Elevations in Mortality Associated with Weaning Persist into the Second Year of Life among Uninfected Children Born to HIV-Infected Mothers

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(See the editorial commentary by Shapiro and Lockman, on pages 445–7.)

Background. Early weaning has been recommended to reduce postnatal human immunodeficiency virus (HIV) transmission. We evaluated the safety of stopping breast-feeding at different ages for mortality of uninfected children born to HIV-infected mothers.

Methods. During a trial of early weaning, 958 HIV-infected mothers and their infants were recruited and followed up from birth to 24 months postpartum in Lusaka, Zambia. One-half of the cohort was randomized to wean abruptly at 4 months, and the other half of the cohort was randomized to continue breast-feeding. We examined associations between uninfected child mortality and actual breast-feeding duration and investigated possible confounding and effect modification.

Results. The mortality rate among 749 uninfected children was 9.4% by 12 months of age and 13.6% by 24 months of age. Weaning during the interval encouraged by the protocol (4–5 months of age) was associated with a 2.03-fold increased risk of mortality (95% confidence interval [CI], 1.13–3.65), weaning at 6–11 months of age was associated with a 3.54-fold increase (95% CI, 1.68–7.46), and weaning at 12–18 months of age was associated with a 4.22-fold increase (95% CI, 1.59–11.24). Significant effect modification was detected, such that risks associated with weaning were stronger among infants born to mothers with higher $CD4^+$ cell counts (>350 cells/μL).

Conclusion. Shortening the normal duration of breast-feeding for uninfected children born to HIV-infected mothers living in low-resource settings is associated with significant increases in mortality extending into the second year of life. Intensive nutritional and counseling interventions reduce but do not eliminate this excess mortality.

Human immunodeficiency virus (HIV) transmission continues to occur throughout the duration of breast-feeding, prompting many advocates of prevention of mother-to-child HIV transmission programs to recommend early weaning for infants born to HIV-infected mothers [1–4]. However, benefits of breast-feeding for the survival and well-being of infants and young children are well established [5, 6], creating a tragic impasse for the communities, primarily in sub-Saharan Africa, that are most severely affected by the HIV/AIDS pandemic.

We hypothesized that early weaning at 4 months of age could be made safe enough to justify recommending this practice to prevent HIV transmission and conducted a trial to test this hypothesis in Lusaka, Zambia. Because benefits of breast-feeding are thought to decrease as children age [7], we hypothesized that, by 4 months, children would have passed the critical developmental age when breast-feeding is essential to their survival. We also provided a fortified weaning cereal that needed cooking in order to minimize risks associated with preparing infant formula with contaminat-

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Table 1. Maternal, Household, and Infant Characteristics of 749 Uninfected Children Born to Human Immunodeficiency Virus–Infected Mothers in Lusaka, Zambia

Characteristic	Living when last seen (n = 658)	Died at <24 months of age (n = 91)	P
Maternal $CD4^+$ cell count at enrollment during pregnancy			
Median cells/μL	372	315	.03
<200 cells/μL	113 (17.2)	22 (24.2)	
200–349 cells/μL	185 (28.2)	35 (38.5)	.02
350–499 cells/μL	188 (28.7)	16 (17.6)	
⩾500 cells/μL	170 (25.9)	18 (19.8)	
Maternal plasma viral load at enrollment during pregnant			
Median viral load, copies/mL	25,899	40,874	.03
<1000 copies/mL	56 (8.5)	5 (5.5)	
1000–9999 copies/mL	148 (22.5)	18 (19.8)	.19
10,000–99,999 copies/mL	314 (47.8)	40 (44.0)	
⩾100,000 copies/mL	139 (21.2)	28 (30.8)	
Eligible for antiretroviral therapy at enrollment during pregnancy[a]	193 (29.3)	34 (37.4)	.12
Initiated antiretroviral therapy during pregnancy or first 6 months after delivery	9 (1.4)	2 (2.2)	.54
Mother died within 24 months after delivery	27 (4.1)	16 (17.6)	<.001
Maternal age, mean years	26.0	26.4	.50
Parity			
First child	98 (14.9)	8 (8.8)	
Second or third child	315 (47.9)	42 (46.2)	.18
Fourth child or greater	245 (37.2)	41 (45.0)	
Marital status			
Married	564 (85.7)	81 (89.0)	.69
Single	59 (9.0)	6 (6.6)	
Widowed/divorced/separated	35 (5.3)	4 (4.4)	
Maternal education			
No school	37 (5.6)	5 (5.5)	.72
Primary school (<8 years)	335 (50.9)	48 (52.8)	
Some high school (⩾8 years)	226 (34.4)	33 (36.3)	
High school completed or more	60 (9.1)	5 (5.5)	
Domestic water source			
Tap within dwelling	44 (6.7)	3 (3.3)	.35
Tap on property outside	68 (10.3)	6 (6.6)	
Community tap	520 (79.0)	79 (86.8)	
Other	26 (4.0)	3 (3.2)	
Electricity in the home	264 (40.1)	34 (37.4)	.61
Cooking facilities			
Stove/hotplate	229 (34.9)	33 (36.3)	.90
Charcoal/wood	428 (65.1)	58 (63.7)	
Report ⩾1 day in past month with no food at home	139 (21.1)	33 (36.3)	.001
Full-time paid job	44 (6.7)	8 (8.8)	.46
More than 1 child <5 years of age in household	103 (15.7)	22 (24.2)	.04
Place of birth			
Home	58 (8.8)	12 (13.2)	.42
Clinic	515 (78.3)	63 (69.2)	
Hospital	80 (12.2)	15 (16.5)	
Other	5 (0.8)	1 (1.1)	
Male sex	342 (52.1)	46 (50.6)	.79
Birth weight, median g	3069	2812	<.001
Birth weight <2500 g	50 (7.8)	21 (23.6)	<.001
Reported duration of breast-feeding of previous child, median months	18	18	.63
Duration of breast-feeding of study child, median months	12	9	.001

