

Commentary: Revisiting the Risk of HIV Infection from Breastfeeding

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History of this Paper

This paper has been submitted to Lancet (where the Dunn paper was originally published in 1992), the British Medical Journal in 2004 and the Journal of Human Lactation in 2005 and was rejected by all three. Lancet gave no reasons. BMJ sent the paper for review to a scientist with significant financial conflicts of interest with the formula industry. That reviewer implied that the Nduati studies from Kenya had largely supplanted Dunn, a contention we challenge here and in a letter published in JAMA. The JHL reviewer recommended against publication because the Dunn paper is so old. They noted that there is newer research, but only provided two citations for conference abstracts, not fully documented peer-reviewed papers, and one mathematical model, which is of course fully dependent on various assumptions, some of which we question.

We disagree that Dunn is irrelevant. The paper is still heavily referenced as a source for statements that breastfeeding comes with a 14% or 15% risk of HIV transmission. Furthermore, the flaws in the Dunn research have never been the subject of as much detailed discussion as in this paper. Many recent papers have relied on Dunn's conclusions, unaware of the deficiencies.

Rather than continue to try to find a journal willing to publish this information, and thus delay making it public even longer, we decided it was most appropriate to publish it on the internet so that people can make up their own minds on this important issue.

Biographical Statements

David Crowe: David Crowe has been the President of the Alberta Reappraising AIDS Society since its founding in 1999. He has had articles and letters on AIDS published in a number of magazines and scientific periodicals.

George Kent: George Kent is professor in the Department of Political Science at the University of Hawai'i. He works on human rights, international relations, peace, development, and environmental issues, with a special focus on nutrition and children. His book entitled *Freedom from Want: The Human Right to Adequate Food* was published by Georgetown University Press in 2005.

Pamela Morrison: Pamela Morrison worked in Zimbabwe as an International Board Certified Lactation Consultant in private practice from 1990 to 2003. During this time she also served as a Baby Friendly Hospital Initiative facilitator and assessor, as a member of the Zimbabwe National Multi-sectoral Breastfeeding Committee, and on committees formed to facilitate national legislation of the International Code of Marketing of Breastmilk Substitutes and to develop policy on HIV and infant feeding.

Ted Greiner: Ted Greiner has worked at policy, program and research levels on breastfeeding promotion since 1974 and on HIV and infant feeding since the first WHO Expert Meeting on HIV and Breastfeeding in 1987.

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Abstract

A 1992 meta-analysis by Dunn *et al* published in Lancet estimated that 14% of babies of HIV-positive mothers would become infected with HIV due to breastfeeding. This conclusion has been widely accepted, and is used to encourage formula feeding by HIV-positive mothers. The meta-analysis suffered from a lack of randomized trials for source data, the use of data which were neither then, nor later ever published, inconsistent definitions of HIV infection and of breastfeeding and no consideration of potentially confounding factors or of other health outcomes. The flaws in this meta-analysis may have led to errors in estimation of the risk of mother-to-child transmission of HIV through breastfeeding, making it inappropriate to use Dunn's final estimate of a 14 percent transmission rate as the basis for guiding current public health policy.

Keywords

HIV • AIDS • Breastfeeding • MTCT (Mother-to-Child Transmission) • PMTCT (Prevention of MTCT) • Meta-analysis • Transmission

Background

One of the most influential papers published on mother to child transmission of HIV through breastfeeding was the meta-analysis of Dr. David Dunn and his colleagues.¹ As of January 30, 2004, 389 scientific papers have referenced this meta-analysis.² Using the results of six previous studies, Dunn estimated that the rate of mother-to-child transmission of HIV for breastfed children would be 14% higher than for those who were formula fed.¹ Our concern is that current public health policies are based on this conclusion. It is particularly important for health workers advising HIV-positive mothers of the safest feeding method.

