

East African Medical Journal Vol. 78 No. 2 February 2001

TIMING OF BREAST MILK HIV-1 TRANSMISSION: A META-ANALYSIS

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**TIMING OF BREAST MILK HIV-1 TRANSMISSION: A META-ANALYSIS**

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**ABSTRACT**

**Objective:** To define the frequency and timing of breast milk transmission of HIV-1.

**Design:** Meta-analysis of data abstracted from published literature.

**Subjects:** Participants in prospective cohort studies of MTCT of HIV-1. Cohorts were separated on the basis of breast feeding duration.

**Interventions:** None.

**Main outcome measures:** HIV-1 transmission rates.

**Results:** Two thousand three hundred and seventy five HIV-1 infected women and their infants, 499 of whom breast fed, the estimated risk of breast milk HIV-1 transmission was 16% (95% CI: 9, 22%). Among breastfeeding infants, forty seven per cent of HIV-1 infections were attributable to breast feeding. Breast milk transmission risk was 21% (95% CI: 10, 33%) in cohorts with mean/median duration of breast feeding  $\geq 3$  months and 13% (95% CI: 4, 21%) in cohorts with median duration of breast feeding  $< 2$  months. In a separate analysis of 702 infants with prolonged duration of breast feeding, the risk of late postnatal transmission (infection occurring later than three to six months of age) was four per cent (95% CI 2, 5%).

**Conclusions:** This analysis suggests that breast milk transmission of HIV-1 is substantial and continues throughout the postnatal period. Early cessation of breast feeding at six months would avert some but not most infant HIV-1 infections due to breast feeding. While recently published studies showing some effectiveness of antiretrovirals early during the breast feeding period are encouraging, prevention of breast milk HIV-1 transmission needs to remain a high research priority.

**INTRODUCTION**

As intervention strategies to decrease mother-to-child transmission of HIV-1 are developed, it is increasingly important to determine the frequency and timing of HIV-1 transmission through breast feeding. Perinatal HIV-1 transmission rates range from 22% to 48% in breast feeding populations, while the use of peripartum zidovudine in combination with formula feeding can reduce perinatal HIV-1 transmission to less than ten per cent(1-3). Recently, short-course antiretroviral regimens have been demonstrated to have greater efficacy for reduction of perinatal HIV-1 transmission in formula feeding cohorts than in breastfeeding cohorts(3-5). While antiretrovirals appear to decrease perinatal HIV-1 transmission in breast feeding cohorts, there is, as yet, insufficient follow up to know what their net benefit will be among infants breast feeding for prolonged duration. Determination of breast milk HIV-1 transmission risk, therefore, is essential for designing effective interventions to decrease infant HIV-1 infection in settings of high HIV-1 prevalence in which breast milk substitutes may be unsafe or unfeasible.

Estimation of the frequency of HIV-1 transmission through breast feeding has been challenging because few

observational cohorts have had sufficient numbers of both breast and formula feeding HIV-1 infected mothers to evaluate breast milk transmission risk. Since 1985, after the first case report of HIV-1 transmission through breast milk, the Centers for Disease Control (CDC) has recommended that HIV-1 infected women avoid breast feeding their infants(6). In areas of the world with a high prevalence of infectious diseases and unsafe water supply or sanitation, breast milk alternatives have been associated with increased infant mortality. Thus, until 1996 the World Health Organisation recommended that HIV-1 infected women in these settings breastfeed their infants unless they had access to safe alternatives(7). In most observational HIV-1 vertical transmission studies in Africa and Asia, therefore, breastfeeding has been universal, while in European and US cohorts, breast feeding is rare.

In 1992, Dunn and colleagues estimated breast milk transmission rates in a meta-analysis of six published studies of cohorts that included both breast and formula feeding mothers who had acquired their HIV-infection before delivery(8). This analysis was limited by the paucity of cohorts at the time that included both breast and formula feeding mothers. Even within cohorts in the analysis, there was relative uniformity of feeding practice; in the five non-African cohorts, only seven per cent of infants breastfed,

many for a short duration, and in the single African study a total of ten infants (nine per cent of the cohorts) were formula fed. More recently, our group conducted a randomised clinical trial of breast feeding versus formula feeding in Nairobi, Kenya and determined that 44% of mother-to-child transmission in the breastfed arm was attributable to breastfeeding and that a majority of breast milk transmission occurred early(9).

