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Do the benefits of breastfeeding outweigh the risk of postnatal transmission of HIV via breastmilk?

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SUMMARY
Conflicting recommendations have been offered about whether HIV+ mothers should breastfeed. Since there is a strong precedent for US infant feeding practices to be imitated in developing countries, a model was constructed to estimate infant mortality if the CDC admonition for HIV+ mothers not to breastfeed were upheld in less developed settings Estimates are given for infant mortality in the presence and absence of breastfeeding across several baseline levels of infant mortality and across several theoretical rates of transmission through breastfeeding. The infant mortality associated with HIV infection acquired through breastfeeding is estimated to be lower than the mortality associated with the diseases of infancy that would result if breastmilk were withheld. The difference in these estimates is greater in areas with high baseline levels of infant mortality.

INTRODUCTION
The World Health Organization (WHO) and the US Centers for Disease Control (CDC) have offered conflicting advice about whether mothers with HIV infection should breastfeed their infants. WHO's advice is aimed at women in developing countries and recommends that where the alternatives are not safe, breastfeeding should continue to be the feeding method of choice, regardless of the mother's HIV infection status[1]. On the other hand, the CDC, targeting US American women, recommends that: 'HTLV-III/LAV-infected women should be advised against breastfeeding to avoid postnatal transmission to a child who may not yet be infected.'[2] In Britain, the recommendations of the Department of Health and Social Services are similar to those of the CDC[3].

Although the CDC recommendation that HIV+ mothers refrain from breastfeeding has not been directed to women in developing countries, the danger exists that this recommendation will be heeded in situations for which it was not intended. There is a clear precedent for changes in infant feeding practices - namely the decline of breast-feeding and the rise of artificial feeding - to follow the lead of the industrialized nations[4]. The purpose of this paper is to compare the infant mortality expected among children who are infected with HIV by breastfeeding to that expected among infants who are bottlefed across a variety of circumstances.* This exercise will argue that if breastfeeding practices erode in less developed countries in order to adhere to a CDC-like recommendation, the result will be greater infant mortality than if breastfeeding were maintained.

BACKGROUND
In the United States only about 8% of all persons with AIDS (a reflection of the proportion with positive serostatus) are women[5], and many of these belong to groups with a low prevalence of breastfeeding. In developing countries, on the other hand, roughly half of identified AIDS cases are women[6], and dependence on breastfeeding is near universal. The risk of infant mortality is far greater among bottlefed than breastfed babies in the developing world, where the cost of infant formula can be prohibitive and access to clean water is limited.

It is difficult to estimate the number of women and babies potentially affected by advice about whether to breastfeed. In a hypothetical African population of 10 million persons with a crude birth rate of 50 per 1000, about 500 000 women would deliver per year. Since heterosexual transmission is the predominant mode of HIV infection in Africa, a 10% seroprevalence rate is not unreasonable**,

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*Reference is made to 'bottlefeeding' and 'bottlefed' infants. These terms are meant to refer to both the absence of breastfeeding and the presence of other foods and feeding modes which comprise vectors of endemic disease. No attempt has been made to separate exclusive from partial breastfeeding, although it is assumed that exclusively breastfed infants are at lowest risk of diarrhoeal disease and possibly at highest risk of HIV seroconversion.

**Seroprevalence among apparently healthy persons in rural areas of Uganda has been found to be 1.4-12.5% and 10.6-24.1% in urban areas[7]. Prevalence among healthy African populations (blood donors) have ranged from 0.7% in the Congo to 18% in Kigali, Rwanda[8]. Ten per cent was used in the current analysis for convenience.

and then about 50 000 women would be pregnant and seropositive. Roughly half of their babies would be born infected*, leaving 25 000 babies born uninfected to HIV + mothers in a year. (However, these mothers are likely to bear more than one child before dying from AIDS.)

The evidence that breastfeeding constitutes a mode of HIV transmission is incomplete, yet consistent and suggestive enough to warrant consideration. Case reports suggest that individual mothers have been infected by postpartum blood transfusion and transferred the virus to their infants through breastfeeding[10-12]. The transmission of the HTLV-1 virus by breastmilk[13] and the presence of cell-free virus in the milk of three HIV positive mothers[14] have been documented, although it has been suggested that the presence of HIV within cells is a necessary condition for virus transfer[15]. It is not clear that HIV can be transmitted by asymptomatic seropositive mothers. The known cases of breastfeeding transmission have involved only mothers who were first infected while breastfeeding or who had clinical AIDS[16]. We have argued elsewhere that the opportunities for transmission to occur in this way are probably rare[17]. Nevertheless, for the purpose of this analysis, it is assumed that transmission of HIV by breastmilk is possible.

