

# HIV Transmission Through Breastfeeding

## A Study in Malawi

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**M**OTHER-TO-CHILD TRANSMISSION of human immunodeficiency virus (HIV) can occur in utero, intrapartum, and postnatally.<sup>1,2</sup> Postnatal HIV transmission through HIV-contaminated breast milk is of particular concern in many developing countries, where HIV infection in women is common and breastfeeding is almost universally practiced. Transmission of HIV through breast milk has been documented in many studies,<sup>3-12</sup> and HIV has been found in breast milk samples of HIV-infected women.<sup>13-16</sup>

Ascertaining the transmission risk of HIV at different times during the breastfeeding period has become particularly important, because it has recently been shown that in utero and intrapartum transmission can be decreased by approximately 50% when short-course, oral antiretroviral therapy is used during pregnancy through labor.<sup>17</sup> In breastfeeding populations, however, any decrease in in utero and intrapartum transmission of HIV achieved through such regimens or other methods of prevention will re-

**For editorial comment see p 781.**

**Context** Understanding the risk of human immunodeficiency virus (HIV) transmission through breastfeeding is essential for advising HIV-infected mothers and formulating public health policy recommendations.

**Objective** To measure the frequency, timing, and risk factors of HIV transmission through breast milk.

**Design** Prospective cohort study conducted between 1994 and 1997, with follow-up of infants through 24 months of age.

**Setting** Postnatal clinic of tertiary care hospital, Blantyre, Malawi.

**Participants** A total of 672 infants (HIV-negative at birth) born to HIV-infected women who had not received antiretroviral drugs during or after pregnancy.

**Main Outcome Measure** Incidence of HIV in breastfed infants by age and maternal and infant risk factors for HIV transmission, using proportional hazard models to derive risk ratios (RRs) and 95% confidence intervals (CIs).

**Results** Forty-seven children became HIV-infected while breastfeeding but none after breastfeeding had stopped. The cumulative infection rate while breastfeeding, from month 1 to the end of months 5, 11, 17, and 23, was 3.5%, 7.0%, 8.9%, and 10.3%, respectively. Incidence per month was 0.7% during age 1 to 5 months, 0.6% during age 6 to 11 months, and 0.3% during age 12 to 17 months ( $P = .01$  for trend). The only factors significantly associated with low risk of postnatal HIV transmission in a multivariate model were high maternal parity (RR, 0.23; 95% CI, 0.09-0.56) and older maternal age (RR, 0.44; 95% CI, 0.23-0.84).

**Conclusions** Our data suggest that the risk of HIV infection is highest in the early months of breastfeeding, which should be considered in formulating breastfeeding policy recommendations.

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sult in a larger number of infants, who, though uninfected at birth, become exposed to HIV through breast milk.

In this study, we investigated the risk of HIV transmission through breastfeeding in an urban setting in Malawi, where HIV prevalence in nursing women is approximately 30%, and breastfeeding is the recommended method of infant feeding. A revised statement in 1998 by the Joint United Nations Programme on HIV/AIDS<sup>18</sup> recommended that women be offered HIV counseling and testing, that they be informed of risks and benefits of breastfeeding if the mother is HIV-infected, and that they make a decision that takes into account their individual and fam-

ily situations. A better understanding of the level of risk and the timing of infant HIV infection throughout the breastfeeding period will help to inform women about transmission risks and to assess policy options about breastfeeding by HIV-infected women.

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## METHODS

### Study Population

Between 1994 and 1997, we studied children of HIV-infected women who had previously participated in a clinical trial of birth canal cleansing to prevent mother-to-child transmission of HIV. Both the clinical trial and the follow-up study on breastfeeding risk took place at Queen Elizabeth Central Hospital, Blantyre, a tertiary care hospital in which approximately 14 000 deliveries occur annually. The follow-up included 37 twin and triplet births. No mothers in the study received antiretrovirals during pregnancy or postnatally. The protocol and consent forms were approved by institutional review boards in Malawi and the United States.

FIGURE 1 shows the number of study infants, those who were excluded from the study, and the reasons for exclusion. Infants found to be HIV-positive by polymerase chain reaction (PCR) at their first postnatal visit, scheduled at age 6 weeks ( $n = 355$ ), were excluded from the study, because most of them would have been infected in utero or perinatally. A small proportion, however, would have been infected through colostrum or early milk. To be included in the study, breastfed infants had to be HIV-negative at their first postnatal visit, have breastfeeding data ( $n = 1012$ ), and have a second follow-up visit ( $n = 672$ ). The interval between the 2 visits was the observation period during which breastfeeding risk was assessed. All postnatal HIV infections in infants were considered to be caused by breastfeeding, because no infant infection was documented after breastfeeding had stopped. Although all blood donations at this hospital were screened for HIV, the history of infants' blood transfusions was also reviewed to exclude possible HIV infection from antibody-negative, virus-infected blood.