UN agency policy recommends that “It is therefore important that women be empowered to make fully informed decisions about infant feeding, and that they be suitably supported in carrying them out.”³ However, in many PMTCT (Prevention of Mother To Child Transmission) programs all mothers are strongly discouraged from breastfeeding or are pressured to start weaning as early as three months postpartum and often to complete it in two weeks or less. We find no evidence to support the safety of such practices. Without such evidence, and since most MTCT occurs in areas in Africa where the risk of illness or death from not breastfeeding is likely to be higher than the risk of illness or death from being infected by HIV by breastfeeding,⁴ it is plausible that for the overwhelming majority of babies the best overall outcome may be achieved if they are breastfed as long as mother and baby desire.

HIV-positive mothers in industrialized countries are rarely supported if they choose to breastfeed their infants, and indeed they may be threatened with loss of custody.⁵ In at least one case, breastfeeding by an HIV-positive mother was prevented through legal proceedings.⁶

Methods

We reviewed Dunn’s research, and all the source studies used in the meta-analysis. We examined the studies for methodological flaws not considered by Dunn. We also examined more recent research that has attempted to quantify the risk of HIV-transmission due to breastfeeding, including using a search of the Cochrane Database for the combined term “HIV and breastfeeding” to ensure all relevant papers were identified. We only included studies that attempted to estimate the postnatal transmission rate, and that included both breastfeeding and formula-feeding mothers.

We specifically considered the definitions of HIV-infection and breastfeeding used by Dunn’s source studies, possible confounding factors, including the duration of breastfeeding and other health risks, and examined these studies for information on health outcomes.

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Findings

Dunn *et al* recognized that it is not easy to distinguish transmission of HIV *in utero* and during birth from early transmission through breastfeeding. The use of HIV antibody tests before a child is 15-18 months old is not reliable because of the persistence of maternal antibodies in infants of HIV-positive mothers.⁷ To avoid this problem, the results of six studies including both breastfeeding and formula feeding mothers were used to estimate the excess rate of HIV transmission due to breastfeeding. The studies were from Europe,⁸ Miami, USA,⁹ France,¹⁰ Switzerland,¹¹ Kinshasa, Zaire,¹² and Australia.¹³

The researchers calculated the weighted average of the difference between the rates of HIV transmission in the breastfeeding group and in the formula feeding group.¹ The rates of HIV infection in the breastfeeding group, when compared to the rates in the formula feeding group, varied substantially from 5% lower in one study,⁹ to 33% higher in another.¹³

More Recent Research

Since Dunn's study was published in 1992, there has been little research on pediatric HIV infection due to breastfeeding in industrialized countries, primarily because of the difficulty of finding openly breastfeeding HIV-positive mothers.^{14,15} Many health professionals in these countries now consider it unethical to 'allow' HIV-positive mothers to breastfeed.⁶

There have been more recent attempts to estimate the risk of HIV transmission through breastfeeding in non-industrialized countries. A review paper by de Cock *et al*¹⁶ cites Dunn as well as a Côte d'Ivoire study,¹⁷ an international analysis¹⁴ and a study from Malawi.¹⁸ All of these later studies used a different cutoff to attempt to distinguish breastfeeding transmission ('late postnatal transmission') from transmission during pregnancy or birth. The cutoffs were 6 weeks,¹⁸ 2.5 months¹⁴ and 3-15 months.¹⁷ The two African studies did not include a comparison group of non-breastfeeding mothers^{17,18} and the international pooled analysis had scant information on breastfeeding in Western countries (151 months out of 62,568 total months of follow-up), and little on formula feeding in African countries (2,466 months out of 20,950 total months of follow-up).¹⁴ A recent study in Zimbabwe was similar, but did not attempt to estimate

the total transmission due to breastfeeding, did not include a comparison group, and stopped monitoring at 6 months, well before antibody tests are believed to be reliable.¹⁹

In contrast to these studies, Dunn's analysis avoided an arbitrary cutoff time to distinguish breastfeeding transmission from transmission during pregnancy and birth by comparing the transmission rate of groups of breastfed children of HIV-positive mothers with that of groups of formula fed children.

