

Exclusive breastfeeding reduces risk of mortality in infants up to 6 mo of age born to HIV-positive Tanzanian women^{1–3}

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ABSTRACT

Background: Despite the benefits of exclusive breastfeeding (EBF), exposure to HIV from breast milk has relegated EBF to an option only when formula feeding is not affordable, feasible, safe, and sustainable. Mixed feeding remains the norm in sub-Saharan Africa.

Objective: We evaluated whether the duration of EBF was associated with mortality and HIV infection in children followed to ≤ 5 y of age.

Methods: A total of 690 mother-infant pairs from the Trial of Vitamins with information on infant feeding, HIV status, and at least one visit in the first year were included in the analysis. The duration of EBF was defined in months as a time-varying covariate at each follow-up visit. Associations of the duration of EBF with mortality, HIV infection, and HIV infection or death were estimated by using Cox proportional hazards models and Kaplan-Meier survival curves.

Results: A 1-mo increase in EBF was associated with a 49% reduction in early infant mortality in the first 6 mo of life (RR: 0.51; 95% CI: 0.28, 0.93) and a nonsignificant 15% reduction in risk of HIV infection or death (RR: 0.85; 95% CI: 0.71, 1.01; $P = 0.07$) over the first 5 y of life. EBF was not associated with HIV infection (RR: 0.93; 95% CI: 0.76, 1.15).

Conclusion: Longer EBF by HIV-positive mothers was associated with reduced mortality in the first 6 mo of life without increased HIV infection, which makes EBF the best option for women who cannot sustain exclusive formula feeding. This trial was registered at clinicaltrials.gov as NCT00197743. *Am J Clin Nutr* 2012;96:1071–8.

INTRODUCTION

Exclusive breastfeeding (EBF)⁴ provides infants nourishment at a lower risk of contamination than does the mixing and storage of formula with water, especially in poor households (1). Growth factors in breast milk are known to improve the maturation of the infant's gastrointestinal system while maintaining mucosal integrity that limits the passage of pathogens and antigens from the lumen (2, 3). Secretory immunoglobulin A antibodies, chemokines, complement, and other immune factors in breast milk (3–7) protect against viral as well as bacterial infections. Protective effects of breastfeeding also occur from other substances that may augment the immune system and growth such as lactoferrin, lysozymes, nucleotides, and oligosaccharides (6, 7).

The WHO recommends that women breastfeed their infants exclusively in the first 6 mo of life to maximize the benefits of breastfeeding (8). With consideration of risk of mother-to-child transmission of HIV through breast milk (9, 10) and the benefits of breastfeeding, the WHO adopted new guidelines in 2010 that provided the following 3 choices to HIV-positive mothers: 1) EBF for the first 6 mo of life, introduction of appropriate complementary foods thereafter, and the continuation of breastfeeding for the first 12 mo of life; 2) formula feeding, if acceptable and affordable and if safe, clean water is available and home conditions support such feeding; and 3) the use of expressed heat-treated breast milk in specific circumstances (11). The WHO recommends that all HIV-positive mothers receive antiretrovirals, at least during breastfeeding if not lifelong (11). The social stigma of HIV infection, economic conditions, and beliefs about breast-milk quality and transmission of HIV through breast milk govern infant-feeding decisions (12). A lack of sustained access to safe, clean water and strong cultural norms that surround breastfeeding make adherence to non-breastfeeding options extremely difficult. Therefore, most women end up practicing a mixture of non-EBF along with formula or animal-milk feeding, thereby exposing the child to the health risks of all of the choices provided by the WHO (13).

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⁴ Abbreviations used: ART, antiretroviral therapy; EBF, exclusive breastfeeding; MUAC, midupper arm circumference.

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EBF has been shown to be associated with lower mortality and HIV infection. In an intervention cohort study in South Africa, the cumulative 3-mo mortality in infants given replacement feeds was higher at 15.1% (range: 7.63–28.73%) than at 6.1% (range: 4.74–7.92%) in exclusively breastfed infants (HR: 2.06; 95% CI: 1.00, 4.27; $P = 0.051$) (14). Infants who also received solids with breastfeeding were 11 times more likely to acquire HIV infection than exclusively breastfed infants (HR: 10.87; 95% CI: 1.51, 78.00; $P = 0.018$). The more widespread availability of antiretroviral therapy (ART) has made breastfeeding safer for longer in mothers who receive ART, which has led to recommendations for longer periods of breastfeeding for women who receive ART (11).