Enrolled infants and their mothers were scheduled to attend the study clinic at 1½, 3, 6, 9, and 12 months after delivery and at 15, 18, and 24 months in the second year. At each visit, a history of health complaints, breastfeeding practices, and breast problems (painful swell-

ing, other signs of infection, cracked or bloody nipples) was obtained. Questions about breast problems started at the 6-month visit. Physical examination and collection of biological samples were performed every 6 months. In accordance with World Health Organization and government of Malawi recommendations at the time of this study, HIV-infected women, who were told their HIV-infection status, were not discouraged from breastfeeding. Routine clinical care and, when necessary, referrals were provided to mothers and infants.

### Time of Postnatal HIV Infection or Censoring

The time of infants' HIV infection was estimated as the midpoint between the last negative and the first positive PCR result. For infants who did not seroconvert, the date of the last negative PCR result was used as the date at which the infant was still uninfected. Infants were censored on the date when breastfeeding was stopped, as ascertained by the mother's interview. If breastfeeding was discontinued during the infection interval, the first positive HIV result was moved backward in time to the date of last breastfeeding. Because infants were more closely followed in the first few months of life, the intervals were smaller for younger than for older infants. Thus, midpoint estimates are more reliable for earlier months of life. For infants who were weaned but for whom the exact weaning date was not provided, the midpoint between the date of last known breastfeeding and the date when the infant was known to have been weaned was used. Observations were truncated at 24 months, because the follow-up data after that time were sparse (16 person-months of follow-up between 24 and 31 months, with no additional HIV infections).

### Infant Weaning

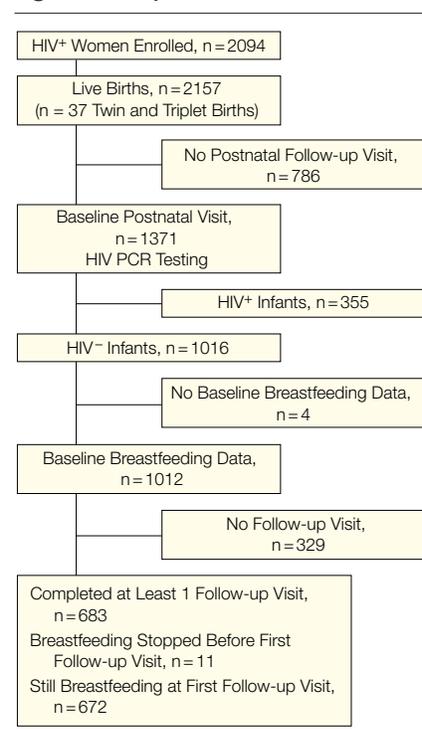
The time when breastfeeding ended was based on the mother's report. We examined the duration of breastfeeding for all HIV-infected and uninfected women to determine if breastfeeding patterns

were affected by informing the women of their HIV status. We also examined transmission risk in uninfected infants after they had been weaned.

### Laboratory Assays

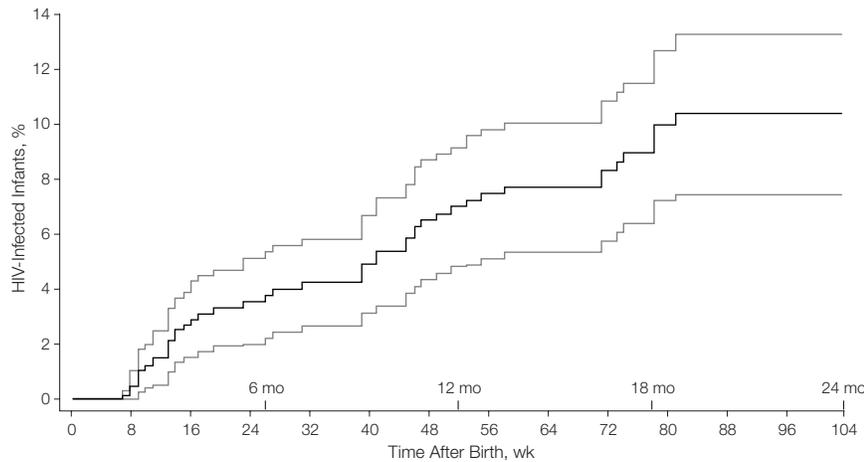
The mothers' HIV infection was established by repeated positive results from enzyme-linked immunosorbent assay (ELISA) HIV antibody tests performed on umbilical cord blood. Borderline HIV ELISA results were confirmed by immunoblotting. Infants' HIV status was determined with DNA PCR using blood collected by heel stick and adsorbed on filter paper, as previously described.<sup>19</sup> Positive and negative test results in Malawian infants had predictive values of 98% and at least 96%, respectively.<sup>19</sup> The presence of HIV antibody (ELISA) was used to confirm

