

# Mother-to-child transmission of HIV: implications of variation in maternal infectivity

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**Objectives:** To examine the implications of variation in maternal infectivity on the timing of mother-to-child HIV transmission through breastfeeding.

**Design and methods:** A mathematical model of mother-to-child HIV transmission was developed that incorporates two main features: (i) the fetus/child potentially experiences a series of exposures (*in utero*, intrapartum, and via breastmilk) to HIV; and (ii) variation in maternal infectivity. The model was estimated from different sources of epidemiological data: a retrospective cohort study of children born to HIV-1-infected women in Sao Paulo State, Brazil, the International Registry of HIV-Exposed Twins, and the AIDS Clinical Trials Group 076 trial, which assessed the effectiveness of zidovudine in preventing mother-to-child HIV transmission.

**Results:** Variation in maternal infectivity results in higher average risk of breastfeeding-related transmission in the early stages of breastfeeding than in the late stages, even in the absence of a direct relationship between transmission risk and the age of the child. However, the available data were unable to resolve the quantitative importance of this mechanism.

**Conclusions:** Our model has helped identify a previously unrecognized determinant of the timing of breastfeeding-related HIV transmission, which may have adverse implications for the effectiveness of certain interventions to reduce mother-to-child HIV transmission such as maternal antiretroviral therapy in breastfeeding populations and the early cessation of breastfeeding.

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**Keywords:** HIV, breastfeeding, infectivity, vertical transmission

## Introduction

By the year 2000, an estimated 5 million children will have been infected with HIV, the majority of them in sub-Saharan Africa [1]. Breastfeeding is an important route of transmission and could be responsible for 30–50% of these infections [2,3]. There is consensus that HIV-infected women in developed countries should not breastfeed, but there is a dilemma in environments where infectious diseases and malnutrition are the primary causes of death during infancy, since artificial feeding substantially increases children's risk of illness and death [4,5]. In such environments there is growing interest in advising HIV-infected women to cease breastfeeding early, rather than avoiding breast-

feeding completely [6,7]. Thus, the child would receive breastmilk for the first few months of life when it is most beneficial while eliminating the risk of late postnatal transmission of the virus. Another proposal to reduce postnatal transmission is withholding colostrum, a concept successfully applied in veterinary medicine to other viruses [2], although this approach is not being actively considered in humans [3].

The effectiveness of both early cessation and delayed onset of breastfeeding critically depend on the timing of breastfeeding-related transmission. Several biological mechanisms that would result in either a decreasing or increasing risk of transmission have been postulated, but empirical data are lacking [8–10]. One factor that

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has been overlooked, however, is variation in maternal infectivity, which clearly exists. Viral concentration in plasma and breastmilk varies up to 1000-fold between infected women [11,12], maternal viral concentration and CD4 cell count are interrelated and predict transmission risk [11–13], and twins of HIV-infected women tend to be concordant in infection status [14]. In addition, partner studies of sexual HIV transmission have identified the key importance of the infectivity of the index case [15].

This study examines the effect of variation in maternal infectivity on the timing of breastfeeding-related HIV transmission through a new model of mother-to-child HIV transmission, using data from three different epidemiological studies to derive estimates of model parameters. The model gives new insights into the potential impact of limiting the duration of breastfeeding by HIV-infected mothers. Moreover, it raises concern that interventions to reduce intrapartum transmission, including maternal antiretroviral therapy, may be less effective in breastfed than in non-breastfed populations [16,17].

## Methods

### Model

The notation used in the study is described in Table 1. For each mother–child pair the risk of transmission due to breastfeeding is assumed to remain constant with age but may vary between pairs. Specifically, we postulate a proportional frailty model [18], where the factor  $\exp(\sigma z_i)$  scales the underlying hazard of transmission *in utero*, intrapartum, and throughout breastfeeding for the *i*th mother–child pair. A large positive value of  $z_i$  indicates that a woman is relatively infectious, and a large negative value indicates that she is relatively non-infectious. The parameter  $\sigma$  controls the degree of variation in infectivity.

