Breast-Feeding and HIV Transmission in Developing Countries

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By Grace John-Stewart, MD, MPH, PhD; Ruth O. Levine, MA; and Marcia Weaver, PhD

Introduction

Breast-Feeding: A Public Health Paradox

Breast-feeding is a basic and extremely successful component in child survival, but it takes on another significance in countries with high HIV prevalence. Although the mechanisms of transmission are not well defined, it is now known that HIV can be transmitted from mother to child via breast-feeding. Therefore, a mother with HIV infection and her spouse must weigh the pluses and minuses of breast-feeding against alternative infant-feeding options, which in many parts of the developing world, can be less-than-perfect alternatives.

Dr. Grace John-Stewart has counseled pregnant women in Nairobi, Kenya, on infant feeding practices for several years. Counseling in a country with high HIV prevalence is an intensive, demanding process. It involves multiple visits to clinics; the attention of on-staff nutritionists; and an understanding of each individual's HIV status, infant feeding preferences, housing situation, and finances. A woman's infant-feeding choices may be surprising. Some women with HIV infection may have the resources to use infant formula, but they will breast-feed to hide their HIV status. Some women may not have clean water or the other essentials to prepare hygienic formulas, but they are desperate to try another path after a child has died.

The World Health Organization Technical Consultation Group (2000) recommended that women with HIV infection practice replacement feeding when possible, in which she feeds her infant commercial or home-prepared formula rather than breast milk. When replacement feeding is neither feasible nor safe, mothers are encouraged to exclusively breast-feed; that is, to provide only breast milk or expressed breast milk, for the first three to six months. Weaning is advised as soon as it is physically and emotionally realistic to do so, in order to reduce the possibility of HIV transmission. Underlying these recommendations is the concept of informed choice: providing women with counseling on the benefits and risks associated with exclusive breast-feeding and formula-feeding, and supporting their decisions in whatever ways possible.

> The median age [of a mother with HIV infection] is 24; they never thought they were at risk for HIV; they go to the pregnancy clinic happy they are having a baby, and then they are diagnosed with HIV, which they didn't expect. They cope with all these things: Are they going to die? What's going to happen to their baby? Should they tell their husband? And this is a time at which within a few weeks, you are trying to talk with them about [infant] feeding.
>
> Grace John-Stewart

At the heart of this issue is the need for information that will help pregnant women with HIV infection arrive at a difficult and personal decision about infant feeding. But this is too simple a picture. Mother-to-child transmission prevention programs are relatively new, and they face practical challenges in their implementation and operation, including those of adequate staffing and training, supplies of free or subsidized infant formula, and access to HIV testing facilities and antiretroviral drugs. In the background—driving the public discussion—are two impassioned, polarized camps of advocates: those pressing for exclusive breast-feeding, and those urging formula-feeding. Both are deeply concerned with child survival and maternal health.

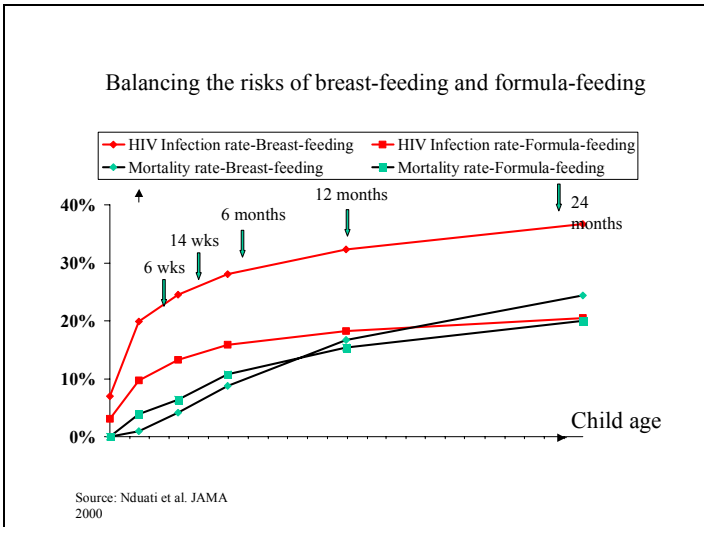
In this paper we examine two recent studies in an attempt to deepen our understanding of the issues involved.