A study in Nairobi, Kenya performed a similar analysis to Dunn's, although just on a single, highly selected population.²⁰ Access to safe water (limited in Africa) was a criterion for inclusion, which would likely reduce the risks of formula feeding more than that of breastfeeding. Although the study was randomized, 82% of eligible HIV-positive mothers were not included, often because they refused to allow researchers to choose their feeding method. Another difficulty with the study was that mixed feeders were included in the analysis of both the 'breastfeeding' and 'formula feeding' study arms, and exclusive breastfeeding was not analyzed separately from mixed feeding.²¹

An anomaly was that 3.9 percentage points more of the babies in the breastfeeding arm had PCR evidence of HIV infection at birth. The difference in HIV status observed among babies at 24 months was similar to Dunn's estimate – 16.2% of the breastfed babies had transmission attributed to breastfeeding (12.3% if the imbalance in HIV status at birth is corrected for).

Problems with Dunn's Analysis

Despite the strengths referred to above, Dunn's analysis has several weaknesses, including some in the source studies that cannot be overcome by a meta-analysis. They are described in the following sections.

a. The Use of Unpublished Data

Dunn used unpublished data from four of the six source studies. According to a footnote to Table II, updated data were obtained for three of the studies^{8,10,13} but this was not noted for a fourth.¹¹ Dunn's use of unpublished data means that his estimates were partially based on research not subjected to peer review.

However, in the European Collaborative study⁸ and the French study,¹⁰ the differences in rates of transmission were so small that the exclusion of the unpublished portion of the data would not significantly change the results of the analysis.

The study referenced in Dunn as the source of the Australian data¹³ did not have any formula-feeding data. Consequently, it is impossible to evaluate the methodology used to extract these data from an Australian registry of women believed to have become HIV-infected after birth (as opposed to women infected before or during pregnancy). This is important because these data provided the largest difference between rates of HIV transmission in breastfeeders versus non-breastfeeders (33%). Without these data, the estimated risk of HIV transmission would drop from 14% to 12% (using the same weighted average technique).²² These data also should have been excluded because they were not composed of “children born to mothers known to be infected at the time of delivery” which Dunn claimed is necessary to obtain “valid estimates of the additional risk of transmission through breastfeeding”¹.

The Swiss study¹¹ did not publish breastfeeding data for all trial participants. However, it did report that at least 22 children were breastfed (11% of 210 children in cohort A), which is more than the 13 breastfed children reported by Dunn for both cohorts in the study, a discrepancy which has not been explained by either Dunn or Kind, the lead author of the Swiss study.²³

b. Lack of Randomization

None of the studies incorporated into the Dunn meta-analysis were randomized clinical trials. Mothers chose the method of feeding their babies. However, in at least two studies, breastfeeding was discouraged.^{8,10} Furthermore, only the Zaire study was designed to compare feeding methods.¹² Data on feeding method were collected during the studies, except in the case of the Australian study where the data were retrieved retrospectively from a registry.¹³

c. Inconsistent Definitions of HIV Infection

Table 1 shows that the definition of HIV infection for children varied considerably among the studies. A number of anomalies were encountered, including children who did not fit either the definition of ‘infected’ or ‘uninfected’.

Table 1: Summary of Studies Quoted by Dunn¹

Study	Sample Size	Definition of HIV infection	Anomalies
Europe ⁸	808	AIDS ²⁴ OR HIV-related death OR Antibody detection after 18 months OR Detection of virus or p24 antigen at least twice	4 children had positive cultures but negative antibody tests and were excluded.
Miami ⁹	79	Positive culture (2 consecutive detections of p24 antigen) OR Increasing p24 antibody titers OR Increasing gp41/gp120 antibody titers	Among infants believed to be infected, 1 was culture negative until 30 months. 2 had no p24 antibody (at 3 visits), 2 had no antibody to p24 and to gp41/120 at 6 and 9 months but positive culture and HIV-related disease.
France ¹⁰	606	Western Blot antibody test at 18 months (any one HIV antibody present) OR (Death before 18 months AND (an Opportunistic Infection OR HIV isolation (culture)))	9 infants (8%) were seronegative but with nonspecific clinical signs possibly related to HIV infection at 18 months and 1 at 24 months. 5 seronegative infants were PCR positive.
Switzerland ¹¹	141	AIDS ²⁴ OR Antibody positive after 24 months (ELISA/WB) OR Positive culture or antigen or PCR in at least two different samples at any age.	20 children lost maternal antibody, had no symptoms and had at least one atypical test result. All were excluded.
Zaire ¹²	106	WHO Pediatric AIDS definition ²⁵ OR Positive antibody test at 12 or 18 months (ELISA and 2 bands on Western Blot)	4 who died without antibody tests after 18 months, and 2 lost to follow-up were classified as infected based on clinical symptoms.
Australia ¹³	32	Positive ELISA or Immunofluorescence Assay AND Positive Western Blot	None described