**Figure 1.** Study Profile



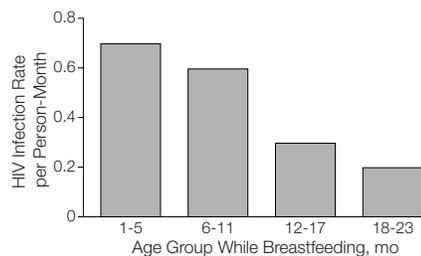
Schema of inclusion and exclusion of mother-infant pairs enrolled. Schema starts from initial study of delivery-related factors and continues to subsequent study of mother-infant pairs providing data for postnatal human immunodeficiency virus (HIV) transmission. Numbers of person-months of follow-up in each interval were as follows: months 1 to 5, 2034; months 6 to 11, 2376; months 12 to 17, 1996; and months 18 to 23, 735.

**Figure 2.** Infants' Risk of HIV Infection While Breastfeeding



Actuarial calculation of human immunodeficiency virus (HIV) infection risk (black line) and 95% confidence interval (gray lines) while breastfeeding. The risk of breastfeeding in the first month of life could not be estimated. Beyond 23 months of age, data are too sparse to provide information.

**Figure 3.** Average Monthly Hazard Rate, Human Immunodeficiency Virus (HIV) Infection Rate Per Month\*



Estimated by dividing the change in the cumulative risk during the period by the number of months in the period.

HIV infection in infants aged 15 months or older, and all new, repeated positive results in infants were confirmed by immunoblotting.

**Statistical Methods**

For analysis, the time at risk for HIV infection was the time under observation from the infant's first postnatal negative HIV PCR result. Risk was assessed by Kaplan-Meier method.<sup>20</sup> Period risk was derived from cumulative risk at 6-month intervals, such that the additional risk in each period was divided by the months during the interval to provide an average monthly hazard rate. Because 1 criterion for entry

into the study was a negative PCR result after the first month, the first 6 months of life had no data about risk in the first month of life, and the average monthly hazard rate is therefore based on only 5 months. Tests of trend assumed a Poisson distribution. To examine the association between maternal, delivery, and infant factors and mother-to-child HIV transmission, we used a univariate proportional hazard model, with left and right truncation of data dependent on time of entering and leaving the study. The significance of risk factors was also assessed by a backward stepwise regression model, a multivariate model that starts with all factors and proceeds by stepwise removal of nonsignificant factors.

Cofactor analysis was expressed as risk ratios (RRs) and confidence intervals (CIs). Analysis of the time breastfeeding stopped was done by Kaplan-Meier method,<sup>20</sup> with infants censored when breastfeeding was stopped or when follow-up ended.

**RESULTS**

Median age of first visit with a negative HIV PCR result was 1.7 months (25%-75% interquartile range, 1.4-2.1; range, 0.7-16.8 months). Thus, any postnatal infections did not involve co-

lostrum or very early milk. Infants uninfected at enrollment were followed up for 7155 person-months (596 person-years) while breastfeeding. No infant became infected after breastfeeding had stopped (268 person-months of follow-up), and none of the infants who were found to be PCR-positive had blood transfusions during the interval of infection. Thus, all of the new infections were attributable to breastfeeding.

Of the 672 infants with at least 2 follow-up visits (Figure 1), 47 became HIV-infected through breastfeeding. The median duration of follow-up while breastfeeding was 11.5 months (25%-75% interquartile range, 4.5-22.0 months). There were no data for the first month, because entry required a negative PCR result at the first postnatal visit (see "Methods, Study Population" section). Infants were followed up for a total of 2034 person-months in the 1- to 5-month interval (21 infections), 2375 person-months in the 6- to 11-month interval (15 infections), 1995 person-months in the 12- to 17-month interval (7 infections), and 735 person-months in the 18- to 23-month interval (4 infections).

