The impact of breastfeeding on the health of HIV-positive mothers and their children in sub-Saharan Africa

Taha E Taha,[a] Newton I Kumwenda,[a] Donald R Hoover,[b] George Kafulafula,[c] Susan A Fiscus,[d] Chiwawa Nkhoma,[e] Shu Chen,[a] & Robin L Broadhead[c]

Objective We assessed the impact of breastfeeding by women infected with human immunodeficiency virus (HIV)-1 on their morbidity and risk of mortality and on the mortality of their children.

Methods We analysed longitudinal data from two previous randomized clinical trials of mother-to-child transmission of HIV conducted between April 2000 and March 2003 in the Republic of Malawi, Africa. Mothers infected with HIV, and their newborns, were enrolled at the time of their child's birth; they then returned for follow-up visits when the child was aged 1 week, 6–8 weeks and then 3, 6, 9, 15, 18, 21 and 24 months. Patterns of breastfeeding (classified as exclusive, mixed or no breastfeeding), maternal morbidity and mortality, and mortality among their children were assessed at each visit. Descriptive and multivariate analyses were performed to determine the association between breastfeeding and maternal and infant outcomes.

Findings A total of 2000 women infected with HIV were enrolled in the original studies. During the 2 years after birth, 44 (2.2%) mothers and 310 (15.5%) children died. (Multiple births were excluded.) The median duration of breastfeeding was 18 months (interquartile range (IQR) = 9.0–22.5), exclusive breastfeeding 2 months (IQR = 2–3) and mixed feeding 12 months (IQR = 6–18). Breastfeeding patterns were not significantly associated with maternal mortality or morbidity after adjusting for maternal viral load and other covariates. Breastfeeding was associated with reduced mortality among infants and children: the adjusted hazard ratio for overall breastfeeding was 0.44 (95% confidence interval (CI) = 0.28–0.70), for mixed feeding 0.45 (95% CI = 0.28–0.71) and for exclusive breastfeeding 0.40 (95% CI = 0.22–0.72). These protective effects were seen both in infants who were infected with HIV and those who were not.

Conclusion Breastfeeding by women infected with HIV was not associated with mortality or morbidity; it was associated with highly significant reductions in mortality among their children.

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Introduction

In sub-Saharan Africa, women infected with human immunondeficiency virus (HIV)-1 continue to breastfeed their infants for several reasons. Breastfeeding satisfies the nutritional needs of an infant and is frequently encouraged by other family members as a cultural norm. Women who do not initiate and maintain breastfeeding raise suspicion in the community about their HIV status, and this may lead to discrimination. Furthermore, substitutes for breast milk are either expensive or not safe to use owing to a lack of safe water, and containers for feeding the infant are easily contaminated.[1] Breastfeeding protects the infant against diarrhoeal and upper respiratory diseases, and has many other well documented biological benefits.[2–6]

However, breastfeeding is the most important route of postnatal HIV transmission to the infant.[7] To counterbalance the benefits and risks of breastfeeding when the mother is infected with HIV, WHO, UNICEF and others have developed guidelines to assist women in making an informed decision about whether to breastfeed.[8] In settings where formula feeding is not affordable, it is generally recognized that women infected with HIV should continue to exclusively breastfeed their infants until they are aged 6 months and then abruptly wean them. The adverse effect of breastfeeding on the health of mothers has appeared minimal in settings where HIV is not a major problem.[9] However, the impact of breastfeeding on the health of women infected with HIV is not well understood.

Several studies from sub-Saharan Africa have reported the effects of breastfeeding on the health of mothers. A randomized trial conducted in Kenya compared breastfeeding to formula feeding and reported there was an increased risk of maternal death among women who breastfed their infants.[10] However, the number of events in this secondary analysis was small (24 deaths). Two subsequent observational studies from South Africa and the United Republic of Tanzania found no association between breastfeeding and maternal mortality among women infected with HIV.[11,12]

[a] Johns Hopkins University, Bloomberg School of Public Health, Department of Epidemiology, Room E7138, 615 N. Wolfe Street, Baltimore, MD 21205, USA. Correspondence to Dr Taha (email: ttaha@jhsph.edu).

[b] Department of Statistics and Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA.

[c] Departments of Obstetrics and Gynaecology and Pediatrics, College of Medicine, University of Malawi, Blantyre, Republic of Malawi.

[d] Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, NC, USA.

[e] Johns Hopkins University, College of Medicine, Ministry of Health Research Project, Blantyre, Republic of Malawi.

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A randomized study in Zambia of women infected with HIV that compared those who abruptly ceased breastfeeding at 4 months with those who engaged in prolonged breastfeeding reported no difference in mortality based on duration of breastfeeding.[13] Additionally, a meta-analysis that used data from several clinical trials conducted in Africa found that the risk of mortality among women infected with HIV did not differ according to how the child was fed.[14]

In this study from the Republic of Malawi, we examined the impact of breastfeeding by women infected with HIV-1 on both their and their children's mortality and on several indicators of maternal morbidity.