The rules for interpretation of the Western Blot (i.e. what combinations of bands are interpreted as positive, negative and indeterminate) were not specified in most studies, nor were the signals used to identify a positive culture always identified (e.g. detection of a certain level of p24 antigen or reverse transcriptase).

Inconsistencies among the studies in their definitions, choices of indicators, and classification of children with anomalous results means that they are not directly comparable.

d. No Definition of Breastfeeding

Breastfeeding is not defined in the Dunn meta-analysis, nor in most of its source studies. Notwithstanding calls by lactation experts for clearer definitions of breastfeeding (e.g. exclusive, nearly-exclusive, partial or token breastfeeding)²⁶ “breastfeeding” is clearly defined only in one of the source studies.¹² The lack of clear distinctions between feeding categories plague much infant feeding research, which means that conclusions regarding infant morbidity and mortality deserve serious challenge.²⁶ Mothers who breastfed for only a few days were given as much weight as those who breastfed for longer than six months. In addition, only 28 babies included in all the studies quoted by Dunn are described as having been exclusively breastfed.¹² These cases were combined with babies who were fed with breast milk together with infant formula or other foods. This is unfortunate because, outside the context of HIV, exclusive breastfeeding appears to produce the best health outcomes,²⁷ and there are indications that health outcomes for infants of mothers diagnosed as HIV-positive may be better if they are exclusively breastfed than if they are formula fed or mixed fed,^{28,29,30} However, there is a need for further research.

e. No Minimum Duration of Breastfeeding

A strict definition of breastfeeding should also include a minimum duration. In all but the Zaire study, where breastfeeding lasted for an average of 9.9 months,¹² the median duration of breastfeeding was very short - 2 weeks in the Swiss study,¹¹ 4 weeks in the European study⁸ and 7 weeks in the French study.¹⁰ Most babies were breastfed less than the 90 days required at that time to distinguish postnatal transmission from infection acquired *in utero* or during birth.³¹ No measure of breastfeeding duration was available for the Australian or Miami studies.^{13,9}

Other Weaknesses in the Source Studies

The source studies used by Dunn had weaknesses unrelated to the HIV transmission rate that limit their usefulness for determining whether breastfeeding by HIV-positive women is a health risk for their babies. These weaknesses are found in many more recent papers as well.

a. Ignoring Other Health Risks

Some of the trials documented a high rate of morbidity and mortality among the babies of HIV-positive mothers, but not all of this can be ascribed to HIV-infection. Some may be due to confounding factors which should be controlled for. In particular, the health of the mothers may have been a major factor. For example, more than half of those in the European studies were intravenous drug users.^{8,10,11}

Two of the source studies^{10,11} noted that the abnormally high rate of SIDS (Sudden Infant Death Syndrome) was not associated with HIV status, but was associated with maternal recreational drug use. A shorter duration of breast-feeding has also been correlated with a higher risk of SIDS.³²

The Australian study used a register containing information on women, most of whom were found to be HIV-positive after a blood transfusion, indicating that some of them may have had a serious pre-existing health problem.

The Zaire study¹² found that HIV-negative, formula-fed children of HIV-positive mothers had a greater rate of acute diarrhea, acute fever and lower respiratory tract infections than formula-fed children of HIV-negative mothers. This may indicate that children of HIV-positive mothers are less resistant to disease at birth than infants of HIV-negative mothers, even when they themselves were not HIV-infected, or that there may have been other confounding factors.

b. No Assessment of Health Outcomes

It is known that formula feeding, when compared to breastfeeding, leads to higher rates of morbidity and mortality among children in the general population,³³ even in wealthy nations.^{34,35} Therefore for any specific population, studies based on actual health outcomes are necessary to

show how the overall consequences of breastfeeding (including possible higher rates of HIV transmission) differ from those of formula feeding.