We conducted a secondary analysis of infants born to HIV-infected, ART-naive women enrolled in a trial of vitamins in Tanzania to examine whether the duration of EBF is associated with child mortality, HIV infection, or HIV infection or death (either HIV infection or death).

SUBJECTS AND METHODS

The Trial of Vitamins enrolled HIV-infected pregnant women who were residents of Dar es Salaam, Tanzania, and between 12 and 27 wk of gestation from April 1995 to July 1997. The trial aimed to examine the effects of oral supplementation of multivitamins on HIV-disease progression in women, mother-to-child transmission of HIV-1, and morbidity and mortality outcomes in women and children. Enrolled women and infants born to them were followed up at monthly intervals after delivery at study clinics. During these visits, women were asked about infant-feeding practices in the previous month or since the last clinic visit. Information obtained and recorded included current breastfeeding status and frequency, any other food or liquid introduced, age at weaning, and age of introduction of the following foods: cow milk, formula, fruit juices, or solids in the past month. Detailed descriptions of the trial design and follow-up procedures have been published (15–18). EBF was defined as the feeding of breast milk to a child without the introduction of any other liquid, milk, or solid (19). The duration of EBF was defined as the time in months from birth to the time when the mother first reported having given the child any other foods in addition to breast milk or medications. Only singleton children were included in the analysis because feeding patterns in twins are significantly different and few twins are both exclusively breastfed.

Information collected at enrollment provided data on a number of socioeconomic and demographic characteristics. These included the age of parents, their occupation and education, the mother's marital status, family income and size, the number of children living in the household, and obstetric history. During monthly visits, study nurses performed anthropometric measurements on women and their children. Weight, height, and midupper arm circumference (MUAC) were measured by using a standard set of regularly calibrated instruments and procedures (15–18).

Every month, enrolled women and children were evaluated and treated by a study clinician for any health problems or illnesses that were shown. Clinicians also staged HIV disease in mothers and examined them for breast conditions such as mastitis, breast discharge, and cracked nipples. Staging of HIV was performed by

using criteria described by the WHO (20). Hemoglobin, erythrocyte sedimentation rate, HIV status, absolute counts of T cell subsets ($CD4^+$ and $CD8^+$), and total lymphocytes were measured at 6 mo of age and at 3-mo intervals in children who were followed up. $CD4^+$ cell counts in the infant were also measured at birth. Children whose peripheral blood sample tested positive on a polymerase chain reaction test at any age before 18 mo were considered HIV positive. Subsequent samples after 18 mo of age were analyzed by using an enzyme-linked immunosorbent assay. Positive results were confirmed by using Western blot tests before a child was labeled HIV positive.

Survival duration was defined as the time from birth to either the end of follow-up (≤ 60 mo), the last time the child was known to be alive, or the date of death. Infant mortality was defined as death between birth and 12 mo of age. The duration to HIV infection or death was the duration for which a child was alive and HIV free. Children were eligible for this analysis only if they were HIV negative at birth.

Ethics

The Research and Publications Committee of Muhimbili University College of Health Sciences, the Ethical Committee of the National AIDS Control Program of the Tanzanian Ministry of Health, and the Institutional Review Board of the Harvard School of Public Health approved the study protocol. Informed consent was obtained from caregivers.

Statistics

Cox proportional hazards regression models were used to examine the relation between EBF and child mortality, HIV infection, and HIV infection or death (21). A data structure with one record per child visit was used to facilitate the handling of time-varying covariates. EBF was entered into the model as a time-varying continuous variable (duration of EBF in months) during the 0–5-mo period, and as a fixed continuous variable thereafter because no children were exclusively breastfed after 6 mo. Children were censored at the end of 60 mo if they were event free. Analyses were run for the entire study period and for the following periods: 0–5, 6–11, 12–23, and 24–60 mo of age. For inclusion in the model, we considered potential confounders and independent risk factors for outcomes from a list of candidate variables. Potential confounders were categorized as previously reported for this trial (15–18), maternal HIV disease stage by WHO criteria (20), and maternal blood $CD4^+$ counts as ≥ 350 and < 350 cells/ μL . Variables were included in multivariate models if the estimated risk ratio for EBF changed by $\geq 10\%$ compared with in the saturated main-effects model (22). Confounders that were identified were applied to the respective models for each endpoint. RRs and their corresponding 95% CIs are reported. Kaplan-Meier survival curves were generated for EBF (23).