To make infant feeding policy recommendations for HIV- 1 infected women, it is also critical to know when breast milk HIV- 1 transmission occurs. Early analyses evaluating the effect of duration of breast feeding on breast milk HIV- 1 transmission risk were conducted using data from studies that had not initially been designed for this purpose, had methodological limitations, and are difficult to interpret(10-12). More definitive data on late postnatal HIV-1 transmission (infection occurring after three to six months of age) are now available from studies of infants using serial testing for viral DNA with polymerase chain reaction (PCR) assays(13-17).

Since the 1992 meta-analysis, there have been a number of studies with additional information on breast milk HIV- 1 transmission. We conducted a meta-analysis by reviewing published reports and abstracts from all prospective cohorts that included evaluation of breast milk HIV- 1 transmission risk. In addition to an estimate of breast milk HIV- 1 transmission risk overall, we provide separate estimates of HIV- 1 transmission risk in cohorts in which duration of breast feeding was short, and those in which duration was long. Finally, a second meta-analysis of four studies was performed that contribute data regarding late postnatal transmission, permitting evaluation of the relative contributions of early and late breast milk HIV-1 transmission.

## MATERIALS AND METHODS

*Data sources:* Published studies and abstracts were identified through searches of MEDLINE and AIDSLINE for the period 1985-1998 and of Current Contents for the period 1996-1998. The key words "vertical transmission with HIV", "perinatal transmission with HIV", "(breastfeeding or breastfed or breastfeeding or breastfed or breast-feeding or breast-fed) with HIV", and "feeding with HIV" were used as search criteria and resulted in 1006 English language articles and abstracts.

*Study selection:* All prospective HIV-1 vertical transmission cohorts that included breast feeding and formula feeding infants, and that reported data on the number of children and the number of HIV- 1 infected in each feeding group were included. For the late postnatal transmission meta-analysis, articles or abstracts were included if they reported the number of infants uninfected at three to six months of age who later became infected.

*Measures:* For the analysis of formula feeding versus breast feeding, the percentage of HIV-1 infected breast fed infants and formula fed infants was compared within each study. Cohorts were divided into those with mean/median breast feeding duration >3 months and <2 months, and summary estimates of HIV- 1 transmission risk were separately calculated. Most analyses of late postnatal transmission have used the number of infants known to be uninfected at three to six months as the denominator for late postnatal transmission risk estimates. This conditional

probability estimate (risk among infants uninfected at three to six months) cannot be validly subtracted from overall breast milk HIV- 1 transmission risk because the denominator does not include all breast feeding infants, and the subset of infants who are uninfected at three to six months may be different from all breast feeding infants. For example, infants who are uninfected at three to six months despite previous breast milk HIV-1 exposure may be a selected group with lower susceptibility. For the late postnatal transmission analysis, therefore, we estimated the late transmission risk among all breast feeding infants. This estimate could be used to determine the relative contribution of late breast milk HIV- 1 transmission.

*Data abstraction:* All abstracts obtained from the literature searches were reviewed separately by two of the authors (GJ and BR). Any article that contained potentially relevant data was reviewed in detail and relevant data were abstracted.

*Data analysis:* Chi-square tests of homogeneity were performed for each meta-analysis to test the hypothesis of equal effect sizes in all of the studies(18). Failure to reject this hypothesis for all analyses allowed valid use of a general variance-based method of meta-analysis(19).

## RESULTS

We included data from eight studies, including three from Africa, two from Europe, and one each from the US and Brazil (Table 1)(20-27). There have been several published analyses of the Italian Multicentre cohort, some of which have included retrospectively identified infants(11,28). We did not include data from this study or a study from Spain because children in these studies were included in the larger European Collaborative Study(22,29). An Australian study and a recently published study from Brazil were also excluded because the infant infections were identified retrospectively(30,31). Our analysis included 2,375 HIV-1 infected mothers and their infants, 499 (21%) of whom breast fed. There were 1,870 infants from European/US cohorts, six per cent of whom breast fed, and 505 from African/Brazilian cohorts, 78% of whom breast fed.

Pooling observations from the eight cohorts, we estimated that the HIV-1 transmission risk due to breast feeding was 16% (95% CI: 9, 22%) (Table 1). Among breast feeding infants, 47% (95% CI: 32, 58%) of infections were attributable to breast milk HIV-1 transmission.