The postnatal HIV-infection rate is shown in FIGURE 2. The cumulative risk of infection for infants continuing to breastfeed after month 1 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. The HIV-infection rates per person-month in the first 2 years of life were 0.7% (months 1-5), 0.6% (months 6-11), 0.3% (months 12-17), and 0.2% (month 18-23) (FIGURE 3). This decline in HIV incidence was statistically significant ( $P = .01$ ).

The TABLE presents the univariate analysis of the association between infant HIV infection through breastfeeding and maternal, delivery, and infant factors. Reported maternal HIV-related illnesses or maternal deaths within 2 years of giving birth were analyzed, because symptomatic women with poorer immune systems and possibly higher viral levels may be more likely to transmit HIV infection through

breast milk.<sup>13</sup> Compared with asymptomatic mothers, symptomatic mothers and mothers who died had a similar transmission rate (RR, 1.2; 95% CI, 0.6-2.6). We postulated that older mothers may have been infected longer and thus may have had more advanced HIV disease. However, the postnatal transmission RR for women younger than 25 years was not different from that among older women (0.9; 95% CI, 0.5-1.6). Similarly, women who had several children and were therefore older may have been HIV-infected longer than women with fewer children. A lower postnatal transmission rate, however, was found for higher ( $\geq 4$ ) compared with low birth order ( $< 4$ ) infants (RR, 0.4; 95% CI, 0.2-0.9). The higher transmission rate to earlier births was not attributable to a higher transmission rate to first-born infants, because the greatest risk was to second-born infants.

The postnatal HIV-infection status of infants delivered by cesarean birth was analyzed, because we found previously that in these infants, cesarean delivery was associated with a lower infant HIV-infection rate than vaginal delivery.<sup>21</sup> Thus, infants who avoided infection through a cesarean delivery could have been at a higher risk of acquiring HIV infection postnatally. The RR for postnatal transmission was 1.6 (95% CI, 0.8-3.2) in cesarean-delivered infants compared with vaginally delivered infants.

Breast problems (painful swelling, infections, and cracked or bloody nipples) reported in the interval in which infant infection occurred were considered. The HIV transmission rate in women with and without breast complaints was similar (RR, 0.8; 95% CI, 0.3-2.3). This assessment only applies to older infants, because the question was asked at 6 months or later. It is based on a smaller number of infections ( $n = 28$ ) and may be valid only for breastfeeding after the first 6 months. We studied the association of infant birth weight, a weak predictor of milk intake, and postnatal HIV infection, postulating that heavier infants may have had a higher risk of postnatal in-

**Table.** Risk Factors for HIV Transmission Through Breastfeeding\*

Comparison	No. Infants		Risk Ratio (95% Confidence Interval)	
	HIV Infected	Not Infected		
Mother symptomatic/died	No (575) vs yes (92)	47	624	1.23 (0.57-2.63)
Mother's age, y	$\geq 25$ (256) vs $< 25$ (413)	46	623	0.89 (0.49-1.59)
Parity	1-3 (478) vs $\geq 4$ (194)	47	625	0.39 (0.17-0.86)
Delivery mode	Vaginal (578) vs cesarean (94)	47	625	1.57 (0.78-3.16)
Breast problems†	No (354) vs yes (73)	28	399	0.81 (0.28-2.34)
Birth weight, g	$< 2500$ (111) vs $\geq 2500$ (559)	47	623	0.69 (0.29-1.62)

\*Univariate analysis was for time interval when infection occurred. Models assume proportional hazard rates in a univariate model. Number of women with characteristic is in parentheses in the comparison column.

†Questions about breast problems (painful swelling, other signs of infection, cracked nipples, bloody nipples) were asked after month 6.

fection if they ingested larger volumes of HIV-contaminated milk. This association was not significant. The RR for HIV infection was lower in infants weighing 2500 g or more (RR, 0.7; 95% CI, 0.3-1.6) than it was in smaller infants.

In a backward stepwise regression model, higher parity (RR, 0.23; 95% CI, 0.09-0.56) and older maternal age (RR, 0.44; 95% CI, 0.23-0.84) were both significantly protective against postnatal HIV infection in infants. This model excluded breast problem data, which were only available for some women. In a separate model, applied to the set of women for whom data about breast problems were available, the point estimates were generally similar, but the CI was larger.