Current State of Research

Infant Feeding: New Findings from Africa

Two studies on infant feeding, one in Kenya and the other in South Africa, have generated much interest. Their findings may at first appear contradictory, but together they help paint a more detailed picture about the benefits of exclusive feeding, the safety of formula feeding, and the risks of mixed feeding, or providing both breast milk and other liquid and solid foods to infants. [Note: Although the World Health Organization (WHO) has reviewed the data in both studies, it has not altered its infant feeding recommendations based on the findings. WHO does, however, urgently call for additional research in these areas.]

Figure 1. Infant HIV infection and mortality rates.



Kenya

Nduati and colleagues (2000) found that 44 percent of HIV-1 infections in breast-feeding infants were attributable to breast-feeding and could therefore have been avoided by formula-feeding.

During a 1992–98 clinical trial, researchers assigned 401 mothers with HIV-1 infection at random to two groups, and were asked to either breast-feed or formula-feed their children. The 401 mother-infant pairs were followed for an average of two years. The group of formula-fed infants, compared with the breast-fed infants, had a lower cumulative probability of HIV-1 infection at two years (21 percent vs. 37 percent) and a higher rate of remaining HIV-negative and alive (70 percent vs. 58 percent). Figure 1 shows the benefit of formula-feeding in this particular study population.

The rate of HIV-1 transmission via breast milk was estimated to be 16.2 percent in an infant's first two years, with the majority of HIV-1 infections occurring in the first six months. Because compliance was only 70 percent in the formula-fed group, indicating that some mothers were also breast-feeding, the rate of HIV-1 transmission via breast milk could be higher than estimated.

These results are disquieting, partly because six months of locally produced dried milk formula costs the equivalent of US$300 (slightly less than the average annual salary in Kenya), and is beyond the financial reach of many women unless they receive it free or at subsidized prices.

The Mechanics of HIV Transmission

Children may become infected with HIV while in the uterus, during delivery, or during breast-feeding. Breast-feeding accounts for one-third to one-half of all mother-to-child HIV-1 infections (Fowler and Newell 2002).

Women with established HIV disease who breast-feed have a 14 percent risk of transmitting HIV infection to their children (Van de Perre 1999), whereas women who become infected with HIV during breast-feeding have a 29 percent risk of transmission (Fowler and Newell 2002).

HIV exists as a free-floating virus in breast milk and in the cells of the lining of the breast ducts. Little is known about the biological process and timing of how HIV is transmitted from mother to child.

Several factors associated with increased transmission risks have been identified, including the level of detectable HIV in the breast milk, maternal CD4 count, mastitis (inflammation of the breast), bleeding nipples, and breast abscesses (John et al. 2001; Fowler and Newell 2002).

Whereas the risk of HIV-1 infection was significantly lower for formula-fed infants, the data cannot be generalized outside of the study population, because all enrolled mothers had access to clean water and formula preparation instructions. A primary concern with formula feeding is the risk of diarrhea and related illness or death, resulting from bacteria introduced during preparation of formula or from unclean water.

On the basis of these study findings, the same group of researchers wanted to more closely examine formula feeding to determine whether the benefits of formula feeding would be outweighed by the risks associated with not breast-feeding. Breast-feeding guards against infant illness and death and confers protective antibodies from the mother. Mbori-Ngacha et al. (2001), using the same study population, determined that formula-fed and breast-fed infants had similar mortality rates (20 percent and 24.4 percent at two years), a similar incidence of diarrhea (155 and 149 incidents per 100 person-years), and an identical incidence of pneumonia (62 per 100 person-years), but breast-fed infants overall had faster growth and weight increase, particularly in the first six months.