The probability of *in utero* or intrapartum transmission ( $u_i$ ) and the hazard rate of breastfeeding-related transmission ( $\lambda_i$ ) can be expressed as follows:

$$(1) \log_e[-\log_e(1 - u_i)] = \alpha + \sigma z_i, \quad \log_e(\lambda_i) = \beta + \sigma z_i$$

The probability that the *i*th child is not infected postnatally, assuming breastfeeding to be the only route of postnatal transmission, is the survivor function of the exponential distribution,  $\exp(-\lambda_i t_i)$ . A child is ultimately uninfected only if all potential exposures to the virus (*in utero*, intrapartum, and breastmilk) are avoided. Thus, conditional on  $z_i$ ,

$$(2) \Pr(Y_i = 0 | z_i) = (1 - u_i) \exp(-\lambda_i t_i) = \exp[-t_i \exp(\beta + \sigma z_i) - \exp(\alpha + \sigma z_i)]$$

Integrating out the random effect,

$$(3) 1 - \pi_i = \int_{-\infty}^{\infty} \Pr(Y_i = 0 | z_i) f(z) dz = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \exp[-t_i \exp(\beta + \sigma z) - \exp(\alpha + \sigma z) - z^2/2] dz$$

### Special cases

$\sigma$  lies in the interval  $(0, \infty)$ . When  $\sigma = 0$ , that is, all women are equally infectious,  $u_i \equiv u$  and  $\lambda_i \equiv \lambda$  for all *i*. It follows that,

$$(4) 1 - \pi_i = (1 - u) \exp(-\lambda t_i), \quad \log_e(1 - \pi_i) = \log_e(1 - u) - \lambda t_i,$$

a generalized linear model, which is easily estimated.

As  $\sigma \rightarrow \infty$  (variation in infectivity becomes arbitrarily large), each woman is predetermined, given the random effect  $z_i$ , to either (i) not transmit the infection, or (ii) transmit the infection *in utero* or intrapartum, or (iii) transmit the infection through breastfeeding, independent of duration. This extreme model is not biologically plausible.

### Sources of data

#### Sao Paulo Collaborative Study

The design and main findings of this retrospective cohort study of children born to HIV-1-infected women have been previously described [19,20]. Information on breastfeeding history was elicited from hospital notes and an interview with the mother. The infection status of 432 children was ascertained. Children breastfed for at least 1 day (36% of all

**Table 1.** Notation.

Symbol	Type	Description
$Y_i$	Observed variable	Infection status at cessation of breastfeeding (0 = uninfected, 1 = infected)
$t_i$	Covariate	Duration of breastfeeding in days (0 if exclusively bottle-fed)
$u_i$	Latent variable	Probability of <i>in utero</i> or intrapartum transmission, function of $z_i$
$\lambda_i$	Latent variable	Hazard rate of transmission through breastfeeding, function of $z_i$
$z_i$	Latent variable	Standard normal deviate
$\pi_i$	Parameter	Probability of infection, function of $t_i$
$\alpha$	Parameter	Average (transformed) probability of <i>in utero</i> or intrapartum transmission
$\beta$	Parameter	Average (transformed) hazard rate of transmission through breastfeeding
$\sigma$	Parameter	Degree of variation in maternal infectivity

The subscript *i* denotes the *i*th mother–child pair.

children; median duration, 45 days) had a significantly higher rate of HIV infection (23 versus 12%), and transmission risk increased with duration of breastfeeding. Because early diagnostic tests were not performed we have no knowledge of when transmission occurred. The model was estimated by maximizing numerically [21] the log-likelihood function,

$$(5) \sum_i [Y_i \log(\pi_i) + (1 - Y_i) \log(1 - \pi_i)]$$

where  $\pi_i$  is substituted by equation (3).

Because inference is sensitive to the parameter  $\sigma$ , which controls variation in infectivity, this was re-estimated from two other studies and equation (5) remaximized with respect to  $\alpha$  and  $\beta$ . The overall probability of mother-to-child transmission by duration of breastfeeding was then determined for each set of parameter estimates.