We performed secondary analyses to examine whether the associations of EBF with the outcomes were modified by the time-varying HIV status of the children, maternal baseline $CD4^+$ cell counts, $CD8^+$ cell counts, and lymphocyte counts. Likelihood-ratio tests were used to assess the interactions examined. All statistical analyses were performed with the statistical software package SAS 9.1 (SAS Institute Inc). Significance tests were 2-sided, and differences were considered significant at $P < 0.05$.

RESULTS

From a total of 939 singleton live births to HIV-infected women in the study conducted between April 1995 and July 1997, we excluded children in whom the duration of breastfeeding could not be determined (85 children with no follow-up visits ever or after 3 mo from birth); the first follow-up visit was after 2 y of age, which made the duration of breastfeeding unreliable (156 children); or a time sequence between EBF and death could not be established (8 children who died within 1 mo after EBF was stopped) (**Figure 1**). Information was available from 690 children to examine the association between EBF and mortality. Ninety-nine children who were HIV positive at the time of the first follow-up visit were excluded from the analysis of EBF and HIV infection or death. In addition, 6 more children whose HIV status was not known were excluded from the analysis of EBF and HIV infection.

Only 30% of the children were exclusively breastfed for ≥ 3 mo; other liquids or solids were introduced before 3 mo in the remaining 70% of children (**Figure 2**). The distribution of maternal and paternal sociodemographic characteristics, maternal indicators of nutritional, immunological status and HIV stage, obstetric history, and child HIV and nutritional status are shown in **Table 1**. In the remaining sections, we present results on the associations between EBF and child mortality, HIV infection, and HIV infection or death.

A total of 113 children (17%) died within the first 2 y, and a total of 142 children (20%) died during the first 5 y of life. Univariate and multivariate adjusted associations (adjusted for mother's social support, maternal time-varying BMI, maternal CD4 counts, child sex, delivery type, child time-varying HIV status, and child MUAC) between EBF and child mortality at different risk periods are presented in **Table 2**. Risk of early infant mortality (0–5 mo) was inversely associated with the duration of EBF (RR: 0.51; 95% CI: 0.28, 0.93) after maternal

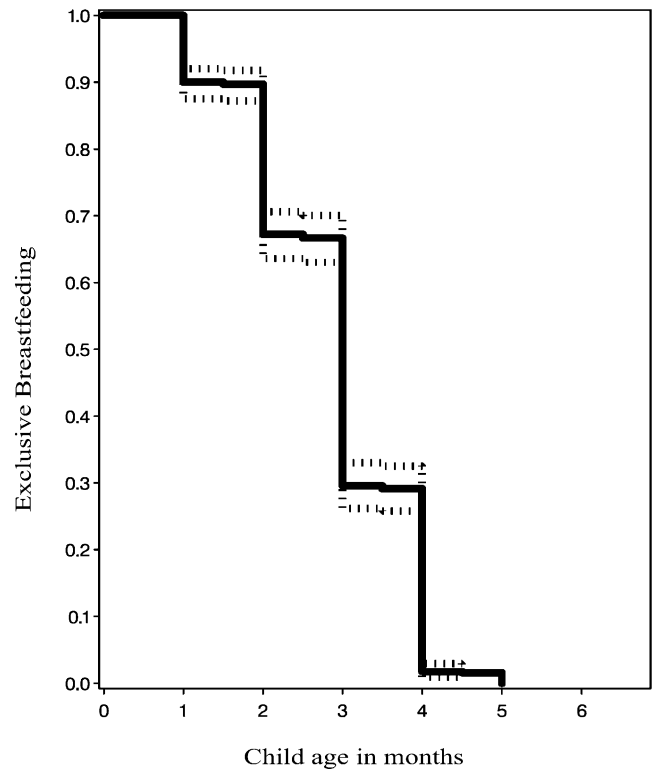


FIGURE 2. Rates (95% confidence bounds) of exclusive breastfeeding by age in children born to HIV-infected mothers (estimated by using Kaplan-Meier survival curves).

