI: 18.2%–30.7%) among children whose mothers were randomized to breastfeeding and 20.0% (95% CI: 14.4%–25.6%) among those children whose mothers were randomized to formula feeding. Additionally, infants in the breastfeeding arm had better nutritional status than did those in the formula feeding arm, particularly during the first 6 months of life, although the overall prevalence of malnutrition was not different in the 2 study groups. The better growth of breastfed infants during the first 6 months of life highlights the importance of nutritional counseling for mothers who decide to give formula to their children, and the WHO recommends that HIV-1-infected women who decide not to breastfeed their children should receive specific guidance and support during at least the first 2 years of their children's lives to ensure adequate replacement feeding.[81]

Interventions Among Breastfeeding Women

Before considering specific interventions to prevent breastfeeding transmission of HIV-1, it is important to consider the potential effects of breastfeeding on the HIV-1-infected woman herself. One such potential effect is an increased mortality rate among breastfeeding HIV-1-infected women.

Potential Consequences of Breastfeeding for the Mother

The results of 2 studies evaluating the risk of mortality among HIV-1-infected women according to infant feeding modality (breastfeeding compared with formula feeding) have been conflicting. Data from the randomized clinical trial of breastfeeding versus formula feeding in Kenya were analyzed to assess maternal mortality according to infant feeding modality.[83] Analysis of maternal mortality was by intention to treat (ie, by randomized assignment of mothers to breastfeeding or formula feeding). Maternal mortality over the 2-year period after delivery was higher among those in the breastfeeding group (18 deaths among 197 [9%]) compared with those in the formula feeding group (6 deaths among 200 [3%]; $P = .009$). The cumulative probability of maternal death at 24 months after delivery was 10.5% in the breastfeeding group and 3.8% in the formula group ($P = .02$). The relative risk of death for mothers assigned to breastfeeding compared with those assigned to formula feeding was 3.2 (95% CI: 1.3%–8.1% [$P = .01$]), and the attributable risk of maternal death attributable to breastfeeding was 69%. There were significant associations between $CD4^+$ lymphocyte counts and maternal death as well as between viral load and maternal death. The authors hypothesized that a combination of the metabolic demands of breastfeeding on HIV-1-infected women (who already might have borderline nutritional status) and of HIV-1 infection itself could be associated with substantial nutritional impairment, which could result in an increased risk of death. Indeed, women in the breastfeeding group had greater weight loss after delivery than did women in the formula-feeding group.

Data from a second study, a randomized clinical trial of vitamin A supplementation in South Africa, were analyzed to assess maternal mortality among HIV-1-infected women according to infant feeding modality (breastfeeding or not breastfeeding).[84] In this trial, mothers chose whether to breastfeed or not (ie, there was no randomization regarding infant

feeding modality). Of 566 mothers whose data were analyzed, 410 breastfed their infants and 156 never breastfed. No differences in maternal mortality rates according to infant feeding modality were observed. Over a mean follow-up period after delivery of 10 months, 0.49% (2 of 410) of women who ever breastfed were known to have died, compared with 1.92% (3 of 156) of those who never breastfed. Morbidity among those who breastfed for more than 3 months was similar to that of women who breastfed for less than 3 months.

The reasons for the differences in the results of these 2 studies are not clear, and additional research is needed in this area. With a pooled sample size of several thousand HIV-1-infected women, the Breastfeeding and HIV-1 International Transmission Study[48] represents a unique resource for further exploration of the issue of maternal mortality and infant feeding modality.

Early Weaning

If complete avoidance of human milk is not possible, early weaning from human milk (eg, at 6 months of age), if feasible, would limit exposure to HIV-1-infected human milk while allowing the child to experience benefits of breastfeeding. Human milk provides sufficient nutritional requirements for optimal growth and development for approximately the first 6 months of life[85–87] (although vitamin D and iron supplementation may be required before 6 months of age in some infants[88]). Although human milk remains a valuable source of nutrition for many months thereafter, it is possible for children to be weaned successfully from human milk and provided other sources of nutrition after 6 months of age. The increased risk of morbidity and mortality associated with replacement feeding (because of malnutrition and infectious diseases other than HIV-1) is especially high during the first 6 months of life and decreases in magnitude thereafter.[89] Assessment of the feasibility of early weaning involves consideration of an individual woman's situation and local circumstances. For many women, early weaning of their children from human milk is not possible because of financial or other constraints. Early weaning from human milk is being evaluated in trials in Zambia[90] and Botswana.[91] The WHO recommends that HIV-1-infected women who decide to wean their children from human milk early receive specific guidance and support during at least the first 2 years of their children's lives to ensure adequate replacement feeding.[81]

Decreasing Viral Load in Human Milk

Maternal Antiretroviral Therapy

Several studies in Africa are planned to evaluate antiretroviral therapy for HIV-1-infected women during breastfeeding for the prevention of breastfeeding transmission of HIV-1. In observational and interventional studies, the effectiveness and efficacy of maternal combination antiretroviral therapy for prevention of mother-to-child transmission, especially breastfeeding transmission, will be assessed.