Nduati and colleagues (2001) also explored the effect of breast-feeding on maternal death rates in the same study. The cumulative probability of maternal death at two years was 3.8 percent among those who fed their children formula versus 10.5 percent for those who breast-fed, representing a threefold increased risk of death. Researchers determined that breast-feeding may have contributed to 69 percent of the deaths among women who were breast-feeding and hypothesized that the higher mortality may be related to the demands of producing breast milk, insufficient food intake, or a higher basal metabolic rate, as caused by HIV-1 infection. A significant association was also found between maternal death and high viral loads and low CD4 counts at the time of study enrollment. Two study limitations are the small number of deaths (24 out of 425 enrollees), and the percentage of enrollees lost to follow up.

South Africa

Coutsoudis et al. (2001b) found substantially higher rates of HIV infection in children who consumed a mixture of breast milk and other liquid and solid foods than in children who were exclusively breast-fed for at least three months or in children who were exclusively formula-fed. This observational study of 551 mother-child pairs was part of a randomized clinical trial exploring the effects of vitamin A on mother-to-child transmission of HIV. Unlike the study in Kenya, women were not randomized to breast-feed or formula-feed; instead, women self-selected their feeding method. Enrollees in the Durban, South Africa study were followed for 15 months between 1995 and 1998.

At six months, the cumulative probability of HIV detection was higher in children who received a mixed feeding (a combination of breast milk and other liquid or solid foods), than in those who were fed breast milk or formula exclusively. It is interesting and important in light of the Kenya study that researchers found that children who were breast-fed or formula-fed exclusively shared the same cumulative probability of HIV detection at six months.

By 15 months, children who received a mixed feeding, as compared with children who were exclusively breast-fed, were at significantly higher risk for HIV infection. Although the reason for the higher transmission rate among mixed-fed children is unknown, researchers hypothesize that children who receive a mixture of breast milk and other foods experience irritation to their bowels and the lining of the gut, and that this disturbed mucosal surface then becomes vulnerable to HIV infection. Alternatively, children may not be accessing the full protective effect of breast milk when they receive a mixed feeding.

In contrast to the Kenya findings that breast-feeding is associated with increased maternal mortality, Coutsoudis et al. (2001a) found no evidence pointing to higher mortality or illness rates for HIV-positive women who fed their children breast milk versus those who fed their children formula.

The Frontier: Mother-to-Child Transmission, Breast-Feeding, and Antiretrovirals

Intensive antiretroviral (ARV) therapy proved successful in reducing mother-to-child transmission of HIV in trials conducted in the United States and Europe in the mid 1990s. In developing countries, the cost and lack of access to drugs limits the availability of multiple-drug or long-term ARV therapy. Working within these constraints, researchers discovered in a 1998 trial in Thailand that a short-course ARV regimen was effective in reducing HIV transmission from mother to child in women who did not breast-feed. This was one of several relatively simple ARV regimens that has proven effective in reducing mother-to-child transmission of HIV.

The underlying concept is that women who take ARVs late in their pregnancy, and during labor and delivery, will significantly reduce their viral load and reduce the possibility of HIV transmission through blood or genital fluids. In some cases, infants are also administered ARVs in a single dose or for the first week of life, in the hope of destroying any virus transmitted during birth. Short-course maternal ARV regimens have become widely accepted as an HIV prevention strategy.

However, children of mothers with HIV-1 infection continue to be exposed to the virus after delivery if they breast-feed. Several large-scale mother-to-child transmission trials in sub-Saharan Africa have found that over time, breast-feeding erodes the initial benefits of ARVs. (Figure 2 describes three of these drug regimens and their efficacy rates in detail.)

The Petra Study Team (2002) reported a randomized, placebo-controlled trial in which 1,457 pregnant women with HIV-1 infection in South Africa, Tanzania, and Uganda were followed between 1996 and 2000, and in which HIV infection and mortality in children were calculated at 6 weeks and 18 months. Women were randomized to receive different regimens of zidovudine or lamivudine. At six weeks, Regimen A, the most successful of the three, reduced HIV-1 transmission by 63 percent. By 18 months, the effect of the combination therapy on HIV transmission was reduced, which researchers attributed to breast-feeding. Children in the Regimen A trial had an 18.9 percent cumulative incidence of HIV-1 infection or death, whereas the cumulative incidence for those in the placebo group was 25.6 percent.