The median duration of breast feeding was less than two months in the Swiss, French, and European studies, with a summary weighted median of four weeks (Table 2). In the three African cohorts, the mean or median duration of breast feeding was  $\geq 3$  months, with a summary weighted median of 5.5 months. In cohorts with duration of breast feeding <2 months, the estimated breast milk HIV-1 transmission risk was 13% (95% CI: 4, 21%), with 48% (95% CI: 25, 59%) of infections among breast feeding infants attributable to breast milk transmission. In cohorts with duration of breast feeding  $\geq 3$  months, the estimated breast milk transmission risk was 21% (95% CI: 10, 33%), with 66% (95% CI: 36, 89%) of infections among breast feeding infants attributable to breast milk HIV-1 transmission. Two studies did not include information on the duration of breast feeding and were excluded from the

Table 1

## Meta-analysis of breast milk HIV-1 transmission risk

Study	Breast fed		Formula fed		TR difference	Attributable risk for breast feeding
	TR%*	N	TR%	N		
Miami 1991(20)	28	25	33	54	-5%	
Zaire 1991(21)	20	96	0	10	20%	
Europe 1992(22)	31	36	14	683	17%†	
France 1995(23)	40	20	19	801	21%†	
Switzerland 1995(24)	16	25	18	226	-2%	
Soweto 1996(25)	46	114	18	49	28%†	
Brazil 1996(26)	52	71	19	32	33%†	
Durban 1997(27)	34	112	24	21	10%	
Summary estimate		499		1,876	16% (9,22%)	47% (32, 58%)

\*TR: mother-to-child HIV-1 transmission rate

†Statistically significant difference between breast fed and formula fed infant infection rates.

Table 2

## Breast-milk HIV-1 transmission estimates by duration of breast feeding

Study	Breast feeding duration	TR* difference (95% CI)	Attributable risk for breast feeding
<i>Cohorts with prolonged breast feeding duration</i>			
Soweto (25)	Mean 3 months	28% (12, 44%)	60%
Zaire (21)	Mean 9 months	20% (-5, 45%)	100%
Durban (27)	Median 5 months	10% (-12, 32%)	30%
Summary estimate	~5.5 months	21% (10, 33%)	66% (36, 89%)
<i>Cohorts with short breast feeding duration</i>			
France (23)	Median 7 weeks	21% (3, 39%)	52%
Europe (22)	Median 4 weeks	17% (5, 29%)	55%
Switzerland (24)	Median 2 weeks	-2% (-17, 14%)	-11%
Summary estimate	~4 weeks	13% (4, 21%)	48% (25, 59%)

\*TR: mother-to-child HIV-1 transmission rate

Table 3

## Late postnatal HIV-1 transmission rates

Study	TR%* (95% CI)	N	Definition of late postnatal transmission
Soweto (14)	3 (1,6%)	189	PCR negative prior to six months, PCR positive after six months
Tanzania (15)	3 (<1,5%)	179	PCR negative at six months, PCR and/or p24 antigen positive after six months
Zaire (16)	3 (1,5%)	252	PCR negative between three to five months, followed by later positive PCR
Ivory Coast (17)	5 (<1,10%)	82	PCR negative at three or six months, positive serology at ≥15 or positive PCR ≥9 months
Summary estimate	4 (2,5%)	702	

\*TR: mother-to-child HIV-1 transmission rate

duration analyses. Thus, the estimate of the overall attributable risk using all eight studies (47%) is slightly lower than the estimates of attributable risk for both the short duration (48%) and long duration (66%) cohorts.

Four studies that included data regarding late postnatal HIV-1 transmission (infant infection occurring after three to six months of age) were pooled in a second meta-analysis (Table 3)(14-17). One study from Malawi was excluded since it was not possible to determine the number of children who ever breast fed in the study(13). Among 702 breastfeeding infants included in our analysis, the

pooled late postnatal transmission risk was four per cent (95% CI: 2, 5%). Thus, approximately 80% of breast milk HIV-1 transmission in cohorts with prolonged duration of breast feeding appears to occur within the first three to six months of life.

## DISCUSSION

In this meta-analysis of approximately 2,400 HIV-1 infected women and their infants, breast milk HIV-1 transmission risk was appreciable, accounting for 47% of

HIV-1 infections among breast feeding infants. The HIV-1 transmission risk was higher in cohorts with prolonged breast feeding duration than in those with short duration (21% versus 13%). In two of the three cohorts with short duration of breast feeding, median duration of breast feeding was less than one month, and many infants in these cohorts breast fed for less than one week. The three cohorts with prolonged duration of breast feeding were African cohorts in which breast feeding sometimes continued for over two years. Within these African cohorts, breast feeding accounted for two thirds of infant infections.