Treating Human Milk

Treatment of human milk with chemical agents or heat to inactivate HIV-1 has been investigated. Sodium dodecyl sulfate, a microbicidal agent active against HIV-1 and other viruses, does not alter protein content of human milk and can be efficiently removed from human milk samples.[92] In one study, allowing expressed human milk to stand at room temperature for 6 hours did not destroy proviral DNA, but boiling expressed human milk appeared to decrease HIV-1 infectivity of the milk.[93] Pasteurization of human milk,[94,95] including using devices that can be used in a home setting,[96–98] can decrease the infectious titer of cell-free HIV-1 and HIV-1-infected cells by more than 5 logs and 6 logs, respectively.[95] Use of any or all of these methodologies would not be feasible in many settings and may not be culturally acceptable. Additionally, although they decrease human milk viral load, these methodologies are unlikely to eliminate HIV-1 from milk completely. Finally, with any treatment to inactivate HIV-1, the extent to which the treatment diminishes the protective or nutritional components of human milk must be carefully assessed.

Preventing or Treating Factors Related to Facilitation of Transfer of HIV-1 From Mother to Child

Preventing or Treating Maternal Breast Abnormalities and Infant Candidiasis

In light of the evidence of the association of maternal breast abnormalities and breastfeeding transmission, the WHO recommends that HIV-1-infected women who breastfeed receive education and counseling to ensure good breastfeeding technique to decrease the risk of development of such conditions, and if such conditions arise, be treated as quickly and completely as possible.[81] Similarly, infant candidiasis should be treated promptly. One program underway in Zimbabwe involves education of women who choose to breastfeed. Individual counseling, if provided, concerns the following subjects: exclusive breastfeeding until the infant is 4 to 6 months of age followed by rapid weaning, proper positioning during breastfeeding, prompt seeking of medical care if breast abnormalities develop or if the infant develops oral candidiasis or other lesions, avoiding breastfeeding from a breast affected by abnormalities, and safe sex practices while breastfeeding.

Avoiding Mixed Breastfeeding

Exclusive breastfeeding during the first 4 to 6 months of life is associated with greater benefits than is mixed feeding in terms of morbidity and mortality from infectious diseases other than HIV-1.[99,100] The suggestive, but not definitive, results of analyses of feeding modality among breastfeeding children of HIV-1-infected women indicating a lower risk of transmission with exclusive breastfeeding compared with mixed breastfeeding[79,80] have prompted the development of additional studies[90,91] to evaluate further the role of exclusive versus mixed breastfeeding in vertical transmission of HIV-1. However, exclusive breastfeeding is not the norm in Africa and other

parts of the world. For example, only approximately half of Indian children younger than 4 months of age are exclusively breastfed.[101] In Zimbabwe, only 39% of infants were exclusively breastfed during the first 3 months of life, and only 7% were exclusively breastfed between 4 and 6 months of age.[102] Despite this, programs to promote exclusive breastfeeding have had some success. For example, the prevalence of exclusive breastfeeding at 5 months of age increased from 6% to 70% with home-based counseling by peer counselors (mothers from the local community with training for 10 days) in Bangladesh.[103] The Section on Breastfeeding of the American Academy of Pediatrics supports exclusive breastfeeding for approximately the first 6 months after birth.[87]

Improving Infant Defenses Against HIV-1 Infection

Passive Immunization

In some animal studies, the presence of circulating antibodies to HIV-1 in infants has been associated with a decreased risk of mother-to-child transmission of HIV-1.[104–108] Therefore, it has been hypothesized that passive immunization with anti-HIV-1 antibodies may decrease the likelihood of mother-to-child transmission of HIV-1 in humans. A clinical trial of HIV-1 immune globulin was conducted in the United States, but because of the unexpectedly low mother-to-child transmission rate among the study population with universal receipt of zidovudine prophylaxis, this trial was discontinued early.[109] Another randomized clinical trial of HIV-1 immune globulin with nevirapine versus 2 different regimens of nevirapine is planned in Uganda.

Active Immunization

Research regarding active immunization of infants to prevent postnatal acquisition of HIV-1 infection through breastfeeding is ongoing. Infant studies to evaluate the safety and immunogenicity of HIV-1 vaccines are underway in the United States and are planned in Africa.[110] Because no vaccine will produce immediate immunity, the goal is to provide protection against early postnatal transmission through administration of antiretroviral drugs or through passive immunization of the infant until an adequate immune response is induced in the infant by the HIV-1 vaccine.

Antiretroviral Prophylaxis to Breastfeeding Infants

The efficacy of continued administration of antiretroviral prophylaxis to breastfeeding infants is being investigated in several studies in India and different parts of Africa. These studies are evaluating administration of different antiretroviral drugs to the infant for varying lengths of time. Antiretroviral drugs being evaluated include zidovudine, lamivudine, and nevirapine. The planned duration of infant prophylaxis in these studies ranges from 1 week to 6 months of age. Preliminary results of some of these studies have been released.[91,111–113]

CONCLUSIONS

HIV-1 transmission through breastfeeding has been demonstrated conclusively. Additionally, the risk of such transmission has been quantified, the timing has been clarified, certain risk factors for breastfeeding transmission have been identified, and interventions to prevent breastfeeding transmission are being developed. Additional research is needed to characterize more completely the mechanism(s) of human milk transmission of HIV-1. Complete avoidance of breastfeeding by HIV-1-infected women remains the only means by which prevention of breastfeeding transmission of HIV-1 can be absolutely ensured. In settings such as the United States, with virtually universal access to clean water and with widespread cultural acceptance of formula feeding as an alternative to breastfeeding, avoidance of breastfeeding by HIV-1-infected women is possible. In other parts of the world where breastfeeding is the norm, affordable, feasible, and culturally acceptable interventions to decrease the risk of breastfeeding transmission of HIV-1 are urgently needed.

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