social support, time-varying BMI, CD4 counts, child sex, delivery type, time-varying HIV status, and MUAC were controlled for. In the multivariate analysis, the duration of EBF was not associated with a significant reduction in risk of mortality between 6 and 11 mo (RR: 0.98; 95% CI: 0.70, 1.36), 12 and 23 mo (RR: 0.85; 95% CI: 0.64, 1.12), or 24 and 60 mo (RR: 0.84; 95% CI: 0.59, 1.21) of age.

EBF was not associated with HIV infection in any age interval from 0 to 60 mo in the univariate analysis. There was no association between risk of HIV infection and duration of EBF in the ages between 0 and 5 mo (RR: 0.75; 95% CI: 0.52, 1.10), 6 and 11 mo (RR: 0.82; 95% CI: 0.49, 1.38) (Table 2), and 12 and 23 mo (RR: 0.72; 95% CI: 0.50, 1.02) in the multivariate analysis (adjusted for the number of living children born to the index mother, maternal social support, maternal time-varying BMI, maternal CD4 counts, maternal hemoglobin concentrations, maternal viral load, child birth weight, and child time-varying MUAC). Only 4 children became HIV positive between 24 and 60 mo of age, and none were among the children who were exclusively breastfed. Overall, from 0 to 60 mo of age, EBF was not associated with increased risk of HIV infection (RR: 0.93; 95% CI: 0.76, 1.15).

HIV infection or death was not associated with EBF in univariate and multivariate analyses during the risk periods of 0–5, 6–11, or 24–60 mo of age (Table 2). However, an increase in duration of EBF by 1 mo was associated with a 32% reduction in HIV infection or death (RR: 0.68; 95% CI: 0.50, 0.93) within the period between 12–23 mo of age.

The time-varying HIV status of the child and maternal baseline CD4⁺, CD8⁺, and lymphocyte counts were assessed as potential

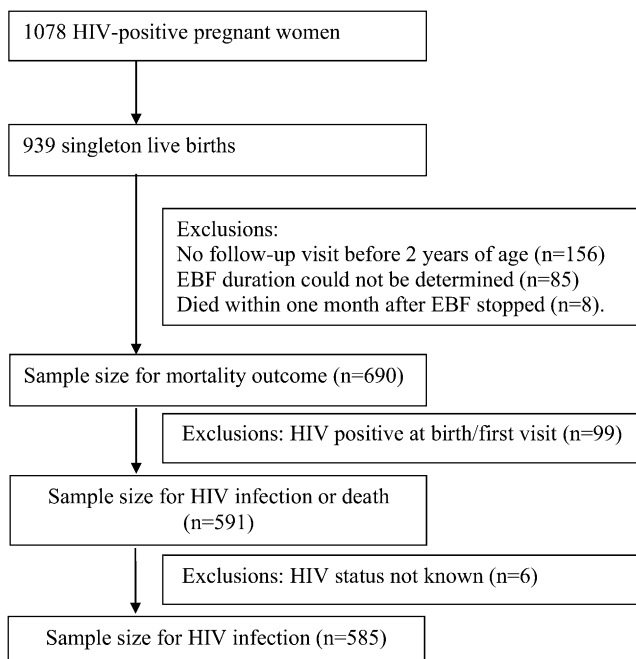


FIGURE 1. Flowchart of infants available for analysis. EBF, exclusive breastfeeding.