*International Registry of HIV-Exposed Twins*

The most recent report from this registry described 115 prospectively followed twin-sets with known infection status [14]. Information on breastfeeding was often missing, but it can be assumed that all, or almost all, of the 98 sets notified from Europe or North America were exclusively bottle-fed. Of these sets, neither twin was infected in 73 sets, both twins were infected in nine sets, and in 16 sets the infection status was discordant.  $\sigma$  is estimable in this study as the hazard of infection for each twin is scaled by the same infectivity factor. Setting  $t_i = 0$  in equation (2) and allowing for a birth order effect [14], the conditional probability that the  $j$ th twin of the  $i$ th mother is infected is as follows:

$$(6) \theta_{ij} = 1 - \exp[-\exp(\alpha_j + \sigma z_i)]$$

Thus, the likelihood contribution from the  $i$ th mother is as follows:

$$(7) \int_{-\infty}^{\infty} [\theta_{i1}^{y_{i1}} (1 - \theta_{i1})^{1-y_{i1}}] [\theta_{i2}^{y_{i2}} (1 - \theta_{i2})^{1-y_{i2}}] \exp(-z_i^2/2) dz_i$$

*AIDS Clinical Trials Group 076 trial*

Given appropriate information,  $\sigma$  can be estimated by assuming that maternal infectivity is entirely mediated through viral load. This assumption is almost certainly incorrect and results in a lower bound estimate. We used the results of linear logistic models,

$$(8) \log_e \frac{(1 - u_i)}{u_i} = a + b \log_{10} (\text{RNA copies}),$$

fitted to the placebo group in the AIDS Clinical Trials Group (ACTG) 076 trial, which assessed the effectiveness of zidovudine in preventing mother-to-child transmission in non-breastfed subjects [11]. The complementary log-log and logistic transformations are almost indistinguishable for values of  $u_i$  below 0.3 [22].

Thus, if viral load plays the role of the latent variable  $z_i$ ,  $\sigma \approx b \times \text{SD}$  from equations (1) and (8), where SD denotes between-individual SD in  $\log_{10}$  RNA copies. We used the largest of the different estimates of parameter  $b$  (viral load assessments by reverse transcription PCR at the time of delivery) [11].

**Results**

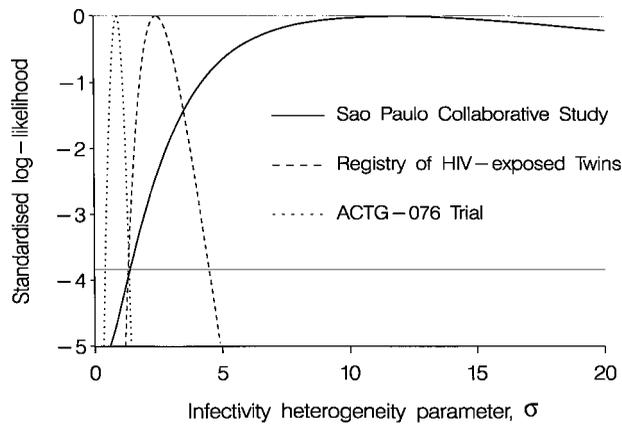
Comparison of the predicted and observed numbers of infected children, cumulated by duration of breastfeeding, indicated reasonable goodness-of-fit of the model to data from the Sao Paulo Collaborative Study (Table 2). This study generated the highest maximum likelihood estimate for the parameter controlling variation in maternal infectivity ( $\sigma$ ), although imprecisely due to limited variation in the duration of breastfeeding (Fig. 1). Even the extreme heterogeneity model ( $\sigma \rightarrow \infty$ ) was statistically acceptable (likelihood ratio test,  $P = 0.10$ ), consistent with the lack of a significant univariate dose-response effect [20]. Reflected in the convexity of the likelihood functions, the International Registry of HIV-Exposed Twins and the ACTG 076 trial carried considerably more information about  $\sigma$  (Fig. 1), the lower estimates indicating less marked variation in infectivity.

The effect of duration of breastfeeding on the overall probability of mother-to-child HIV transmission, and thus the age-specific risk of breastfeeding-related transmission, is highly sensitive to the degree of variation in infectivity (Fig. 2). When substantial, the average risk of breastfeeding-related transmission declines rapidly with age and most infections occur in the early stages of breastfeeding. When the variation is less, infections attributable to breastfeeding are more evenly spread across the period of exposure to breastmilk, although an imbalance towards early transmission remains.