NOTE. Data are no. (%) of children, unless otherwise indicated. Some data may not sum correctly because of missing data.

[a] Defined as $CD4^+$ cell count <200 cells/μL at any clinical stage or $CD4^+$ cell count 200–350 cells/μL if clinical stage III.

Table 2. Causes of Death among 91 Uninfected Children Born to Human Immunodeficiency Virus–Infected Mothers, by Age

Cause of death	0–3 Months	4–5 Months	6–11 Months	12–24 Months
All-cause mortality[a]	20	6	36	29
Diarrhea	…	2	23	17
Pneumonia	11	4	15	9
Malaria	2	1	4	8
Measles	…	…	2	1
Septicemia	6	1	2	1
Malnutrition	1	…	3	5
Tuberculosis	…	…	2	1
Injury	…	…	…	1
Prematurity	2	…	…	…
Unknown	3	…	1	1

[a] Data are total no. of deaths; more than 1 cause could be assigned to a death.

ed water. The cereal contained all the macro- and micro-nutrient requirements of 4–6-month-old infants. Trimethoprim-sulfamethoxazole was given to all infants, and intensive counseling and education for mothers.

Elsewhere, we have reported that the trial found no benefit of early weaning for HIV-free survival [8]. Here, we investigate the effects of weaning at different ages on mortality of uninfected children born to HIV-infected mothers. Specifically, we were interested in whether we could determine a safe age when weaning could be recommended.

METHODS

Study design. We recruited a cohort of 958 HIV-infected mothers into a randomized trial of early weaning in Lusaka, Zambia. All women planned to breast-feed for at least 4 months and were counseled to breast-feed exclusively [9]. One-half of the cohort was encouraged to abruptly wean at 4 months, and the other half of the cohort was encouraged to continue breast-feeding and to wean at a time of their own choosing. Here, we examine whether the actual age of the child at the time when all breast-feeding ended (ie, weaning age) was associated with mortality through 24 months among uninfected children.

Study procedures. HIV-infected pregnant women were recruited from May 2001 through September 2004 from 2 antenatal clinics in Lusaka, Zambia, that offered voluntary HIV counseling and testing and single-dose nevirapine prophylaxis. All women signed informed consent. The study was approved by Human Subjects Committees at the investigators' institutions.