TABLE 1Social and clinical characteristics of HIV-infected mothers and children born to them¹

Characteristic	Value
Maternal age (<i>n</i>)	690
<20 y [<i>n</i> (%)]	80 (12)
20–24 y [<i>n</i> (%)]	272 (39)
25–29 y [<i>n</i> (%)]	222 (32)
≥30 y [<i>n</i> (%)]	116 (17)
Maternal education (<i>n</i>)	690
0–8 y [<i>n</i> (%)]	618 (90)
≥9 y [<i>n</i> (%)]	72 (10)
Maternal occupation (<i>n</i>)	666
Housewife [<i>n</i> (%)]	487 (73)
Other [<i>n</i> (%)]	179 (27)
Partner education (<i>n</i>)	611
0–8 y [<i>n</i> (%)]	397 (65)
≥9 y [<i>n</i> (%)]	214 (35)
Maternal BMI 6 wk after delivery (<i>n</i>)	604
<18.5 kg/m ² [<i>n</i> (%)]	54 (9)
18.5–24.99 kg/m ² [<i>n</i> (%)]	447 (74)
≥25 kg/m ² [<i>n</i> (%)]	103 (17)
Maternal baseline hemoglobin (<i>n</i>)	682
<8.5 g/dL [<i>n</i> (%)]	175 (26)
≥8.5 g/dL [<i>n</i> (%)]	507 (74)
Maternal WHO HIV disease stage (<i>n</i>)	689
I [<i>n</i> (%)]	559 (81)
II [<i>n</i> (%)]	125 (18)
III [<i>n</i> (%)]	4 (<1)
IV [<i>n</i> (%)]	1 (<1)
Maternal baseline CD4 ⁺ T cell count (<i>n</i>)	655
0–199 cells/μL [<i>n</i> (%)]	68 (10)
200–499 cells/μL [<i>n</i> (%)]	382 (58)
≥500 cells/μL [<i>n</i> (%)]	205 (31)
Maternal baseline CD8 ⁺ T cell count (<i>n</i>)	690
<565 cells/μL [<i>n</i> (%)]	225 (33)
≥565 cells/μL [<i>n</i> (%)]	475 (67)
Maternal baseline lymphocyte count (<i>n</i>)	690
<1340 cells/μL [<i>n</i> (%)]	189 (27)
≥1340 cells/μL [<i>n</i> (%)]	501 (73)
Maternal viral load (<i>n</i>)	315
<50,000 copies/mL [<i>n</i> (%)]	169 (54)
≥50,000 copies/mL [<i>n</i> (%)]	146 (46)
Child sex (<i>n</i>)	688
M [<i>n</i> (%)]	353 (51)
F [<i>n</i> (%)]	335 (49)
Child birth weight (<i>n</i>)	635
<2500 g [<i>n</i> (%)]	52 (8)
≥2500 g [<i>n</i> (%)]	583 (92)
Child HIV status at 3 mo (<i>n</i>)	684
Not infected [<i>n</i> (%)]	551 (81)
Infected [<i>n</i> (%)]	133 (19)
Child MUAC ² at 3 mo (<i>n</i>)	431
<13 cm [<i>n</i> (%)]	147 (34)
≥13 cm [<i>n</i> (%)]	284 (66)

¹Women were pregnant and between 12 and 27 wk of gestation at enrollment. Percentages may not total to 100% because of rounding.

²MUAC, midupper arm circumference.

effect modifiers of the associations between the duration of EBF and mortality (Table 3). Although an every-month increase in duration of EBF was associated with a 38% reduction in child mortality (95% CI: 0.43, 0.91; *P* = 0.01) in HIV-negative children, the duration of EBF was not associated with mortality in

children who were HIV positive (RR: 0.95; 95% CI: 0.79, 1.15; *P* = 0.63; *P*-interaction = 0.06). We observed a borderline association between the duration of EBF and reduced child mortality (RR: 0.80; 95% CI: 0.63, 1.00; *P* = 0.05) born to mothers with counts of ≥565 CD8⁺ cells/μL at baseline but not in children born to women with baseline counts <565 CD8⁺ cells/μL (*P*-interaction = 0.06). We did not observe interactions by amounts of maternal CD4⁺ and total lymphocyte counts.

We further examined whether maternal immunologic status, represented by CD4⁺, CD8⁺, and lymphocyte counts, modifies the associations of EBF duration with HIV infection and HIV infection or death (Table 4). Although *P*-interaction values were not significant, a longer duration of EBF was associated with lower risk of HIV infection and lower risk of HIV infection or death in infants born to women with counts of ≥350 CD4⁺ cells/μL, ≥565 CD8⁺ cells/μL, or ≥1340 lymphocytes/μL at baseline but not in children born to women with counts of <350 CD4⁺ cells/μL, <565 CD8⁺ cells/μL, or ≤1340 lymphocytes/μL at baseline.