These risk factor analyses could have been biased by late entry into the study, because all infants had to be HIV PCR-negative after the first month of life to enter the study. We reexamined data, including every breastfed child who had a postnatal HIV-negative result, even if they had no further follow-up ( $n = 1012$ ). This approach yielded similar results in the risk factor analyses, suggesting no major selection bias among infants who returned for a later follow-up visit.

Among the 672 infants who constituted the follow-up group in this study, the median time of weaning was 21 months (25%-75% interquartile range, 18-24 months). Weaning times by 1511 HIV-infected women (median, 22 months [25%-75% interquartile range,

18-25 months]) and by 3449 uninfected women (median, 22 months [25%-75% interquartile range, 19-25 months]) were similar, suggesting no bias in the weaning practices for enrolled infants. Supplemental foods (typically porridge) were introduced at a mean (SD) time of 4.0 (1.5) months.

## COMMENT

In a previous study,<sup>22</sup> conducted in a similar population of women in urban Malawi, we documented a prepartum, peripartum, and early postnatal HIV transmission rate of 27% among women with vaginal deliveries. The current study extends those results by documenting the HIV-infection rate in infants still uninfected at their first postnatal visit. Our study showed that an uninfected infant, breastfed by an HIV-positive mother for 23 months, had at least a 10.3% risk of becoming infected. This rate of postnatal infection does not include postnatal transmission in the first month of life, which could not be reliably distinguished from intrapartum transmission in this study. The transmission rate in the first month could be substantially higher than in later months, because it includes feeding with colostrum and early milk, which are rich in cells.<sup>23</sup> Our trend data showed a higher risk in the 1- to 5-month period than after 5 months, but we have no data about risk in the first month. Investigators in Brazil<sup>24</sup> noted a substantially higher risk among breastfed infants, even though the average duration of breastfeeding was only about

1 month. A high early transmission rate might be explained by the immaturity of the infant's immune system and by the large number of HIV-infected cells present in early milk.<sup>23</sup> The overall risk of postnatal HIV transmission documented in most previous studies ranged from 4% to more than 20%,<sup>3,5-12</sup> with 1 study<sup>8</sup> estimating a 32% risk in infants breastfed for more than 15 months. The interpretation and comparability of these studies are limited by factors such as small sample size, lack of an assay capable of reliably detecting infection in early infancy,<sup>25</sup> and different ways of defining and calculating postnatal transmission risk.<sup>26</sup> At least 1 study<sup>27</sup> also found a direct relationship between infant infection risk and breastfeeding duration. A meta-analysis<sup>5</sup> of 5 studies estimated the HIV transmission risk through breastfeeding to be 14% (95% CI, 7%-22%).

A recent multicenter study<sup>28</sup> used a standardized method to establish rate and time of postnatal transmission in a large number of children from 4 cohorts in Europe and 4 cohorts in Africa. Among 902 African infants, 49 postnatal HIV infections were documented, for an overall incidence of 3.2 per 100 person-years of breastfeeding. This incidence was less than half the incidence that we observed in Malawi (6.9 per 100 person-years). A large contribution to the data in the multicenter study came from Kenya, which had a substantially lower HIV transmission rate compared with the other 3 African studies presented and with our study. In the multicenter study, the time of HIV infection could be estimated in 20 of the 49 infected infants. Infants with positive PCR test results in the first few months (mean, 2.5) of life were excluded from the analysis, as they were in our study. Both studies, therefore, underestimate the actual postnatal transmission rate. Of the periods that were analyzed, the largest difference in transmission between the 2 studies was in the 1- to 5-month period (5.2% in Malawi compared with 0.7% in the multicenter study). After infants reached 6 months of age, differences in transmission rates between the 2 studies were less

pronounced (6-11 months, 3.4% vs 1.8%; 12-17 months, 2.0% vs 3.8%). Different patterns of weaning and food supplementation may explain these variations. In our population, most infants were weaned between 18 and 25 months (median, 22 months), and the HIV status of the mother did not influence weaning patterns. However, supplemental foods were introduced well before weaning occurred (median, 4 months) and the total volume of breast milk ingested, hundreds of milliliters daily,<sup>29</sup> might have been influenced by giving supplemental foods. However, the time of introduction of supplemental foods was not a statistically significant factor in a time-dependent covariate analysis in our study ( $P = .2018$ ).