Methods

The data for the present analysis were originally obtained as part of two clinical trials (the Nevirapine/AZT (NVAZ) Studies) seeking to prevent mother-to-child transmission of HIV through the use of short-course antiretroviral post-exposure prophylaxis given immediately after birth.[15,16] Women were enrolled in the NVAZ studies based on their time of presentation for delivery. The HIV status of these women was not known on their arrival at the participating health centres. After obtaining informed consent for HIV counselling and testing, and after being enrolled in these trials, women who presented early (with an approximate time of $\geqslant$ 4 hours from arrival to delivery, known as early presenters) were provided with a single dose of nevirapine intrapartum if they were found to be infected with HIV. The babies of early presenters were randomized to receive orally either a standard single dose of nevirapine only or the same dose of nevirapine plus zidovudine twice daily for 1 week. Women who presented late (with an approximate time < 4 hours from arrival to delivery, known as late presenters) did not receive intrapartum nevirapine because the time was not adequate to conduct counselling and HIV testing prior to delivery. These women were counselled and tested postnatally, and if they were infected with HIV, their babies were randomized to receive orally either a standard single dose of nevirapine only or nevirapine plus zidovudine — that is, the same regimen as the babies born to early presenters. Dosing with the drugs started as soon as the infant could swallow fluids. Only singleton births were included in the NVAZ studies.

Following delivery, the women and their infants were seen at 1 week and 6–8 weeks and then at 3, 6, 9, 12, 15, 18, 21 and 24 months. At delivery, sociodemographic information and the obstetric and medical history were obtained. At each subsequent visit, case-report forms were completed to document the health status and survival of the mother and her child (including documentation of intercurrent illnesses based on the history and physical examination). Additionally, a detailed questionnaire was completed at each visit to describe breastfeeding patterns since the last visit.

Blood samples were collected from the mother at enrolment to measure baseline viral load and haemoglobin levels. Samples of the infant's blood were collected at birth and at the 6–8 week visit to determine the child's HIV status (details of sample collection, testing procedures and interpretation of results are described elsewhere).[15,16] Maternal plasma viral load was tested using Roche Diagnostics Amplicor HIV-1 Monitor test, version 1.5 (Indianapolis (IN), USA), and infant dried blood spots were tested for HIV RNA using NucliSens HIV-1 QL (bioMérieux, Durham (NC), USA). These tests were performed in the United States at a central laboratory at the University of North Carolina, Chapel Hill (NC).

The main outcomes of interest in this study were maternal mortality and morbidity, and infant and child mortality during the first 2 years after birth. Deaths of mothers and their children were ascertained through questionnaires and by actively tracing infant–mother pairs when visits were missed. Information on the reported date and cause of death was ascertained to the extent possible. In Malawi most deaths occur at home, and when the death occurs in hospital, postmortem examinations are not done to establish the cause of death.

Maternal morbidity was based on the assessment of three health indicators. The first indicator was hospitalization and the use of any medicines as reported by the women at each visit. The second was HIV disease status as determined using the US Centers for Disease Control and Prevention classification. This created two groups of women: symptomatic (classes 2–4) and asymptomatic (class 1); participants were classified based on their history between visits and examination at each visit.[17] The third indicator was whether the woman was able to perform her routine activities or whether she required assistance from her family, as reported at each visit.

The main exposure variable was breastfeeding at each visit (as assessed from the interval immediately preceding the visit). The first variable was the status of any breastfeeding taking place; this was reported as a "yes" or "no" and was used as an overall assessment of the status of breastfeeding at each visit. The second variable was the frequency of breastfeeding. Women were categorized into two groups: those who breastfed $\geqslant$ 5 times during the day and night or < 5 times during day and night. The third variable was the mode of breastfeeding. Breastfeeding was described as "exclusive" when nothing other than breast milk was given by mouth (excluding oral medications). Feeding was described as "mixed" when other liquid and solid foods were added. It was described as "no breastfeeding" when breastfeeding was not started at all or when breastfeeding stopped at any age. The purpose of these different definitions of breastfeeding patterns was to check for consistency between associations and also to assess whether intensity of breastfeeding (that is, exclusive breastfeeding is considered to be more intense than mixed because it requires more maternal energy) and assumed quantity of breastfeeding (estimated by frequency) increases the risk of maternal mortality or morbidity or conversely whether the intensity of breastfeeding protects infants against death.

Descriptive analyses of breastfeeding and other factors were conducted, and Kaplan–Meier survival analyses were used to estimate cumulative maternal and child mortality. To assess the association of maternal and child mortality with breastfeeding we used Cox proportional hazards survival analyses. We used Generalized Estimating Equations (GEE) logit-link models to assess the association between various maternal morbidity factors (measured at multiple visits for each woman) and breastfeeding to account for correlation between repeated visits and these repeated observations.[18] In both types of analyses, univariate and multivariate estimates (hazard ratios (HR) from Cox models and odds ratios from GEE logit-link models) and 95% confidence intervals (CI) were obtained. These analyses were stratified into shorter time periods of 6 months and 12 months because breastfeeding patterns change

over time (for example, women start by exclusively breastfeeding, change to mixed feeding and ultimately stop breastfeeding). We also repeated the GEE analyses and included the number of months since delivery in these models to act as an indicator variable accounting for the likelihood that women may become more sick at later visits as their HIV infection progresses with advancing age. In other words, women whose disease is advanced might have less time to breastfeed their babies as the study progressed. This could confound the interpretation of these associations and the direction of causality may not be clear.[14]

In the multivariate models we separately included each breastfeeding pattern as a time-dependent variable to assess the direction and magnitude of the association with maternal mortality or morbidity after simultaneously adjusting for the same set of covariates: maternal age (< 25 years versus ⩾ 25 years), viral load and haemoglobin level at enrolment (continuous variables), and nutritional status/wasting at each visit, which was based on an estimate of the mother's body mass index (BMI; a continuous variable). To account for any underlying socioeconomic differences in the models that involved mortality among the children, we adjusted for the antiretroviral prophylaxis the infant received at birth and time of presentation of the mother (early versus late). We also stratified these models by the infant's HIV status to determine the impact of breastfeeding patterns both on children infected with HIV and those who were uninfected, after simultaneously adjusting for other risk factors. SAS statistical software (Cary, NC, USA), version 8.2, was used to conduct these analyses.