The effect on infant mortality of withholding breastfeeding is due to the increased risk of death from diseases of infancy, primarily diarrhoea. This effect applies to both seronegative and seropositive infants. (HIV-infected babies die from both rare and common diseases of infancy, and this is a function of both their exposure to pathogens and their impaired immune response to the infection.) Diarrhoea is a leading cause of infant death in many developing countries, and the higher the infant mortality rate the greater the threat of diarrhoea. Bottlefeeding contributes to the risk of diarrhoea because formula is often mixed with contaminated water and excessively diluted to make it go further. Bottlefed infants also do not receive the maternal antibodies (to non-HIV pathogens) that are in breastmilk. Breastfeeding, on the other hand, acts as natural oral rehydration therapy, since it reduces exposure to pathogens and prevents dehydration. That breastfeeding does more than merely prevent exposure to contaminants is shown by the fact that babies only partially breastfed have better survival probabilities than babies receiving no breastmilk[18,19].

In Malaysia it has been estimated that bottlefed infants have 2.5–5 times the risk of dying (from any cause) before the age of 12 months than breastfed infants[18]. A study in Israel confirms that bottlefed infants have a similarly increased risk of disease episodes (relative risks ranging from 2.0 to 3.7)[20]; and even greater relative risks to bottlefed infants were found in Brazil[19].

METHODS

The infant mortality associated with breastfeeding is compared with that of not breastfeeding in a hypothetical population of 100 000 uninfected infants born to infected mothers. A simple model is applied to countries with different levels of total infant mortality, namely 5%, 10% and 15% (Table 1). The midlevel used is typical of much of East Africa, while the highest level used is more often observed in West Africa. For 100 000 uninfected infants at risk of becoming infected by breastfeeding the following are calculated:

- The deaths expected among breastfed infants. This consists of the number of deaths from HIV-related infections acquired through breastmilk, and the number due to diseases of infancy in the remaining uninfected babies (Table 2).
- The deaths expected among bottlefed infants. This consists of the number of deaths due to diseases of infancy (Table 3).
- The total numbers of deaths among breastfed and bottlefed babies. These are compared for each baseline level of infant mortality. (Table 4)

Table 1. Number of deaths expected in 100 000 HIV – infants breastfed by seronegative mothers*

Number of infants HIV– at birth	*Baseline infant mortality rate*	*Expected number of deaths*
100 000	0.05	5 000
100 000	0.10	10 000
100 000	0.15	15 000

*These are actually the numbers of deaths expected to all infants in the absence of maternal HIV. Especially in areas with low baseline rates of infant mortality, many babies are bottlefed. Therefore, some of this mortality is due to diseases of infancy associated with bottlefeeding. Presumably, then, this is an overestimate of mortality associated with breastfeeding.

*Vertical transmission rates ranging from 12% to 65% have been reported in five cohort studies[9]. A rate of 50% has been used here, but the analysis could be replicated for any population with a known rate of vertical transmission.

Table 2. Breastfeeding model: number of deaths expected in 100 000 HIV− infants breastfed by seropositive mothers

No of infants HIV− at birth (1)	*HIV transmission rate* (2)	*No of HIV deaths** (3)	*IMR†* (4)	*No of non-HIV deaths* (5)	*Total No of deaths* (6)
100 000	0.01	950	0.05	4 953	5 903
100 000	0.05	4 750	0.05	4 763	9 513
100 000	0.10	9 500	0.05	4 525	14 025
100 000	0.20	19 000	0.05	4 050	23 050
100 000	0.01	950	0.10	9 905	10 855
100 000	0.05	4 750	0.10	9 525	14 275
100 000	0.10	9 500	0.10	9 050	18 550
100 000	0.20	19 000	0.10	8 100	27 100
100 000	0.01	950	0.15	14 858	15 808
100 000	0.05	4 750	0.15	14 288	19 038
100 000	0.10	9 500	0.15	13 575	23 075
100 000	0.20	19 000	0.15	12 150	31 150

*Assuming 95% of HIV+ infants die within 12 months. (In fact, most die after the first year.)
†Applied only to infants remaining HIV−.