Late postnatal transmission occurring after three to six months of age has only been assessed in African cohorts in which prolonged breast feeding has been routinely practiced. Our summary risk estimate for late breast milk HIV-1 transmission was four per cent, similar to that recently reported in a meta-analysis of late postnatal transmission(32). This, combined with our analysis of cohorts with a duration of breast feeding  $\geq 3$  months, suggests that late postnatal transmission accounts for only 20% of breast milk HIV-1 transmission overall, and that most transmission occurs in the first six months of life. It is possible that the cumulative amount of breast milk intake after six months of age decreases as other foods are introduced. It is also plausible that maternal transmissibility or infant susceptibility factors that influence the likelihood of breast milk HIV-1 transmission vary over time. The fact that only four per cent of breast feeding infants become infected after the age of three to six months, despite continued prolonged exposure to breast milk, suggests the possibility of effective acquired infant immune responses that protect from ongoing exposure. It is also plausible that infants who avoid infection with HIV-1 to the age of three to six months represent a group with relative resistance, perhaps on the basis of HLA type or other factors, analogous to the resistance described among highly exposed commercial sex workers in Nairobi(33).

Our estimates of breast feeding HIV-1 transmission and late postnatal transmission are based on data from a large number of infants and provide evidence of substantial HIV-1 transmission risk, but must be considered in context. Meta-analysis estimates are often imprecise and limited by the lack of comparability between cohorts, such as follow up time, underlying mortality rates, and sampling frequency, and the quality of individual studies(34). Observational studies may be biased because decisions by women regarding infant feeding modality may be influenced by factors that also affect HIV-1 transmission risk. For example, it is possible that mothers with clinical evidence of disease may be more likely to formula feed their infants. The most definitive study design for determining breast milk HIV-1 transmission risk is a randomised clinical trial, but we are aware of only one such study that has been conducted in Nairobi.

In 1996, UNAIDS advised voluntary antenatal HIV-1 testing in areas with high HIV sero-prevalence with counselling regarding the risks and benefits of breast feeding for women with HIV-1 infection(35). In settings

with high infectious disease mortality, unpredictable water supply, poor sanitation, and lack of access to breast milk alternatives, the safest recommendation for infant feeding is currently unknown. Given the present state of knowledge regarding breast milk transmission of HIV-1, several intervention approaches are possible. These include complete avoidance of breast milk, early weaning (at three to six months), withholding colostrum, vitamin A supplementation of mothers and infants, and antiretroviral therapy while breast feeding. Early weaning is associated with a lower risk of diarrhoeal morbidity and mortality than complete breast milk avoidance and would prevent late postnatal transmission. Mathematical modelling studies have suggested that risk and benefit may best be balanced by weaning at six months in settings where infectious disease mortality is high(36,37). Our meta-analysis, however, suggests that weaning at six months would not prevent the majority of infant HIV-1 infections from breast milk transmission. Short-course antiretroviral therapy which includes one week of drug postpartum, has been shown to significantly decrease vertical transmission at six months of age in a breast feeding cohort(5). It is unknown whether this significant decrease will hold after prolonged breast feeding. A longer duration of antiretroviral therapy throughout the lactation period has unknown efficacy, is prohibitively expensive for resource-poor communities, and may be less practical than breast milk avoidance.

Currently there are a number of ongoing perinatal HIV-1 intervention studies of antiretrovirals, vitamin A supplementation, immunoglobulin, and topical antiseptics, all of which focus on the peripartum period(1). In light of what is currently known about breast milk HIV-1 transmission, it will be critical that these studies evaluate endpoints at least as late as 18 months to determine the effect of the intervention on mother-to-child HIV-1 transmission in breast feeding populations. As shown in the two recently published antiretroviral studies in breast feeding cohorts, if an intervention is effective in averting peripartum HIV-1 transmission, but substantial breast milk transmission still occurs, the overall benefit from short course antiretrovirals can be significantly less than seen in the ACTG 076 and CDC-Thailand studies which involved only non-breast fed infants(2-5). Ongoing long-term follow up of breast feeding infants in perinatal intervention trials will be useful to determine whether the decreased HIV-1 transmission seen at six months of age among infants of mothers who received peripartum and postpartum antiretrovirals will persist despite continued exposure to HIV-1 in breast milk.

Most children who are at risk of acquiring HIV-1 come from areas of the world where identification of safe and economically feasible alternatives to breast milk will require creative approaches. Unfortunately, it appears that breast milk transmission of HIV-1 contributes to a significant proportion of infant HIV-1 infections in these settings. As perinatal intervention strategies are developed for resource-poor communities, the subject of breast milk

HIV transmission and its prevention will need to remain a high research priority.

#### ACKNOWLEDGEMENTS

This work was funded by the following grants: NIH HD-23412, Fogarty D43-TW00007, and Fogarty T22-TW00001.

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