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## Are HIV-infected women who breastfeed at increased risk of mortality?

Breastfeeding has a well-established historical role in bringing multiple benefits to infants and improving the health of mothers. The most serious threat to this practice in modern times was the replacement of breastmilk through promoting the use of artificial milks, particularly, but not only, in developing countries. A protracted dispute between the advocates of breastfeeding and the manufacturers of formula milk led to the development of the International Code of Marketing of Breastmilk Substitutes, which was adopted by the World Health Assembly in May 1981.

In more recent times the recognition that breastfeeding transmits HIV-1 to the infant has resulted in the avoidance of this feeding method by HIV-infected women in the industrialized world. In developing countries, however, the majority of seropositive women continue to breastfeed even after counselling. The reasons for this are unclear, but may have less to do with free choice than with the pressure of adverse circumstances (cost of formula, disclosure of HIV status, and cognisance of the substantial non-HIV morbidity and mortality risks associated with formula feeding in impoverished environments) [1]. Accordingly, the attention of research workers has been focused on making breastfeeding, by HIV-infected women, safe for their babies.

In this context, a report from Kenya [2] that breastfeeding by HIV-infected women was associated with a higher maternal mortality rate than that observed in mothers who formula fed, requires urgent consideration. We present the results of morbidity, mortality, and CD4 cell counts for mothers in a vitamin A intervention trial [3], in which women self-selected the feeding method, and careful records were kept of breastfeeding and formula feeding practices. Details of the study population have been described previously [3]. Briefly, the mother–infant pairs in the study were participating in a vitamin A intervention trial to reduce mother to child transmission of HIV-1. The study was conducted at antenatal clinics at two hospitals in Durban, South Africa: the King Edward V111th Hospital and McCords Hospital. Women were recruited between July 1995 and April 1998 and were randomly selected to receive vitamin A or placebo. No women on the study received any antiretroviral therapy, which was not available at the time the study was conducted. During antenatal visits, all women were counselled about the risks of the transmission of virus through breastmilk and of the other health benefits of breastfeeding. Women were asked to make an informed choice on whether to breastfeed or formula feed in accordance with the recent recommendations from UNAIDS, WHO and UNICEF. Women who chose to breastfeed were counselled to consider exclusive breastfeeding because of all its benefits for infant health and development and to avoid gut wall damage possibly relevant to HIV transmission.

Within the two hospitals, 566 mothers were followed with their infants after delivery for a mean of 10.4 months in those who ever breastfed ($n = 410$) and for a mean of 10.6 months in those who never breastfed ($n = 156$). The analysis was conducted at the level of the mother. Only those followed sufficiently long to establish their feeding practice, in which the child had at least one follow-up morbidity visit record, and the child had at least one HIV result available were included.

There was no evidence of any increase in maternal mortality rates among the breastfeeders: two out of 410 (0.49%) women who ever breastfed were known to have died compared with three out of 156 (1.92%) who never breastfed. Two of the deaths were attributable to tuberculosis (one breastfeeder and one who never breastfed), one to pneumonia (never breastfed), one to cervical cancer (never breastfed), and one was of unknown cause (breastfeeder). Two of the deaths took place within 2 weeks of delivery (one breastfeeder and one who never breastfed), two between 7 and 8 months post-delivery (one breastfeeder and one who never breastfed), and one more than 18 months post-delivery (one who never breastfed) (Table 1).

There was no significant increase in the accumulation of clinical problems over the duration of follow-up by feeding practice (Table 1). Among the breastfeeders, the proportion with any morbidity was similar among those who breastfed for more than 3 months 34/239 (14.23%) compared with those who breastfed for less than 3 months 18/171 (10.53%; $P > 0.10$). There was no difference in the proportion with any morbidity by feeding choice, stratified separately by those randomly assigned to the vitamin A group or to the placebo group. In a multivariate logistic regression model, there continued to be no difference in the risk of morbidity

**Table 1.** Mortality and morbidity among 410 HIV-seropositive women electing to breastfeed and 156 electing not to breastfeed.

| | Ever breastfed | Never breastfed | *P* value |
|---|---|---|---|
| Maternal death | 2/410 (0.49) | 3/156 (1.92) | 0.10 |
| Any morbidity recorded on follow-up | 52/410 (12.7) | 23/156 (14.7) | > 0.1 |
| Specific conditions recorded on follow-up | | | |
| Pulmonary tuberculosis | 11/410 (2.68) | 2/156 (1.28) | > 0.1 |
| Candidiasis (> 2 sites) | 1/410 (0.24) | 1/156 (0.64) | > 0.1 |
| Pneumonia | 6/410 (1.46) | 1/156 (0.64) | > 0.1 |
| Ear, nose, throat infections | 1/410 (0.24) | 5/156 (3.21) | 0.002 |
| Gastroenteritis | 1/410 (0.24) | 3/156 (1.92) | 0.033 |
| Gynecological infections | 11/410 (2.68) | 3/156 (1.92) | > 0.10 |
| Cesarean wound sepsis | 5/410 (1.22) | 3/156 (1.92) | > 0.10 |
| Other | 7/410 (1.71) | 4/156 (2.56) | > 0.10 |

among the breastfed compared with the never breastfed group [odds ratio (OR) 0.78; 95% confidence interval (CI) 0.43–1.39] after adjusting for low CD4 cell counts of less than 200 (OR 2.70; 95% CI 1.33–5.48) and low hemoglobin levels of less than 10 (OR 2.36; 95% CI 1.36–4.09).