The NVAZ study was approved in Malawi by the Research and Ethics Committee at the University of Malawi College of Medicine and in the United States by the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health. All women gave written informed consent for HIV testing and enrolment. Women and children received free routine clinical care. Referral for antiretroviral treatment for eligible participants is available as part of the programme of the Global Fund to fight AIDS, Tuberculosis and Malaria in Malawi.

Findings

A total of 2000 women were enrolled in the two NVAZ randomized clinical trials; 889 (44.5%) were early presenters and 1111 (55.5%) were late presenters. The mean maternal age was 24.9 years (median = 24.0 years); mean parity was 3.0 children; 220 women (11%) had had no education; 1260 (63%) had attended primary school; and 520 (26%) had had more than a primary-school education. Of the 2000 women enrolled in this study, 1838 (91.9%) returned for any postnatal follow-up visit; and it was known for 9 of the mothers who did not return (0.4%) that their child had died. Therefore, 153 (7.7%) women were lost to follow-up and did not contribute follow-up data to this analysis. The sociodemographic and biological characteristics of the 1838 women who returned and 162 (153 + 9) women who did not return for follow-up were comparable, including in terms of baseline maternal viral load.

Overall, 44 (2.2%) of the 2000 women and 310 (15.5%) of their children died. Cumulative maternal mortality at 12 months based on Kaplan–Meier analysis was 18/1000; and at 24 months it was 32/1000. The reported causes of death among the 44 mothers who died were tuberculosis (21%), pneumonia (18%), malaria (16%), diarrhoea (14%), herpes zoster or Kaposi's sarcoma or meningitis (7%), and other diseases (9%); the cause of death was unknown for 18% of women. Among children, the cumulative mortality based on the Kaplan–Meier analysis at 12 months was 132/1000, and at 24 months was 195/1000. Among children infected with HIV mortality was significantly higher compared with mortality among children who were not infected: mortality was approximately tenfold higher at 12 months (45/1000 versus 457/1000, $P < 0.0001$, Log–Rank test) and approximately sevenfold higher

Table 1. **Hazard ratios for risk factors associated with death of women infected with HIV, Malawi, 2000–03 (Cox proportional hazards models)**

Maternal characteristics	Univariate hazard ratio	Multivariate hazard ratio		
		Model 1[a]	Model 2[b]	Model 3[c]
Breastfeeding				
Status	0.31 (0.10–0.96)[d,e]	0.35 (0.12–1.03)	–	–
Frequency	1.83 (0.91–3.69)	–	1.66 (0.81–3.40)	–
Type				
Mixed feeding versus no breastfeeding	0.28 (0.09–0.91)[f]	–	–	0.31 (0.10–0.96)[e]
Exclusive versus no breastfeeding	0.79 (0.17–3.82)	–	–	0.97 (0.21–4.55)
Age (< 25 years versus ⩾ 25 years)	0.63 (0.31–1.26)	0.71 (0.35–1.46)	0.70 (0.34–1.43)	0.68 (0.33–1.39)
Maternal viral load (Log_{10})[g]	5.34 (2.94–9.70)	3.84 (2.06–7.16)	3.89 (2.10–7.22)	3.82 (2.05–7.14)
Maternal haemoglobin[g]	0.76 (0.66–0.88)	0.80 (0.68–0.93)	0.79 (0.68–0.93)	0.79 (0.68–0.92)
BMI[h]	0.82 (0.73–0.92)	0.87 (0.75–1.00)	0.86 (0.74–1.00)	0.87 (0.75–1.00)

[a] Adjusted for breastfeeding status at each visit (yes versus no).
[b] Adjusted for breastfeeding frequency at each visit (⩾ 5 times during the day and night versus < 5 times).
[c] Adjusted for type (mode) of breastfeeding at each visit, comparing mixed feeding or exclusive breastfeeding versus no breastfeeding.
[d] Values in parentheses are 95% confidence intervals.
[e] $P = 0.04$.
[f] $P = 0.03$.
[g] Maternal viral load and haemoglobin as continuous variables measured at baseline.
[h] BMI = body mass index (weight (kg)/height (metres)^2); used as a continuous variable to indicate nutritional status/wasting at each visit.