DISCUSSION

In children born to HIV-infected women, we showed that every additional month of EBF was associated with a 49% reduction in mortality from birth to 6 mo of age. The associations between the duration of EBF and child mortality and HIV infection or death, until 5 y of life in this study, were of borderline significance. The duration of EBF was not associated with risk of acquiring HIV during the first 5 y of life.

This analysis confirmed similar findings reported previously in HIV-negative and -positive populations (14, 24–31). A community-based, nested case-control study conducted in rural Tanzania showed that mixed feeding in the first 3 mo of life compared with EBF was associated with 40% increased risk of mortality in children <5 y of age (24). However, the study did not report the HIV status of children and their mothers. Contrary to our findings, a cohort study from South Africa in infants born to HIV-infected women reported higher mortality in HIV-infected infants who were exclusively breastfed (19%) than in infants who were mixed fed (13%), and no deaths were observed in children who were exclusively formula fed (0%) (25). Risk of infant mortality in EBF compared with mixed feeding groups was not significant. This study in South Africa was limited by its small sample size (*n* = 133) with 17 deaths that occurred in HIV-infected children (7 children were in the EBF group, and 10 children were in the mixed-feeding group). A number of studies since 1997 have reported lower risks of HIV infection in infants of HIV-infected women who were exclusively breastfed than in infants who received a mixture of breast milk and top feeding (formula or animal milk) (26–31). However, in our study, risk of HIV infection was not different between exclusively breastfed and mixed-fed infants. Variations in associations between EBF and mortality or HIV infection compared with mixed or formula feeding depend on access to clean water and hygiene in infant-feeding practices. All of these studies followed infants to ≤24 mo of age (and most studies followed infants to 6–11 mo of age), whereas infants in our cohort were followed to ≤60 mo of age by which time more HIV-related deaths would have occurred. This analysis demonstrates that EBF by HIV-positive

TABLE 2Duration of exclusive breastfeeding in relation to child mortality, HIV infection, and HIV infection or death during the first 5 y of life in children born to HIV-infected mothers¹

Outcome	<i>n</i>	Total <i>n</i>	Univariate		Multivariate	
			RR (95% CI)	<i>P</i>	RR (95% CI)	<i>P</i>
Mortality²						
0–5 mo	16	662	0.58 (0.35, 0.95)	0.03	0.51 (0.28, 0.93)	0.03
6–11 mo	43	625	0.91 (0.67, 1.24)	0.56	0.98 (0.70, 1.36)	0.89
12–23 mo	54	557	0.87 (0.67, 1.14)	0.31	0.85 (0.64, 1.12)	0.24
24–60 mo	29	477	0.82 (0.58, 1.17)	0.28	0.84 (0.59, 1.21)	0.37
0–60 mo	142	690	0.87 (0.74, 1.03)	0.10	0.87 (0.73, 1.03)	0.11
HIV infection³						
0–5 mo	47	560	0.75 (0.53, 1.06)	0.10	0.75 (0.52, 1.10)	0.14
6–11 mo	19	493	0.84 (0.53, 1.32)	0.45	0.82 (0.49, 1.38)	0.46
12–23 mo	39	439	0.78 (0.56, 1.07)	0.13	0.72 (0.50, 1.02)	0.06
24–60 mo	4	369	1.07 (0.38, 2.99)	0.90	— ⁴	—
0–60 mo	109	585	0.92 (0.76, 1.12)	0.41	0.93 (0.76, 1.15)	0.52
HIV infection or death⁵						
0–5 mo	50	564	0.75 (0.54, 1.05)	0.10	0.74 (0.51, 1.07)	0.11
6–11 mo	33	497	0.73 (0.52, 1.03)	0.07	0.69 (0.47, 1.02)	0.06
12–23 mo	50	439	0.74 (0.56, 0.97)	0.03	0.68 (0.50, 0.93)	0.02
24–60 mo	10	370	0.74 (0.40, 1.38)	0.34	0.77 (0.38, 1.54)	0.46
0–60 mo	143	591	0.82 (0.70, 0.98)	0.03	0.85 (0.71, 1.01)	0.07

¹ Time-varying Cox proportional hazard regression models were used to estimate RRs and 95% CIs. Five months includes infants <6 mo of age (similarly for each age group).