Drug Therapy and Viral Bursts

Van de Perre and colleagues (2001) were curious about the difference in long-term efficacy results between those of the Petra Study Team, which used a combination of zidovudine and lamivudine drug therapy, and monotherapy drug trials. They speculate that one probable cause of the lowered efficacy rates in the Petra study may be a temporary surge in viral load immediately after drug therapy is discontinued. The more efficacious the drug therapy, they reason, the higher the viral rebound. While this viral burst does not necessarily affect the mother, it may increase the transmissibility of HIV, placing infants at risk for infection just as they are beginning to breast-feed.

Dr. Grace John-Stewart outlines the type of speculative questions that arise around the possibility of a viral rebound. If an aggressive combination therapy approach is used, as compared to single-drug regimens, will breast-feeding infants be at additional risk? If a woman discontinues therapy abruptly, perhaps returning home to her rural area, is there danger of a viral rebound? There are also unknowns related to drug efficacy and drug adherency issues: For example, how will short-course drug regimens that women are taking now to protect their children from HIV infection affect drug effectiveness once women have access to long-term ARV therapy for their own disease?

As a beginning point, a study is underway in Burkina Faso to more closely examine the viral load and natural history of HIV-1 in breast milk after women stop taking oral zidovudine (Van de Perre, 1999).

In another set of drug therapy trials, researchers found a distinct difference in drug efficacy based on maternal CD4 cell count. Leroy and colleagues (2002) analyzed data from two randomized controlled trials conducted in Abidjan, Côte d'Ivoire, and Bobo-Dioulasso, Burkina Faso, between 1995 and 1998. In one trial, women with HIV-1 infection were given oral zidovudine or a placebo during late-stage pregnancy and delivery, and

in the other trial, zidovudine drug therapy was extended for an additional week after delivery. Researchers followed 629 children for two years and found that the zidovudine regimen reduced the estimated cumulative risk of HIV-1 infection in breast-fed children at 24 months by 26 percent. For women with less-advanced HIV disease (or CD4 cell counts ≥500/mL), the regimen had an even more dramatic effect, whereas for women with advanced HIV-1 disease, the estimated cumulative risk of HIV-1 infection was similar to that of the placebo group.

Guay and colleagues (1999), in a large-scale study in Kampala, Uganda, during 1997–99, assigned 626 pregnant women with HIV-1 infection at random to one of two groups, to receive either nevirapine or zidovudine during delivery. From other studies, it is now clear that unlike zidovudine short-course therapy, administered a month before delivery, zidovudine administered at delivery and after is minimally effective. Thus, a comparison of nevirapine to this regimen of zidovudine is similar to comparing nevirapine to a placebo. At 14–16 weeks, the estimated HIV-1 transmission risk in the nevirapine group was 13.1 percent, and in the zidovudine group it was 21.3 percent. Nevirapine, a drug that is low in cost and easy to administer, holds much hope. Follow-up data collected at 18 months shows nevirapine's continued efficacy. In addition, in contrast to the observation in West Africa, the efficacy of nevirapine was highest in women with immunosuppression (Nakabiito et al. 2000). In women with CD4 counts ≤200/mL, the HIV transmission rate at 18 months for those in the women who received nevirapine was 31.6 percent, whereas the rate was 54.9 percent in women who received zidovudine.

Researchers are now turning their attention to how the protective effect of ARVs can be safeguarded in breast-feeding populations. One possibility just beginning to be explored is the administration of drug therapy to infants during the entire course of breast-feeding. The other is continued ARV treatment for mothers during the breast-feeding period. Basic research is also underway to better understand the mechanisms of how nevirapine and zidovudine work, and to explore why 85 percent of the infants who are exposed to HIV via breast milk do not become infected.