The homogenous infectivity model ( $\sigma = 0$ ) was estimated from the Sao Paulo Collaborative Study data and yielded a transmission probability of 0.05% per day of breastfeeding. However, this model overestimated the combined risk of *in utero* and intrapartum transmission, underestimated the additional transmission risk of limited breastfeeding (Table 2), and was statistically

**Table 2.** Goodness of fit of the model to data from the Sao Paulo Collaborative Study.

Duration of breastfeeding (days)	No. infected children		
	Observed	Predicted under unrestricted model	Predicted under homogenous infectivity model
0	34	34.2	39.5
1-15	13	12.7	10.1
16-180	13	13.4	9.7
> 180	9	8.7	9.3

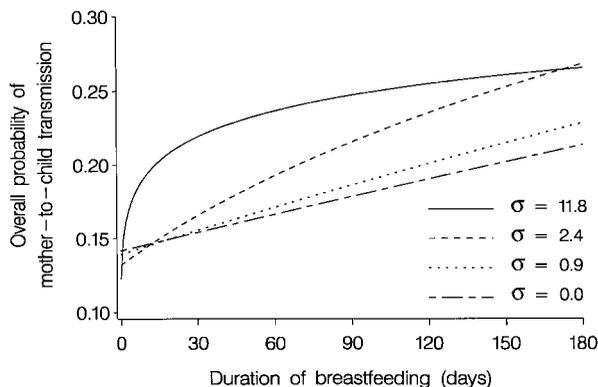


**Fig. 1.** Profile log-likelihood for infectivity heterogeneity parameter  $\sigma$  from the three different studies, showing the plausibility of different values of  $\sigma$  in light of the observed data. Values above the horizontal line form the 95% confidence region.

rejected (likelihood ratio test,  $P = 0.01$ ). The International Registry of HIV-Exposed Twins and the ACTG 076 trial were also inconsistent with the hypothesis of homogenous infectivity (Fig. 1).

## Discussion

Researchers studying the timing of HIV transmission through breastfeeding have focused on the role of age-related factors [8–10]. Several mechanisms that would result in an increasing age-specific risk of transmission have been proposed, including volume of breastmilk ingested, introduction of supplementary foods to the diet, and declining concentrations of specific and non-specific immune substances in breastmilk [9,10]. Conversely, infection risk may be enhanced in the early



**Fig. 2.** Overall probability of mother-to-child transmission by duration of breastfeeding according to different estimates of  $\sigma$ .  $\sigma = 0$  corresponds to the homogenous infectivity model.

stages of breastfeeding because of an immature immune response, increased gut permeability, or high antigen levels in colostrum [8,10]. The high additional risk of HIV infection associated with even a few weeks of breastfeeding [19,23] would appear to indicate that this second set of factors is more important than the first.

However, our model has helped identify a previously unrecognized determinant of the timing of breastfeeding-related HIV transmission. Because of variation in maternal infectivity, the population age-specific risk of transmission declines, even if the risk of transmission for each individual mother-child pair remains constant. This apparent paradox arises because the pool of mothers who have not already transmitted the virus becomes relatively less infectious. This effect is known as ‘frailty’ in the context of survival analysis [18]. Variation in infectivity does not exclude a direct effect of the age of the child, and these must jointly determine the timing of breastfeeding-related transmission. The degree of variation in maternal infectivity, the importance of intrinsic age effects, and thus the relative contributions of the two mechanisms, are unresolved questions.

The three sources of data that we examined produced different estimates of the parameter  $\sigma$  that controls the degree of variation in maternal infectivity. The true variation may be different in the different studies, related to the phase of the HIV epidemic and referral patterns. In addition, the estimate generated by the Sao Paulo Collaborative Study is inversely related to the strength of the observed association between the duration of breastfeeding and the risk of HIV transmission, which could have been weakened by age-related effects and by a number of biases in the data. Breastfeeding was curtailed in some HIV-infected children who died in early infancy and there may have been related effects due to morbidity of the child or morbidity/mortality of the mother. A potentially more important bias is inaccuracy in the recorded duration of breastfeeding, which mothers were asked to recall up to 7 years after the birth of the study child [19]. Conversely, the ACTG 076 trial resulted in an estimate of the frailty parameter which is almost certainly too low, since measured viral load, the basis for the estimate, only partly explained the large reduction in transmission risk in the group that received zidovudine [12].