Table 2. **Odds ratios for the association between breastfeeding and maternal morbidity in women infected with HIV, Malawi, 2000–03 (Generalized Estimating Equations (GEE) models)[a]**

Variables	Univariate analysis[b]	Multivariate analysis		
		Model 1[c]	Model 2[d]	Model 3[e]
Hospitalization and use of medicines				
Breastfeeding				
Status	0.94 (0.77–1.14)	0.91 (0.73–1.13)	–	–
Frequency	0.99 (0.87–1.13)	–	0.97 (0.85–1.12)	–
Type				
Mixed feeding versus no breastfeeding	1.05 (0.86–1.29)	–	–	0.99 (0.79–1.24)
Exclusive versus no breastfeeding	0.74 (0.60–0.92)[f]	–	–	0.76 (0.60–0.96)[g]
Maternal HIV disease status (symptomatic versus not symptomatic)				
Breastfeeding				
Status	0.93 (0.75–1.15)	0.89 (0.69–1.14)	–	–
Frequency	1.01 (0.88–1.15)	–	0.97 (0.84–1.13)	–
Type				
Mixed feeding versus no breastfeeding	0.93 (0.75–1.16)	–	–	0.87 (0.68–1.12)
Exclusive versus no breastfeeding	0.93 (0.73–1.17)	–	–	0.92 (0.70–1.21)
Limitation of maternal physical activities				
Breastfeeding				
Status	0.77 (0.59–1.00)	0.70 (0.53–0.93)	–	–
Frequency	1.03 (0.86–1.25)	–	0.99 (0.81–1.22)	–
Type				
Mixed feeding versus no breastfeeding	0.76 (0.57–0.99)	–	–	0.67 (0.49–0.90)
Exclusive versus no breastfeeding	0.79 (0.59–1.05)	–	–	0.77 (0.56–1.05)

[a] The outcome in each of these GEE models was maternal morbidity based on reported maternal hospitalization and use of medicines, maternal HIV disease status and limitations of physical activity. See Methods for definitions. Other variables adjusted for in these models in addition to breastfeeding were age, baseline maternal viral load and haemoglobin, and body mass index (weight (kg)/height (metres)^2), which was used as an indicator of nutritional status/wasting, at each visit (see Table 3).

[b] Values are odds ratios (95% confidence intervals).

[c] Adjusted for breastfeeding status at each visit (yes versus no).

[d] Adjusted for breastfeeding frequency at each visit ($\geq$ 5 times during the day and night versus < 5 times).

[e] Adjusted for type (mode) of breastfeeding at each visit by comparing mixed feeding or exclusive breastfeeding versus no breastfeeding.

[f] $P = 0.008$.

[g] $P = 0.02$.

at 24 months (83/1000 versus 639/1000, $P < 0.0001$, Log–Rank test). The reported causes of death were respiratory infections (33%), gastroenteritis (16%), septicaemia (11%), malnutrition (8%), malaria (8%), meningitis (5%), other diseases (4%), and unknown (15%).

At the postnatal visits at 1 week 1831/1838 (99.6%) of women who returned for follow-up were still breastfeeding; at 6 weeks the number was 1827 (99.4%). The mean duration of breastfeeding was 15.4 months (median = 18 months; interquartile range (IQR) = 9.0–22.5 months). Women exclusively breastfed their infants for a mean of 2.4 months (median = 2 months; IQR = 2–3 months), and practised mixed feeding for a mean of 11.7 months (median = 12 months; IQR = 6–18 months). Because breastfeeding is the main factor of interest in this study and women may opt to breastfeed or not breastfeed based on their health, we compared the characteristics of women who were breastfeeding to those who were not at various time points. At 3 months, 6 months and 12 months after birth there were no differences in important characteristics, such as baseline maternal viral load and haemoglobin and BMI at each visit among women who breastfed (exclusively or engaged in mixed feeding) or did not breastfeed. However, the number of women who did not breastfeed at all time points was small (for example, only 50 women were not breastfeeding at 12 months).

To minimize bias, mothers' data were censored if their children died first. In the univariate and multivariate analyses used to assess the association between breastfeeding and maternal mortality and morbidity, data from 11 women were censored at the time of their infant's death. In the univariate analysis all patterns of breastfeeding (overall status, frequency and mode) at each visit were not significantly associated with increased risk of maternal death (Table 1). Controlling for maternal age, viral load, haemoglobin and BMI did not change these findings (Table 1). Higher maternal viral load was strongly and consistently associated with higher risk of maternal death; the risk of maternal death was threefold greater for each 1 $\log_{10}$ unit in each of the three multivariate models that included breastfeeding status, frequency or type. In adjusted models, higher maternal haemoglobin level at enrolment and BMI values at each visit were significantly associated with maternal survival (that is, they were protective).

Table 3. **Odds ratios for risk factors associated with maternal morbidity in women infected with HIV, Malawi, 2000–03 (Generalized Estimated Equations (GEE) models)**