² Adjusted for maternal social support, maternal time-varying BMI, maternal CD4 counts, child sex, delivery type, child time-varying HIV status, and child midupper arm circumference.

³ Excludes children who were HIV positive at the first visit after birth (*n* = 99) and children in whom HIV status could not be determined (*n* = 6). Adjusted for number of living children given birth by the index mother, maternal social support, maternal time-varying BMI, maternal CD4 counts, maternal hemoglobin concentrations, maternal viral load, child birth weight, and child time-varying midupper arm circumference.

⁴ RR could not be estimated in the multivariate model because of the small number of events in this age group.

⁵ Excludes children who were HIV positive at the first visit after birth (*n* = 99). Adjusted for number of living children given birth by the index mother, maternal social support, maternal time-varying BMI, maternal CD4 counts, maternal hemoglobin concentrations, maternal viral load, child birth weight, and child time-varying midupper arm circumference.

mothers in Tanzania provides survival benefits over the first 6 mo without increased mortality over follow-up until 5 y of age. Few infants were exclusively formula fed, and thus, EBF was not compared with exclusive formula feeding.

HIV (or the AIDS virus) is shed in breast milk, which exposes and puts the infant at risk of HIV infection (9, 10). What is less well known is whether immune factors and antiviral substances in breast milk may also play a role in protecting the infant from HIV

TABLE 3

Associations between exclusive breastfeeding and mortality within strata of potential effect modifiers

Potential modifier	<i>n</i>	Child mortality (0–60 mo of age)		
		RR (95% CI) ¹	<i>P</i> ¹	<i>P</i> -interaction ²
Time-varying child HIV status				
Negative	28	0.62 (0.43, 0.91)	0.01	0.06
Positive	106	0.95 (0.79, 1.15)	0.63	—
Maternal baseline CD4⁺ cell count				
<350 cells/ μ L	63	0.82 (0.64, 1.05)	0.12	0.31
\geq 350 cells/ μ L	61	0.97 (0.75, 1.26)	0.84	—
Maternal baseline CD8⁺ cell count				
<565 cells/ μ L	39	1.20 (0.85, 1.71)	0.30	0.06
\geq 565 cells/ μ L	85	0.80 (0.63, 1.00)	0.05	—
Maternal baseline lymphocyte count				
<1340 lymphocytes/ μ L	37	1.05 (0.72, 1.55)	0.79	0.27
\geq 1340 lymphocytes/ μ L	94	0.83 (0.68, 1.03)	0.08	—

¹ Values were obtained by using adjusted Cox proportional hazards regression models. Covariates were adjusted as indicated in Table 2.

² *P* values for interaction between exclusive breastfeeding and potential modifiers were obtained by using likelihood-ratio tests.

TABLE 4

Association of exclusive breastfeeding with HIV infection and HIV infection or death within strata of potential modifiers

Potential modifier	HIV infection (0–60 mo of age)				HIV infection or death (0–60 mo of age)			
	<i>n</i>	RR (95% CI) ¹	<i>P</i> ¹	<i>P</i> -interaction ²	<i>n</i>	RR (95% CI) ¹	<i>P</i> ¹	<i>P</i> -interaction ²
Maternal baseline CD4 ⁺ cell count								
<350 cells/ μ L	48	0.86 (0.59, 1.24)	0.42	0.42	65	0.87 (0.64, 1.19)	0.39	0.10
\geq 350 cells/ μ L	61	0.74 (0.55, 1.00)	0.05	—	76	0.64 (0.50, 0.83)	<0.001	—
Maternal baseline CD8 ⁺ cell count								
<565 cells/ μ L	35	0.84 (0.57, 1.25)	0.39	0.35	48	0.85 (0.61, 1.19)	0.35	0.10
\geq 565 cells/ μ L	74	0.75 (0.58, 0.98)	0.04	—	93	0.67 (0.53, 0.85)	<0.001	—
Maternal baseline lymphocyte count								
<1340 lymphocytes/ μ L	28	0.92 (0.55, 1.54)	0.75	0.18	39	0.73 (0.48, 1.12)	0.15	0.32
\geq 1340 lymphocytes/ μ L	81	0.73 (0.57, 0.93)	0.01	—	102	0.71 (0.57, 0.88)	0.002	—