Recommendations for advising HIV-infected women about breastfeeding require an understanding of the risk factors that might affect transmission risk.<sup>30</sup> Our analysis of maternal and infant risk factors, however, identified only lower parity and possibly lower age of the mother as risk factors for HIV transmission to infants. No significant differences were associated with indicators of maternal HIV-related disease or early death. Among infant factors, birth weight was examined as an indicator of larger milk intake, but no significant association with postnatal HIV infection was found. Our ability to determine statistical significance in the analysis of risk factors may have been limited by the small number of postnatal HIV infections. The finding of a higher postnatal transmission risk in women with lower parity was unexpected, as the women's younger age would likely be accompanied by lesser virologic and immunologic compromise. This finding may be consistent with a hypothesis that mothers who are less experienced with breastfeeding are more likely to have subclinical mastitis and thereby a higher HIV transmission rate.<sup>31</sup> This hypothesis may also be consistent with the higher risk of transmission that we documented in the early months of breastfeeding. Surprisingly, clinical mastitis or cracked nipples in mothers were not associated with higher HIV transmission to the in-

fant. A possible explanation is that women avoid feeding from a breast that is tender or has overt lesions.

The main limitation in our study was the lack of data about maternal immunologic and virologic status. These parameters could influence the rate of HIV transmission through breastfeeding.<sup>13</sup> Active viral replication may account for the high transmission risk previously documented in mothers who breastfeed during acute HIV infection.<sup>5</sup> Our study did not investigate mothers who became HIV-infected during lactation. A second, unavoidable limitation was the inability to determine the transmission risk through breastfeeding in the first weeks of life. In Kenya, a study currently in progress has randomized infants into breastfeeding vs bottle-feeding,<sup>32</sup> an approach that should provide valuable insights into the risk from early breastfeeding.

Early weaning has been discussed<sup>10,27,30</sup> as a means to decrease the chance of postnatal HIV transmission. However, the adverse effects of early weaning on growth, morbidity, and mortality have been emphasized.<sup>33</sup> We found that the hazard rate of postnatal HIV infection was highest in the first half-year of life, when breastfeeding is particularly important. Furthermore, HIV transmission continued for as long as breastfeeding continued. The high level of risk in the first 6 months of life limits the value of early weaning as a way of reducing the risk of late postnatal HIV transmission. In the multicenter study,<sup>28</sup> weaning at 4 months would have resulted in no infections and at 6 months in only 3 infections. However, in Malawi, weaning at 4 months would still have resulted in 19 infections and at 6 months in 21 infections, which is nearly half of all infections observed in this study. Moreover, both studies could not detect HIV infection through breastfeeding in the first several weeks of life. Although some infections would undoubtedly be prevented by early weaning, there might also be additional illnesses and deaths due to early weaning. The risk-benefit ratio is thus likely to be widely different in disparate populations, making it difficult to gen-

eralize any weaning recommendation and its optimal timing.

Several conclusions and possible recommendations can be drawn from this study. First, the HIV transmission risk due to breastfeeding was highest in the early months of life, but remained substantial for as long as an infant continued to breastfeed. Our study's postnatal HIV transmission rate and other published rates are underestimates, because they do not include postnatal infections acquired very early in life through breastfeeding. During early breastfeeding, transmission rates could be substantial.

Second, only lower parity and younger maternal age increased transmission risk, factors that may be attributable to the degree of maternal experience with breastfeeding. No obvious factors predicted groups of women who were clearly more likely to transmit HIV

through breastfeeding. Thus, recommendations could not be specifically directed at high-risk HIV-infected women. The social implications of recommending that all HIV-infected women avoid breastfeeding should also be considered, because not breastfeeding may result in social stigma if it identifies women who are HIV-infected. Perhaps further educational efforts to instruct young and inexperienced mothers about breastfeeding might help to lower the likelihood of subclinical mastitis. The role of subclinical mastitis, however, needs to be further elucidated.

Third, early weaning, eg, at 4 or 6 months, is a strategy difficult to generalize. In our study, it would have prevented only about half of the postnatal infections, but also may have resulted in additional morbidity and mortality.

Breastfeeding recommendations for HIV-infected women must carefully balance the risk of HIV transmission with the well-known benefits of breastfeeding (nutritional excellence, reduced morbidity and mortality, psychological and pregnancy-spacing benefits). Recommendations may be most usefully made at the level of the individual mother, because communities in developing countries include women from various socioeconomic strata who have different access to safe breast milk alternatives.

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