Conclusion

There is no best answer for HIV-positive women with infants. Reducing vertical HIV transmission is challenging, particularly in developing countries where mothers with HIV infection do not have access to long-term antiretroviral regimens, formula-feeding, or other preventive strategies that mothers in wealthier countries routinely follow. Mother-to-child transmission research is pointing, however, in a few directions. In settings where formula-feeding is neither possible nor recommended, a policy of exclusive breast-feeding for three to six months is advocated. In acknowledgment that breast-feeding is a feasible, popular, and widely practiced infant feeding method throughout the world, researchers are now turning their attention to strategies for reducing the risk of mother-to-child transmission during breast-feeding. These include further studies to explore the optimal duration of breast-feeding, weaning recommendations, and most prominently, antiretroviral drug therapy for mothers and infants.

Figure 2. Short-course antiretroviral drug regimens in breast-feeding populations

Antiretroviral regimen	Antiretroviral given in late-stage pregnancy	Antiretroviral given during labor/delivery	Antiretroviral given to mother, infant, or both after delivery	Breast-fed	Effectiveness of regimen	Comment
Zidovudine short-course (Leroy et al. 2002)						
DITRAME (Abidjan, Côte d'Ivoire; Bobo-Dioulasso, Burkina-Faso)	Yes	Yes	Mother (1 week)	Majority of infants breast-fed for a prolonged period	• At 24 months, pooled data from both studies shows estimated 26% reduction in HIV transmission risk.	• 54%–60% reduction in HIV transmission risk in women with less-advanced HIV disease. • At 24 months, women with advanced HIV disease had a similar cumulative risk of HIV-1 infection as women in the placebo group.
RETRO-CI (Abidjan, Côte d'Ivoire)	Yes	Yes				
Zidovudine and lamivudine short-course (Petra Study Team, 2002)						
• Regimen A	Yes	Yes	Mother and infant (1 week)	74% of women breast-fed; median duration, 28 weeks	• At 6 weeks, Regimens A and B reduced HIV transmission rates to 5.7% and 8.9%, respectively. (HIV transmission rate in the placebo group was 15.3%.) • At 18 months, Regimens A and B had a cumulative incidence of HIV-1 infection or death of 18.9% and 23.8%, respectively, compared with 25.6% in the placebo group.	• Cumulative incidence of HIV-1 infection or death was higher in breast-fed children (21.6% in Regimen A, 24% in Regimen B, and 28.2% in the placebo group).
• Regimen B		Yes	Mother and infant (1 week)			
Nevirapine vs. zidovudine (Guay et al. 1999; Nakabiito et al. 2002)						
• Nevirapine		Yes	Infant (single dosage)	98.8% of infants breast-fed	• Estimated HIV-1 transmission risk in the nevirapine and zidovudine groups was 8.2% and 10.4%, respectively, at 6 weeks, 11.9% and 21.3% at 6–8 weeks, and 13.1% and 25.1% at 14–16 weeks	• At 14–16 weeks, nevirapine reduced the risk of HIV-1 transmission by almost 50%. • At 18 months, the efficacy of nevirapine was highest in women with CD4 counts ≤200/mL.
• Zidovudine		Yes	Infant (1 week)			

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The Expert

Grace John-Stewart, MD, MPH, PhD, is associate professor in the Department of Medicine and adjunct associate professor in the Department of Epidemiology at the University of Washington. She has been a visiting research scientist at the University of Nairobi, in Kenya, since 1993. She is principal investigator of a five-year study titled "Cytotoxic T Lymphocytes and Breastmilk Transmission of HIV-1," funded by the National Institutes of Health. Dr. John-Stewart was the principal investigator on "The Effect of Breastfeeding on Maternal HIV-1 Disease Progression," a two-year Royalty Research Fund study, and "Couples Counseling to Enhance Infant HIV-1 Prevention," a two-year study funded by the Pediatric AIDS Foundation. Dr. John-Stewart is a member of the World Health Organization Collaborative Center for Research and Training in STDs/HIV in Nairobi, Kenya. She has authored several papers on the subject of mother-to-child transmission of HIV and HIV transmission via infant feeding.

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