The following assumptions are made:

- The probability of HIV transmission by breastfeeding alone is probably quite low, and is presumed to be less than 20%. Therefore, four theoretical probabilities of HIV transmission by breastmilk are presented, namely 1%, 5%, 10% and 20%.
- Ninety-five per cent of infected babies will die before reaching their first birthday. This assumption overstates the effect on infant mortality of acquiring HIV by breastfeeding, since in reality many of the deaths will occur during the second or third year of life.*
- Four different relative risks of death due to diseases of infancy for bottlefed babies compared to breastfed babies are used, (based on other studies) namely 3, 4, 5 and 6. In this exercise, the relative risk of 6 is used only at the highest level of infant mortality (15%). High relative risks of dying from diseases of infancy have been associated with the worst sanitary facilities[18] and presumably also with the highest baseline level of infant mortality rate.

*Authors from WHO have assumed 80% mortality under age 5 years in cases of perinatally acquired HIV, although no basis for this assumption was given[9]. When 80% is substituted for the 95% figure used in the current analysis, the conclusions of this report remain unchanged.

Table 3. Bottlefeeding model: number of deaths expected in 100 000 bottle-fed babies of HIV+ mothers

No of infants (1)	*IMR* (2)	*Relative risk* (3)	*No of deaths* (4)
100 000	0.05	3	15 000
100 000	0.05	4	20 000
100 000	0.05	5	25 000
100 000	0.10	3	30 000
100 000	0.10	4	40 000
100 000	0.10	5	50 000
100 000	0.15	4	60 000
100 000	0.15	5	75 000
100 000	0.15	6	90 000

RESULTS

Assuming a 10% infant mortality rate, which is typical of much of Africa, and assuming the most conservative relative risk estimate (RR = 3, the lowest), 30 000 deaths among 100 000 HIV-uninfected bottlefed babies can be expected (Table 3). If all were breastfed, again assuming 10% infant mortality, and assuming a 5% transmission rate by breastmilk, there would be about 14 000 deaths (Table 2). The breastmilk transmission rate must be about 20% before the expected number of deaths among breastfed babies approaches that associated with bottlefeeding. The more likely transmission rate is 1% or less, which would result in about 11 000 deaths among infants who are breastfed.

Breastmilk transmission at rates of 1%, 5%, 10% and 20% would produce an estimated 950, 4750, 9500 and 19 000 additional infant deaths respectively (Table 2). At a baseline infant mortality rate of 10%, these figures are compared with at least 20 000 additional deaths attributable to bottlefeeding (and this number could well be twice as large) (Table 4).

DISCUSSION

The estimated number of infant deaths associated with bottlefeeding by an HIV+ mother appears to greatly outweigh the comparable number associated with breastfeeding, especially in settings with high baseline levels of infant mortality, such as those in developing countries (Figure 2). (This may also be true in developed countries where HIV infection most often affects women in population groups with higher than average rates of infant mortality.)

Table 4. Number of deaths expected in 100 000 HIV− babies of HIV+ mothers, bottle-fed babies *vs* breastfed babies

IMR (1)	*No of HIV deaths* (2)[a,e]	*No of Non-HIV deaths* (3)[b,f]	*No of deaths among breastfed infants* (4)[c,e]	*No of deaths among bottlefed infants* (5)[d,f]
0.05	950–19 000	10 000–20 000	5 903–23 050	15 000–25 000
0.10	950–19 000	20 000–40 000	10 855–27 100	30 000–50 000
0.15	950–19 000	45 000–75 000	15 808–31 150	60 000–90 000

[a]Column 3 of Table 2; [b]Table 3 column 4 minus Table 1 column 3; [c]Column 6 of Table 2; [d]Column 4 of Table 3; [e]HIV transmission rate by breastfeeding = 0.01 to 0.20; [f]Relative risk of infant mortality due to bottle-feeding = 3.0–5.0 for IMR = 0.05–0.10; 4.0–6.0 for IMR = 0.15.