Variables	Univariate analysis[a]	Multivariate analysis		
		Model 1[b]	Model 2[c]	Model 3[d]
Hospitalization and use of medicines				
Age (< 25 years versus ⩾ 25 years)	0.69 (0.58–0.81)	0.64 (0.54–0.76)	0.67 (0.56–0.81)	0.64 (0.54–0.77)
Maternal viral load (Log_{10})[e]	1.29 (1.15–1.45)	1.24 (1.09–1.39)	1.23 (1.08–1.39)	1.24 (1.10–1.40)
Maternal haemoglobin[e]	0.95 (0.91–0.99)	0.97 (0.93–1.01)	0.98 (0.94–1.02)	0.97 (0.92–1.01)
BMI[f]	0.92 (0.89–0.95)	0.93 (0.90–0.96)	0.95 (0.92–0.99)	0.94 (0.91–0.97)
Maternal HIV disease status (symptomatic versus not symptomatic)				
Age (< 25 years versus ⩾ 25 years)	0.67 (0.56–0.80)	0.63 (0.52–0.75)	0.66 (0.55–0.80)	0.63 (0.52–0.75)
Maternal viral load (Log_{10})[e]	1.83 (1.61–2.07)	1.64 (1.44–1.86)	1.61 (1.41–1.84)	1.63 (1.44–1.86)
Maternal haemoglobin[e]	0.93 (0.89–0.97)	0.96 (0.91–1.01)	0.97 (0.93–1.02)	0.96 (0.91–1.00)
BMI[f]	0.87 (0.84–0.90)	0.89 (0.86–0.92)	0.90 (0.87–0.94)	0.89 (0.86–0.92)
Limitation of maternal physical activities				
Age (< 25 years versus ⩾ 25 years)	0.70 (0.57–0.86)	0.63 (0.50–0.78)	0.66 (0.52–0.83)	0.63 (0.50–0.78)
Maternal viral load (Log_{10})[e]	1.66 (1.41–1.94)	1.50 (1.28–1.77)	1.51 (1.28–1.80)	1.49 (1.27–1.76)
Maternal haemoglobin[e]	0.92 (0.87–0.98)	0.95 (0.90–1.01)	0.97 (0.91–1.03)	0.95 (0.90–1.01)
BMI[f]	0.88 (0.84–0.92)	0.88 (0.84–0.93)	0.90 (0.85–0.95)	0.88 (0.84–0.93)

[a] Values are odds ratios (95% confidence intervals).
[b] Adjusted for breastfeeding status at each visit (yes versus no).
[c] Adjusted for breastfeeding frequency at each visit (⩾ 5 times during the day and night versus < 5 times).
[d] Adjusted for type (mode) of breastfeeding at each visit by comparing mixed feeding or exclusive breastfeeding versus no breastfeeding.
[e] Maternal viral load and haemoglobin as continuous variables measured at baseline.
[f] BMI = body mass index (weight (kg)/height (metres)^2); used as a continuous variable to indicate nutritional status/wasting at each visit.

Similar to the findings above, breastfeeding (yes/no, frequency or type) was not associated with an increased risk of maternal morbidity as assessed by hospitalization and use of medicines, symptomatic HIV disease or limitations on physical activities (Table 2). Controlling for maternal age, viral load, haemoglobin level and BMI did not change these findings (Table 3). In all these models, higher maternal viral load was significantly associated with higher odds of maternal morbidity while higher maternal baseline haemoglobin and BMI at each visit were associated with lower odds of morbidity (that is, they had a protective effect). Younger maternal age (< 25 years) was also significantly associated with lower odds for all morbidity indicators assessed in these models after adjusting for other variables.

At each visit, both the status and type of breastfeeding by women infected with HIV were significantly associated with a 55–60% decreased risk of child mortality: adjusted HR = 0.44 (95% CI = 0.28–0.70) for overall status of feeding; 0.45 (95% CI = 0.28–0.71) for mixed feeding; and 0.40 (95% CI = 0.22–0.72) for exclusive breastfeeding (Table 4). Higher maternal viral load at enrolment was significantly associated with increased child mortality in all models; the risk of child mortality was increased by more than twofold for each $\log_{10}$ unit. Both a higher maternal haemoglobin level at enrolment and higher values of BMI at each visit were also associated with improved survival for children. Maternal age, presentation at time of delivery (early versus late) and prophylaxis with short-course antiretroviral treatment were not associated with risk of child mortality after adjusting for other variables. Limiting this analysis to only deaths among infants (that is, among children aged ⩽ 12 months) did not change these results: breastfeeding status and type (mixed or exclusive) remained highly significantly protective. For breastfeeding status the adjusted HR for infant death was 0.31 (95% CI = 0.16–0.59). For mixed feeding versus no breastfeeding, the adjusted HR for infant death was 0.31 (95% CI = 0.16–0.61). For exclusive feeding versus no breastfeeding the adjusted HR was 0.29 (95% CI = 0.14–0.59). The HIV-free survival estimate at 12 months was 79.8% and at 24 months was 72.8%.

Stratifying the models in Table 4 by the infection status of the infant at 6–8 weeks showed there was a significantly lower risk of death if the child was breastfed both for children who were infected with HIV and those who were not infected, after controlling for the same variables. Among children who were not infected with HIV, the adjusted HR for reported overall breastfeeding (status) was 0.34 (95% CI = 0.18–0.64); for exclusive breastfeeding it was 0.11 (95% CI = 0.04–0.32); and for mixed feeding it was 0.37 (95% CI = 0.20–0.69). Among children infected with HIV the adjusted HR for reported overall breastfeeding was 0.36 (95% CI = 0.19–0.71); for exclusive breastfeeding it was 0.43 (95% CI = 0.20–0.93); and for mixed feeding it was 0.35 (95% CI = 0.18–0.61). As in the analysis not stratified by HIV status (Table 4), maternal viral load was strongly associated with increased risk of death both for children who were infected with HIV and for those who were not, but frequency of breastfeeding was not associated with mortality.