This is particularly important in the formulation of HIV and infant feeding policy because any benefits of a reduction in HIV transmission through breastfeeding will be restricted to the minority of babies who are both uninfected at birth and for whom HIV infection is averted through the avoidance of breastfeeding. A general recommendation that all HIV-positive mothers feed their infants with formula would result in all their babies being exposed to the risks of formula feeding including those who became HIV-positive *in utero* or during birth and those who would remain HIV-negative even if breastfed. In areas where the death rate due to formula feeding (which affects all formula-fed babies of HIV-positive mothers) would be more than the fraction of the death rate associated with breastfeeding-induced HIV infection (which affects only the fraction of babies who acquired HIV from breastfeeding), increasing the proportion of babies fed with formula would result in more deaths.

There is some evidence that breastfeeding might reduce the progression of HIV-positive babies to AIDS. Italian researchers reported that the median time from HIV-infection to AIDS in breastfed children was about double that in formula fed children and that survival was also significantly longer.³⁶ Ryder had only a small number of HIV-infected children (19), but showed a lower rate of AIDS in children exclusively breastfed for 3 months (1/7), compared to mixed fed babies (4/8) and exclusively formula fed babies (1/4).¹² The much larger group of HIV-negative babies of HIV-positive mothers showed dramatically lower morbidity when breastfed rather than formula fed, in all categories monitored (acute diarrhea, acute fever, acute lower respiratory tract infection, acute purulent otitis media and failure to thrive).

The Nairobi randomized study²⁰ showed no difference in death rates between breastfed and formula fed children at two years, though a higher proportion of breastfed babies were HIV-positive. The rate of malnutrition was double in the formula-feeding arm, although this did not reach statistical significance. The rate of dehydration, which often leads to death, was also higher among babies in the formula-fed group, but also was not statistically significant.

Another African study reported that HIV-infected infants who were not breastfed were over four times more likely to have three or more morbidity episodes in their first 15 months of life than HIV-infected infants who were breastfed.²⁸

c. Source Study Variation

In one source study, the rate of HIV infection was 5% lower in the breastfed group than in the formula fed group,⁹ while in another the rate in the breastfed group was 33% higher.¹³ Such wide variation suggests that the transmission rates depend a great deal on modifying or confounding factors, and thus it might not be meaningful to formulate a single global average.

Interpretation

Ethics and Future Research

Informed consent requires that mothers are told what risk to their baby's health and survival is associated with breastfeeding or not breastfeeding. In resource poor settings, a policy of discouraging breastfeeding among HIV-positive mothers to reduce the risk of postnatal transmission could actually increase childhood mortality. This point was made in the conclusion to Dunn's meta-analysis,¹ but it has been ignored by many PMTCT programs. Furthermore, all mothers (not just HIV-positive mothers) in such resource poor settings should be told that there is evidence that exclusive breastfeeding may lead to the best overall health outcomes.²⁷

Because of ethical constraints, based in part on acceptance of Dunn's estimates, it would appear unlikely that another randomized clinical trial of transmission rates in relation to feeding methods will be conducted. However, observational studies using comprehensive health outcomes as end points, in which well-informed women freely chose their method of feeding, would be both ethical and meaningful, as long as strenuous efforts were made to identify and control for confounders related to self-assignment. Observational studies would have the advantage that women who freely chose the method of feeding probably would sustain it longer than women who were told to feed their infants a certain way.

Recommendations

Health practitioners, PMTCT counselors and public health officials should take into account uncertainties and gaps in evidence in the information they provide to mothers. They should take at least the following actions:

- Assist each HIV-positive mother in making an individual risk assessment about the method of feeding most likely to result in the highest attainable standard of health and survival of her baby.
- Inform all mothers that exclusive breastfeeding may minimize the risk of HIV infection while providing much more protection from other diseases than any other feeding method.
- Recommend exclusive breastfeeding for 6 months for mothers who are HIV-negative or of unknown status. As recommended by WHO,³⁷ this should be followed by continued breastfeeding with adequate and appropriate complementary foods for two years or more.

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