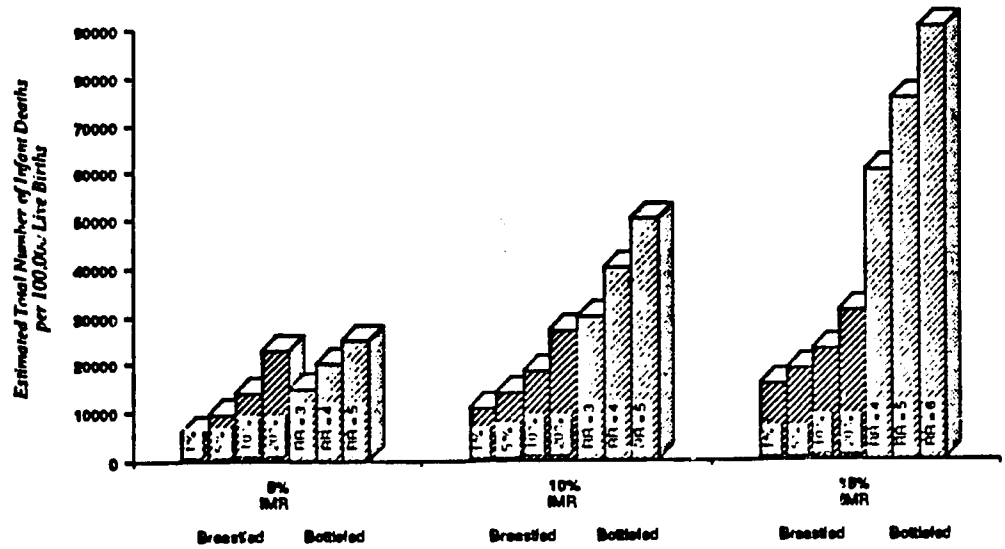

Figure 1. Total infant deaths expected by baseline infant mortality rate (IMR) and by breastfeeding status. % = hypothetical HIV transmission rate via breastfeeding. RR = relative risk of mortality associated with not breastfeeding

Deaths due to HIV acquired through breastfeeding are crudely estimated at between 1000 and 19 000, depending on which assumption about transmission rate is used. Estimates of additional deaths due to diseases of infancy associated with the withholding of breastmilk range from 10 000 to 75 000.

This analysis focuses on uninfected babies born to mothers who became infected before delivery. This group excites the greatest interest, and is the subject of the CDC recommendations, because prevention of HIV transmission is possible. However, especially in developing countries, the resources do not exist to test all mothers (nor the technology to test all babies) at the time of delivery. Thus, breastfeeding usually occurs in ignorance of the mother's serostatus, and rarely is her predelivery status known. The majority of seropositive mothers with uninfected babies live in about 10 African nations. Unfortunately, these are precisely the countries that stand to suffer the most from advice to withhold breastfeeding.

Because the risk of transmission might be greater during the mother's initial exposure to infection, before antibodies have been formed, the mother who acquires the infection postpartum may be at greater risk of passing the infection to her baby through breastfeeding than the mother who was seropositive before delivery. This may be especially true if the mother became infected by the very efficient means of blood transfusion. Four of the probable cases of breastfeeding transmission which have been reported fall into this category. The admonition not to breastfeed if HIV+ would have prevented none of the reported cases since none of the mothers had reason to believe they were infected

or were seropositive when they began breastfeeding. In order for the CDC recommendations to apply and for the risk of mortality from other factors not to be problematic, the mother must also have access to regular and appropriate quantities of high quality breastmilk substitutes and have the possibility of mixing these and providing them to the infant with the minimum of exposure to bacteria and other disease producing agents. Alternatively, she should have access to the milk of another mother who is known to be seronegative and to be at low risk of exposure to HIV.

It has been suggested that policies either advocating or discouraging breastfeeding should be avoided due to the paucity of information available[17]. Until such time as breastfeeding transmission rates become known, we are limited to crude estimates such as those presented here. These models can be adapted to local circumstances where seroprevalence and vertical transmission rates are known.

Much additional research is needed. It is important to know whether infected babies of infected mothers benefit from breastfeeding by being exposed to fewer pathogens and because of the immune protection from the breastmilk. Likewise, it will be increasingly important to determine the extent to which all infants are protected by non-HIV antibodies from breastfeeding by an HIV-infected mother. It is not known whether the usual nutritional and immunological benefits of breastfeeding are maintained when the mother is infected. It is also unknown whether the likelihood of HIV transmission increases as a mother progresses toward clinical AIDS, and one case report suggests this might be true[16]. Finally, it is unknown what proportion of infected babies acquire their infection *in utero*, during delivery, or post partum.

Although there are many unanswered questions, the possibility of transmission of HIV by breastfeeding appears to be real, albeit uncommon. Until some basic questions about HIV and breastfeeding are answered, infected mothers should be encouraged to breastfeed as usual, since bottlefeeding may result in more infant deaths than there would be from HIV infection acquired by breastfeeding, especially in populations with medium to high baseline levels of infant mortality.

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