¹ Values were obtained by using adjusted Cox proportional hazards regression models. Covariates were adjusted as indicated in Table 2.² *P* values for interaction between exclusive breastfeeding and potential modifiers were obtained by using likelihood-ratio tests.

infection (32, 33). In addition, breast milk may improve mucosal integrity by making the intestinal mucosa less permeable to the HIV virus (34). Women who breastfeed their children are also less likely to suffer from breast and nipple conditions that increase the HIV viral load in breast milk (35, 36). It has been well documented that breastfeeding leads to a remarkable reduction in morbidity and mortality from childhood infectious diseases such as diarrhea and respiratory illnesses (37–39). These infections still account for the highest proportions of mortality in infants and children <5 y of age in Africa, Asia, and other less developed and developing regions of the world (40). It is likely that EBF reduces mortality, especially in the first 6 mo of life, by reducing the incidence of the most common childhood infections as has been reported previously from follow-up of the children included in this analyses (41). In these infants, EBF was associated with reductions in risk of cough (51%), cough and fever (56%), cough and difficulty breathing or chest retraction or refusal to feed (69%), acute diarrheal episodes, fever, and outpatient visits during the first 6 mo of life (41).

Women in this study were not assigned to a type of feeding (they chose to exclusively breastfeed or not) or the duration of EBF if they exclusively breastfed. The underlying reasons that influence women to make a feeding choice could confound risk of dying or being infected by HIV. More than 25% women-child pairs could not be included in this analysis because outcomes occurred before the first available visit or information on EBF was unavailable.

Formula feeding continues to remain an expensive and impractical option for many African mothers (42). When a free or unrestricted supply of formula milk powder is unavailable from governments or household finances, it is often excessively diluted with unsafe water and becomes a vehicle for infections as well as being nutritionally inadequate. In such a scenario, exclusive formula feeding, with the complete exclusion of breast milk, is difficult. In fact, not a single mother was able to maintain exclusive formula feeding in our study. Also, mixed messages with different recommendations for HIV-infected and uninfected mothers can be confusing and may have a bearing on EBF rates and durations in HIV-uninfected mothers. ART was not available in Tanzania at the time of this trial, and none of the participants received any ART. As more and more mothers receive ART, their immunological status (CD4⁺, lymphocyte counts, and AIDS

stages) is likely to be better. We have shown that risk of infant mortality can be greatly reduced by EBF, and these associations between EBF and childhood outcomes may be better in mothers with better lymphocyte counts (total and CD4⁺). In 2010, the WHO revised their recommendations for infant feeding in infants born to HIV-positive mothers (11). EBF is now recommended for the first 6 mo of life except when formula feeding is acceptable, feasible, affordable, sustainable, and safe. A word of caution may be added for women with advanced disease (low lymphocyte or CD4⁺ counts) against breastfeeding, especially if they are not on ART. Our results add to other recently published results that support the breastfeeding recommendations of the WHO for all mothers irrespective of HIV status in Africa, except when an uninterrupted availability of formula and safe water can be ensured. Also, these results from children who were followed up for 5 y allay fears that increased mortality later in childhood from mother-to-child transmission of HIV may offset the benefits of EBF in infancy. In addition, the increasing availability of ART for HIV and AIDS should reduce risk of mother-to-child transmission through breastfeeding and make EBF safer for longer in HIV-infected mothers as now recommended by the WHO (11, 43). Although economic progress and political will are necessary to make safe water available, interventions that can make a choice of EBF in HIV-positive women safer for the infant could be evaluated. Early during the HIV epidemic, messages against EBF to HIV-positive mothers may have contributed to many infants being deprived of the benefits of EBF in the absence of safe alternatives and better interventions to reduce infant mortality from infectious diseases. Nevertheless, as access to safe water and quality formula feeding become available along with reductions in infections, disease mortality, and morbidity during childhood, these recommendations on breastfeeding will need to be revisited.

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authors: read and approved the final manuscript. None of the authors had a conflict of interest.

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