Blood samples were obtained from women at enrollment, and 2 subsequent antenatal visits were scheduled for counseling prior to delivery. Sociodemographic data and clinical history were collected at enrollment, and obstetric and neonatal data was collected after delivery. Infant heelstick blood samples were collected onto filter paper on the day of birth, at 1 week, and at 1, 2, 3, 4, 4.5, 5, 6, 9, 12, 15, 18, 21, and 24 months of age. Clinic visits were scheduled at these same times, and detailed questions were asked about infant feeding practices by study staff who were separate from those performing the counseling. Home visits were scheduled at 4 days and then again at times

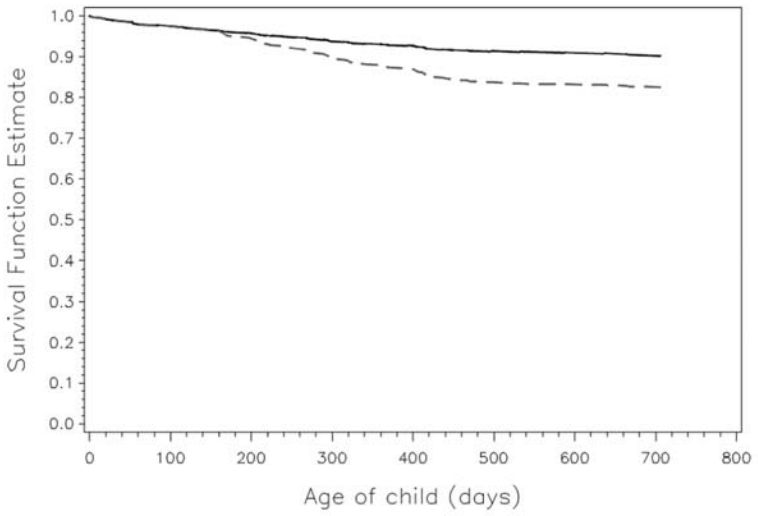

Figure 1. Survival function estimates calculated from a Cox proportional hazards model using breast-feeding cessation as a time-dependent covariate for uninfected children born to human immunodeficiency virus–infected mothers if weaned at 5 months of age *(dashed line)* or if weaned at 18 months of age *(solid line)*.

Table 3. Magnitude of the Elevation in Uninfected Child Death associated with Early Weaning at Different Ages relative to Weaning at Ages Older than 18 Months

Variable	Age when breast-feeding stopped			
	0–3 Months	4–5 Months	6–11 Months	12–18 Months
Weaned at age shown vs weaned at >18 months of age, hazard ratio[a] (95% confidence interval)	3.59 (1.69–7.62)	2.03 (1.13–3.65)	3.54 (1.68–7.46)	4.22 (1.59–11.24)
Proportion of cohort who weaned by end of the interval	0.061	0.349	0.470	0.752
Total no. of infants alive and in follow-up at end of the interval	698	675	586	530
No. of deaths by end of interval	20	26	62	86

[a] Hazard ratios are from a Cox proportional hazards model with mortality of uninfected children born to human immunodeficiency virus–infected mothers as the outcome and weaning as a time-dependent covariate.

interspersed between clinic visits, so that contact occurred every 2 weeks through 5 months. All randomized infants were followed up on this schedule to 24 months. Home visit teams tracked participants who did not return for appointments. Information about all child deaths was sought from hospital and clinic records, as well as from interviews with caretakers and health care personnel. The circumstances of all deaths were reviewed, and verbal autopsies were conducted to identify causes of death.

Antiretroviral drugs were not available in the public sector during most of the study period, but they became available after May 2004 [10]. Women eligible for treatment on the basis of Zambian guidelines initiated first-line regimens if they consented to treatment. Trimethoprim-sulfamethoxazole was given to all women with $CD4^+$ cell counts <200 cells/μL after November 2003 [11]. Trimethoprim-sulfamethoxazole was given to all infants from 6 weeks through 12 months of age. Growth monitoring was done at least monthly, immunizations for children were given according to the national guidelines, and children from either group with evidence of failure to thrive were provided with nutrition supplements. Children in the intervention group were provided with a 3-month supply of commercial infant formula (not premixed) and a fortified weaning cereal, regardless of growth status, from 4 months of age. The cereal was maize meal–based and fortified with milk powder, sugar, oil, and micronutrients.