A further source of information is provided by PCR studies of breastfed children, in which the rate of mother-to-child transmission after age 6 months has been estimated to be 6–7 per 100 child-years of breastmilk exposure [9,16]. This is inconsistent with the minimal late postnatal transmission predicted from versions of the model with large variation in infectivity. However, because of the assumption that each mother’s infectivity remains constant, the model is over-simplistic when breastfeeding is prolonged and

should not be used for prediction in this situation. In many African populations, for example, breastfeeding is routinely practised into the second year of life [4]. Over this period mothers would tend to become more infectious as HIV infection progresses with different mothers experiencing different changes in infectivity, and there may be transient phases of high infectivity concomitant with viraemia or lesions of the nipples [3,20]. In principle, the model could be extended to incorporate age effects in addition to frailty effects and to allow for different, although correlated, frailty effects during pregnancy and breastfeeding. However, the data that are currently available are inadequate to estimate models of this sophistication.

Two studies have assessed mathematically the consequences of early cessation of breastfeeding by HIV-infected mothers, regarding mother-to-child HIV transmission and infant death as equally undesirable events [6,7]. Nagelkerke *et al.* [6] concluded, based on the assumption that the risk of breastfeeding-related transmission was constant with age, that breastfeeding for 3–7 months minimized the number of adverse outcomes given ‘typical’ African parameters. Kuhn and Stein [7] compared the policies of avoiding breastfeeding entirely, breastfeeding to 3 months of age, and prolonged breastfeeding beyond 12 months. Early cessation of breastfeeding was more favourable than prolonged breastfeeding in most scenarios, but the comparison with complete avoidance was highly sensitive to assumptions about the risk of early postnatal transmission. Our analysis indicates that this risk may be substantial and almost certainly rules out uniform breastfeeding-related transmission, as assumed by Nagelkerke *et al.* [6].

Epidemiological evidence for high levels of transmission of HIV in the early stages of breastfeeding supports, at first sight, withholding colostrum as a way of reducing paediatric infection [2]. For this intervention, however, an understanding of the biological determinants of the timing of transmission is essential. Withholding colostrum could be effective if there are high levels of infectious virus in breastmilk in early lactation or enhanced neonatal susceptibility to infection. If, on the other hand, early transmission resulted from a subgroup of highly infectious mothers, delaying the onset of breastfeeding would merely postpone transmission of the virus to older ages.

Similarly, preliminary data from Thailand showed that giving zidovudine to pregnant women from 36 weeks gestation halved transmission risk from 19 to 9% [24], similar to the reduction observed in the ACTG 076 trial, which used a more complex therapeutic regimen [11]. It is important to note that both studies were conducted on bottle-fed subjects, and that no data have been published on the effectiveness of antiretroviral

therapy in a breastfeeding population. In this situation, the pool of children who could potentially be infected through breastfeeding will be enlarged to include those who escape intrapartum infection as a result of maternal treatment. These will tend to be children of mothers who would have been highly infectious in the absence of treatment. Since HIV levels in plasma rapidly return to, or even above, pretreatment levels when antiretroviral treatment is discontinued [17,25], the net effect of therapy may be a displacement of intrapartum infection to breastfeeding infection, without materially reducing overall mother-to-child transmission.

In conclusion, variation in maternal infectivity has important implications for interventions to reduce mother-to-child HIV transmission. Early cessation of breastfeeding is likely to be less effective than predicted by mathematical models, which assume that homogeneous infectivity and reductions in transmission risk through use of antiretroviral therapy in breastfed populations may be less impressive than reductions documented in bottle-fed subjects. In light of uncertainty about the specification of our model and the data used to estimate it, randomized controlled trials in appropriate populations are the only way to reliably quantify the effectiveness of these interventions. Finally, as the use of antiretroviral therapy spreads into routine clinical practice, the number of children exposed to infection through breastmilk will increase. This makes it even more important to find ways to overcome the social and economic barriers that prevent many HIV-infected women utilizing safe alternatives to breastfeeding [3,8].

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