Discussion

In urban Malawi, the prevalence of HIV-1 is approximately 30% among women attending antenatal clinics,[19] and breastfeeding is almost universal.[15,16] National estimates show that levels of

Table 4. **Hazard ratios for risk factors associated with mortality among children born to women infected with HIV, Malawi, 2000–03 (Cox proportional hazards model)**

Variables	Univariate analysis[a]	Multivariate analysis		
		Model 1[b]	Model 2[c]	Model 3[d]
Breastfeeding				
Status	0.42 (0.27–0.66)	0.44 (0.28–0.70)	–	–
Frequency	1.20 (0.95–1.52)	–	1.24 (0.96–1.59)	–
Type				
Mixed feeding versus no breastfeeding	0.42 (0.27–0.66)	–	–	0.45 (0.28–0.71)
Exclusive versus no breastfeeding	0.43 (0.25–0.76)	–	–	0.40 (0.22–0.72)
Age (< 25 years versus ⩾ 25 years)	1.06 (0.84–1.32)	1.10 (0.86–1.42)	1.08 (0.84–1.39)	1.11 (0.86–1.43)
Maternal viral load (Log_{10})[e]	2.69 (2.26–3.20)	2.56 (2.10–3.13)	2.59 (2.12–3.16)	2.56 (2.10–3.13)
Maternal haemoglobin[e]	0.93 (0.88–0.98)	0.97 (0.92–1.03)	0.97 (0.92–1.03)	0.97 (0.92–1.03)
BMI[f]	0.89 (0.85–0.93)	0.94 (0.89–0.98)	0.94 (0.89–0.98)	0.94 (0.89–0.98)
Presentation (early versus late)[g]	0.69 (0.55–0.87)	0.96 (0.75–1.24)	0.84 (0.65–1.10)	0.84 (0.64–1.09)
Treatment (nevirapine + zidovudine versus nevirapine only)	0.98 (0.78–1.22)	0.84 (0.64–1.09)	0.94 (0.73–1.21)	0.96 (0.75–1.24)

[a] Values are hazard ratios (95% confidence intervals).
[b] Adjusted for breastfeeding status at each visit (yes versus no).
[c] Adjusted for breastfeeding frequency at each visit (⩾ 5 times during the day and night versus < 5 times).
[d] Adjusted for type (mode) of breastfeeding at each visit by comparing mixed feeding or exclusive breastfeeding versus no breastfeeding.
[e] Maternal viral load and haemoglobin as continuous variables measured at baseline.
[f] BMI = body mass index (weight (kg)/height (metres)^2); used as a continuous variable to indicate nutritional status/wasting at each visit.
[g] See text for full description of presentation and treatment variables.

maternal and child mortality are high in Malawi: in 2000 the maternal mortality ratio was 1120/100 000 live births and mortality among children younger than 5 years was 188.6/1000 live births.[20] The current analysis showed that breastfeeding is not associated with an increased risk of maternal mortality or morbidity. A lack of association with maternal mortality was observed with all the measures we used to assess breastfeeding: overall (status), type and frequency. For example, we used type of feeding to approximate the intensity of this practice, assuming that exclusive breastfeeding will likely require more maternal energy than mixed feeding.[21] Our results appear to support this argument: mixed feeding was associated with a significantly lower risk of death (HR = 0.31, 95% CI = 0.10–0.96) while exclusive breastfeeding was not (Table 1). As discussed by others,[14] the protective effect of exclusive breastfeeding (as shown in Table 2) is most likely the result of the fact that healthier mothers opt to breastfeed exclusively while sicker mothers do not breastfeed. The lack of an association between breastfeeding and maternal mortality in our study is also in agreement with the results of studies from the United Republic of Tanzania and South Africa.[11,12]

Breastfeeding was also not associated with morbidity indicators, such as maternal hospitalization or use of medicines, symptomatic HIV disease, or limitations of physical activity. These results suggest that breastfeeding does not lead to faster disease progression, advanced HIV disease and, ultimately, death from AIDS. This corroborates the results of the study from the United Republic of Tanzania.[12] Similar to the mortality findings, the most important maternal factor that increased the risk of morbidity in all the outcomes we examined was higher maternal viral load (Table 3). As expected, women with higher haemoglobin and BMI (that is, the healthier women) had significantly reduced morbidity and mortality in all the models. Young age (< 25 years) also appeared protective in all analyses of maternal morbidity, possibly because compared with older women, younger women have better overall health. There also could be differences between younger and older women in factors that we did not assess (for example, nutritional and immunological reserves).

Another important finding of this study is that breastfeeding by mothers infected with HIV is associated with a significantly lower risk of mortality for infants and children (Table 4). Breastfeeding was protective against mortality among infants and children regardless of whether the infant was infected with HIV. Mixed feeding (versus not breastfeeding) was also associated with substantial reductions in mortality in each of the infants regardless of their HIV status (a reduction of approximately 60%). These findings differ from a meta-analysis that included data from several African countries and reported no association between infant mortality and either ever breastfeeding or never breastfeeding.[22] These differences could be due to variability in breastfeeding measurements (ever breastfeeding versus never breastfeeding in the multicountry study) between the two studies and variability in infant mortality among countries. As in the analyses of maternal morbidity and mortality, maternal viral load was significantly associated with increased child mortality, and higher maternal haemoglobin and BMI were significantly associated with lower child mortality.