In one of the hospitals, more detailed clinical follow-up of the mothers took place. Mothers were interviewed at 3 and 6 months about their clinical symptoms since delivery, and their height and weight was recorded. Blood was taken and CD4 and CD8 lymphocyte subsets were enumerated and hemoglobin levels measured. CD4 and CD8 lymphocyte counts did not differ significantly between women who breastfed and women who did not. There was a trend towards an improved hemoglobin level among breastfeeding women, but this did not reach significance. The reported symptoms since delivery did not differ by feeding practice (Table 2).

If those randomly assigned to the vitamin A group were considered separately to those randomly assigned to the placebo group, the stratum-specific differences between breastfeeders and non-breastfeeders in CD4 lymphocyte counts, CD4 : CD8 cell ratios, hemoglobin levels, body mass index, and reported symptoms were essentially similar to those shown in Table 2. However, in stratified analyses, the higher CD4 lymphocyte counts observed among ever breastfeeders compared with never breastfeeders overall (Table 2) became statistically significant in the placebo group ($P = 0.02$), and the higher hemoglobin levels among breastfeeders became statistically significant in the vitamin A group ($P = 0.04$). In multivariate linear regression analysis adjusting for treatment group and baseline CD4

**Table 2.** CD4 and CD8 lymphocyte counts, hemoglobin levels, reported clinical symptoms, and body mass index measured at 3 months post-partum among breastfeeders and never breastfeeders at one of the sites.

| | Ever breast-fed | | Never breast-fed | | |
|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | *P* value |
| CD4 lymphocyte counts | 93 | 548 (239) | 22 | 465 (249) | > 0.10 |
| CD8 lymphocyte counts | 92 | 1081 (546) | 22 | 1055 (588) | > 0.10 |
| CD4 : CD8 cell ratio | 92 | 0.57 (0.33) | 22 | 0.52 (0.28) | > 0.10 |
| Hemoglobin level | 93 | 12.0 (1.10) | 22 | 11.3 (1.65) | 0.07 |
| Body mass index | 145 | 27.5 (5.50) | 34 | 26.9 (5.34) | > 0.10 |
| | N | N (%) with symptom | N | N (%) with symptom | |
| Any reported symptom | 147 | 52 (35.4) | 33 | 13 (39.4) | > 0.10 |
| Loss of appetite | 147 | 11 (7.5) | 33 | 3 (9.10) | > 0.10 |
| Diarrhea | 147 | 10 (6.8) | 33 | 1 (3.03) | > 0.10 |
| Fever | 147 | 20 (13.6) | 33 | 1 (3.03) | 0.09 |
| Swollen glands | 147 | 12 (8.2) | 33 | 4 (12.1) | > 0.10 |
| Fatigue | 147 | 21 (14.3) | 33 | 6 (18.2) | > 0.10 |
| Headache | 147 | 22 (15.0) | 33 | 6 (18.2) | > 0.10 |
| Unintentional weight loss | 147 | 13 (8.8) | 33 | 1 (3.03) | > 0.10 |
| Nausea | 147 | 5 (3.40) | 33 | 0 (0.0) | > 0.10 |
| Lower abdominal pain | 147 | 13 (8.8) | 33 | 3 (9.09) | > 0.10 |
| Night sweats | 147 | 18 (12.2) | 33 | 2 (6.06) | > 0.10 |

lymphocyte count, no significant difference between ever and never breastfeeders was observed in the CD4 lymphocyte counts at 3 months ($B = 21.5$; $P > 0.10$). A significant decline in CD4 : CD8 cell ratios was observed among breastfeeders ($B = 0.09$; $P = 0.02$) after adjusting for baseline ratio and treatment group, and a significant improvement in hemoglobin levels ($B = 0.68$; $P = 0.007$) among breastfeeders was observed after adjusting for baseline hemoglobin values.

In this analysis of results obtained in a vitamin A intervention trial to reduce the mother to child transmission of HIV, we were unable to confirm any deleterious effects of breastfeeding on the health of seropositive women. Our assessments of the putative impact of breastfeeding on HIV-infected women included deaths, illnesses, CD4 and CD8 cell counts, and hemoglobin levels. None of these showed significant differences between formula and breastfeeding women.

The mortality rate in the Kenya study [2], which was unusually high, suggests that the sample size in that report is likely to have been adequate for the purpose of detecting mothers' deaths. Randomized controlled trials (RCT) are difficult for deeply engrained cultural practices such as breastfeeding; indeed to the best of our knowledge all the well-recognized benefits of breastfeeding have been established by observational studies. The Kenya trial [2] was one of the first RCT, and compliance was poor, undermining any clear-cut interpretation. There was also evidence that the two groups may have differed in their underlying risk at the outset of the study. Evidence in support of this theory is that the breastfeeding group had double the risk of transmission at birth [4]. In any RCT there is no guarantee that all co-variates will be equally distributed between the two groups. Rather at conventional statistical significance levels (0.05), on average one out of 20 co-variates is expected to differ significantly between the groups. The lack of a plausible biological mechanism, which can be substantiated in the large breastfeeding literature, also calls into question the validity of this single RCT finding. The authors hypothesized that the mechanism could have been increased weight loss; however, information presented at the congress on the amount of weight loss would not be sufficient to account for the mortality rates observed.

In brief, we could detect no deleterious effects of breastfeeding on the health of HIV-infected women. The counselling provided to HIV-infected women on feeding choice should continue to be based on current recommendations of UNAIDS, amplified to the extent suggested recently by us with regard to exclusive breastfeeding [5].

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