This study has some limitations. We tried to obtain in-depth information about breastfeeding patterns, but information and misclassification biases may have occurred. For example, the reported frequency of breastfeeding was crude, and the cut-off we used (5 times during the day and night) was arbitrary. Likewise, there is no certainty that reported exclusive breastfeeding is completely limited to breast milk, and complementary feeds might occasionally have been given. This study was not a randomized

trial of breastfeeding and formula feeding, and changes in breastfeeding as HIV disease progressed could have introduced bias. We compared the characteristics of women who breastfed (exclusively or engaged in mixed feeding) and those who did not breastfeed at various times during follow-up: there were no significant differences in either sociodemographic or biological factors (such as baseline viral load, haemoglobin or BMI). Loss to follow up from the outset was not substantial; however, the high rates of child mortality and subsequent censoring of mothers may have contributed to some potential biases. There were no differences in the characteristics of women who were lost to follow up and those who returned. The effect of these biases will likely be non-differential.

Conclusion

This study has important policy implications, and confirms findings from other studies in Africa. Breastfeeding patterns were not associated with maternal mortality or morbidity, and did not increase HIV disease progression in this group of women. It is reassuring that breastfeeding by women infected with HIV was not a risk to them and in fact was highly protective against mortality among their infants irrespective of the child's initial HIV infection status. It is also in line with the general recommendations adopted in Malawi and several other countries where breast milk substitutes are not available. It appears that the important immunological and antipathogenic factors in breast milk that provide protection for the child against several childhood diseases are well maintained even if the mother is infected with HIV.[23] However, the fact that the baby may become infected through breastfeeding and, ultimately, the higher risk of death associated with HIV infection as demonstrated in this study should always be acknowledged. The major risk factor associated with mortality for both mothers and their children is AIDS itself (the level of plasma HIV load).[24] Therefore, providing antiretroviral treatment to mothers (and their children) should be a major priority in order to save lives. ■

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Résumé

L'influence de l'allaitement au sein sur la santé des mères positives pour le VIH et sur celle de leurs enfants en Afrique subsaharienne

Objectif Nous avons évalué l'influence de l'allaitement au sein sur la morbidité et le risque de mortalité des mères porteuses du virus de l'immunodéficience humaine (VIH-1) ainsi que sur la mortalité de leurs enfants.

Méthodes Nous avons étudié les données longitudinales tirées de deux essais cliniques randomisés portant sur la transmission du VIH de la mère à l'enfant qui avaient été effectués entre avril 2000 et mars 2003 en République du Malawi (Afrique). Le recrutement des mères porteuses du VIH et de leurs nouveau-nés a été effectué lors de la naissance de leur enfant ; on les a ensuite revues pour des visites de suivi lorsque leur enfant a atteint l'âge de 1 semaine, 6-8 semaines puis 3, 6, 9,15, 18, 21 et 24 mois. A chaque fois, le mode d'allaitement (au sein exclusivement, mixte ou pas d'allaitement au sein), la morbidité et la mortalité maternelle ainsi que la mortalité des enfants ont été notés. On a procédé à des analyses descriptives et à des analyses à variables multivariées pour déterminer l'association entre l'allaitement au sein et l'état de santé de la mère et de l'enfant.

Résultats Au total, 2000 femmes contaminées par le VIH ont été recrutées pour les études initiales. Au cours des deux années suivant la naissance, 44 mères (2,2 %) et 310 enfants (15,5 %) sont décédés. (on n'a pas pris en compte les naissances multiples). La durée médiane de l'allaitement était de 18 mois (intervalle interquartile (IQR) = 9,0 -22,5); celle de l'allaitement exclusivement au sein de 2 mois (IQR = 2-3) et celle de l'allaitement mixte de 12 mois (IQR = 6-18). On n'a pas relevé d'association significative entre le mode d'allaitement et la morbidité ou la mortalité maternelle après correction pour tenir compte de la charge virale maternelle et des autres covariables. Chez les nourrissons et les enfants plus âgés, l'allaitement au sein était associé à une réduction de la mortalité : le rapport des risques ajusté pour l'allaitement au sein en général était égal à 0,44 (intervalle de confiance à 95 % : 0,28 - 0,70) ; il était de 0,45 pour l'allaitement mixte (IC à 95 % : 0,28 - 0,71) et de 0,40 pour l'allaitement exclusivement au sein (IC à 95 % : 0,22 - 0,72). Ces effets protecteurs ont été observés chez les enfants infectés par le VIH comme chez ceux qui ne l'étaient pas.

Conclusion Chez les femmes infectées par le VIH, il n'y avait aucune association entre l'allaitement au sein et la morbidité ou la mortalité. Chez leurs enfants en revanche, il était associé à une réduction très significative de la mortalité.

Resumen

Impacto de la lactancia materna en la salud de las madres VIH-positivas y en sus hijos en el África subsahariana

Objetivo Evaluamos los efectos de la lactancia materna entre las mujeres infectadas por el virus de la inmunodeficiencia humana (VIH-1) en su morbilidad y su riesgo de mortalidad y en la mortalidad de sus hijos.

Métodos Analizamos datos longitudinales de dos ensayos clínicos aleatorizados previos sobre la transmisión del VIH de la madre al niño realizados entre abril de 2000 y marzo de 2003 en la República de Malawi, África. Las madres infectadas por el VIH y sus recién nacidos entraron a participar en el estudio al nacer su hijo; luego regresaban para realizar visitas de seguimiento cuando el niño tenía 1 semana, 6–8 semanas, y 3, 6, 9, 15, 18, 21 y 24 meses. En cada visita se determinaba el tipo de lactancia materna (exclusiva, mixta, o no amamantamiento), la morbilidad y mortalidad maternas, y la mortalidad entre sus hijos. Se realizaron análisis descriptivos y multifactoriales para determinar la relación entre la lactancia materna y los resultados maternos e infantiles.

Resultados Un total de 2000 mujeres infectadas por el VIH participaron en los estudios originales. Durante los 2 años posteriores al nacimiento murieron 44 madres (2,2%) y 310 niños (15,5%). (Se excluyeron los partos múltiples.) La duración mediana de la lactancia materna fue de 18 meses (intervalo intercuartílico (II) = 9,0 - 22,5), la de la lactancia materna exclusiva, de 2 meses (II = 2 - 3), y la de la alimentación mixta, de 12 meses (II = 6 -18). El tipo de lactancia materna no influyó de forma significativa en la mortalidad y la morbilidad maternas después de ajustar en función de la carga viral materna y de otras covariables. La lactancia materna se asoció a una reducción de la mortalidad entre los lactantes y los niños: el cociente de riesgos instantáneos (*hazard ratio*) ajustado para la lactancia materna en general fue de 0,44 (intervalo de confianza (IC) del 95% = 0,28 - 0,70); para la alimentación mixta, de 0,45 (IC95% = 0,28 - 0,71); y para la lactancia materna exclusiva, de 0,40 (IC95% = 0,22 - 0,72). Estos efectos protectores se observaron tanto entre los lactantes que estaban infectados por el VIH como entre los que no lo estaban.

Conclusión La lactancia materna entre las mujeres infectadas por el VIH no se asoció a diferencias de la mortalidad o la morbilidad, pero sí a una disminución muy importante de la mortalidad entre sus hijos.

ملخص

تأثير الإرضاع من الثدي على صحة الأمهات الإيجابيات لفيروس العوز المناعي البشري وصحة أطفالهن في البلدان الواقعة جنوب الصحراء الأفريقية

الهدف: قيَّمنا تأثير الإرضاع من الثدي لدى الأمهات المصابات بعدوى النمط الأول من فيروس العوز المناعي البشري على معدلات المراضة لديهن وخطر المراضة والوفيات ولدى أطفالهن.

الطريقة: أجرينا تحليلاً طولانياً للمعطيات المجموعة من دراستين سريريتين (إكلينيكيتين) سابقتين حول سراية فيروس العوز المناعي البشري من الأمهات إلى أطفالهن في الفترة بين نيسان/أبريل 2000 وآذار/مارس 2003، في جمهورية مالاوي في أفريقيا. وقد شملت الدراسة الأمهات المصابات بعدوى فيروس العوز المناعي البشري منذ لحظة ولادتهن، ثم استقدمن مع ولدانهن لزيارات متابعة عند بلوغ الوليد من عمره أسبوعاً، ثم 6 – 8 أسابيع، ثم 3 أشهر، ثم 9 أشهر، ثم 18 شهراً، ثم 21 شهراً، ثم 24 شهراً. وقد صنفت أنماط الرضاعة من الثدي إلى الاقتصار على الإرضاع من الثدي، ورضاعة مختلطة، وعدم الرضاعة من الثدي. وفي كل زيارة كنا نقيِّم أنماط الرضاعة من الثدي، معدلات المراضة والوفيات لدى الأمهات، معدلات الوفيات بين الولدان، ثم أجرينا تحليلات وصفية ومتعددة المتغيرات للتعرُّف على الترابط بين الرضاعة من الثدي والحصائل لدى الأمهات ولدى الرضع.

الموجودات: شملت الدراسة الأصلية 2000 مصابة بالعدوى بفيروس العوز المناعي البشري. وخلال السنتين التاليتين للولادة مات 44 من الأمهات (2.2%) و310 من الولدان (15.5%)، مع استبعاد الولادات بأجنة متعددة، وقد بلغ المعدل الوسطي لفترة الرضاعة من الثدي 18 شهراً، إذْ تراوحت قيم الشرائح الربعية بين 9.0 و22.5 شهراً، فيما بلغ المعدل الوسطي لفترة الاقتصار على الرضاعة من الثدي شهرين، وتراوحت قيم الشرائح الربعية بين 2 و 3 أشهر، وبلغ المعدل الوسطي لفترة الإرضاع المختلط 12 شهراً، وتراوحت قيم الشرائح الربعية بين 6 – 18 شهراً. ولم يكن هناك ترابط ذو أهمية بين معدلات الوفيات أو معدلات الوفيات لدى الأمهات بعد تصحيح الحمل الفيروسي لدى الأمهات وتصحيح العوامل الأخرى. وقد ترافق الإرضاع من الثدي بنقص معدلات الوفيات لدى الرُّضَّع والأطفال، فيما بلغت النسبة المصححة للمخاطر لمجمل عملية الإرضاع من الثدي 0.44 بفاصلة ثقة 95% ، إذْ تراوحت النسبة المصححة للمخاطر بين 0.22 و0.72. وقد شوهدت هذه التأثيرات الواقية لدى كلٍّ من الرُّضَّع المصابين بالعدوى بفيروس العوز المناعي البشري والرُّضَّع غير المصابين بها.

الاستنتاج: لم يترافق الإرضاع من الثدي لدى أمهات مصابات بالعدوى بفيروس العوز المناعي البشري بمعدلات مراضة أو وفيات، بل بانخفاض ملحوظ في الوفيات لدى أطفالهن.

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