Table 4. Factors Associated with Mortality among Uninfected Children <2 Years of Age Born to Human Immunodeficiency Virus–Infected Mothers

Variable	Relative hazard (95% confidence interval)		
	Univariable model	Multivariable model 1[a]	Multivariable model 2[b]
Breast-feeding cessation (time-dependent covariate)[c]	2.57 (1.53–4.30)	2.12 (1.25–3.60)	4.02 (1.84–8.78)
Maternal $CD4^+$ cell count <350 cells/μL	1.87 (1.22–2.86)	1.61 (1.02–2.52)	2.87 (1.41–5.82)
Maternal viral load (log RNA copies/mL)	1.33 (1.02–1.74)	…	…
Maternal death	3.75 (2.18–6.44)	2.36 (1.33–4.19)	2.43 (1.37–4.32)
Birth weight <2500 g	3.10 (1.90–5.06)	2.54 (1.54–4.21)	2.60 (1.57–4.32)
More than 1 other child <5 years of age in the household	1.77 (1.09–2.85)	1.85 (1.13–3.02)	1.86 (1.14–3.04)
Household has water source on own property	0.57 (0.29–1.13)	…	…
Household has electricity	0.86 (0.56–1.32)	…	…
Wood/charcoal used for cooking	1.01 (0.66–1.55)	…	…
Household has refrigerator	0.88 (0.44–1.55)	…	…
Maternal education ⩾8 years	0.88 (0.58-1.33)	…	…
Report food insecurity	1.98 (1.29–3.04)	2.14 (1.38–3.31)	2.14 (1.38–3.31)

[a] Model 1: Cox Proportional Hazards model ignoring effect modification and entering each of the variables shown in the table simultaneously.

[b] Model 2: Cox Proportional Hazards model taking into account significant effect modification by maternal $CD4^+$ cell count (*P* value interaction term, .03) and including each of the other variables shown in the table simultaneously.

[c] This time-dependent covariate covers the full period to 24 months of age, and thus, the de facto reference group is those who weaned at ages >24 months.

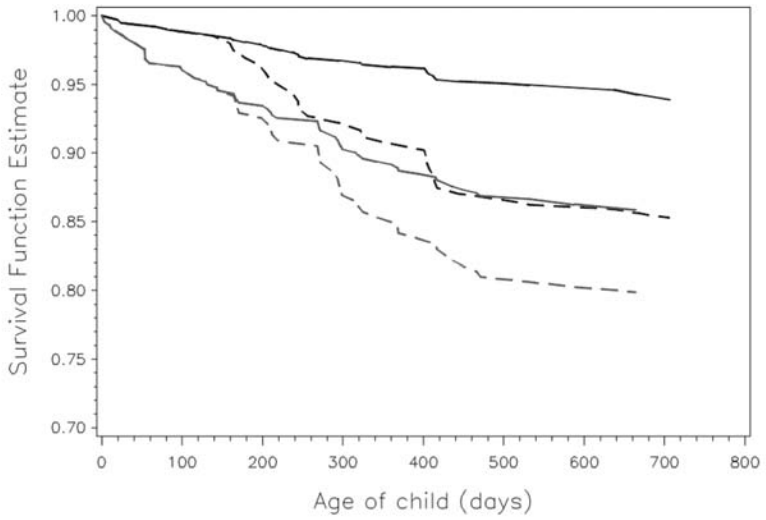

Figure 2. Survival function estimates calculated from a Cox proportional hazards model using breast-feeding cessation as a time-dependent covariate for uninfected children born to human immunodeficiency virus–infected mothers if weaned at 5 months of age *(dashed line)* or if weaned at 18 months of age *(solid line),* stratified by maternal $CD4^+$ cell count <350 cells/mL *(thin)* or maternal $CD4^+$ cell count ⩾350 cells/μL *(thick)* at enrollment.

Laboratory methods. Maternal blood samples collected at enrollment were tested to determine $CD4^+$ and $CD8^+$ cell counts (FACSCount; BD Immunocytometry Systems), hemoglobin level (Hemocue system), and plasma viral load (Roche Amplicor 1.5; Roche). Maternal $CD4^+$ cell counts were repeated 12 months after delivery. Infant heelstick samples were tested for HIV-1 DNA by real-time polymerase chain reaction (PCR) at the end of the study. All positive results were confirmed by testing of at least 2 samples, if available; if 2 samples were not available, the same sample was re-tested to confirm the result. Amplification of the β-globin gene was performed for all samples to ensure adequate cell numbers, thereby minimizing the possibility of a false-negative result caused by an inadequate sample.

Statistical methods. Children were considered to be uninfected if their last available PCR test result was negative. Three children who died without a prior PCR test result were excluded. Mortality among uninfected children through 24 months of age was analyzed using Cox Proportional Hazards models. Children were included in the analysis up to the time of their last negative test result or until their death (if they died without ever having a positive test result). Breast-feeding cessation (weaning) was treated as a time-dependent variable. The age of weaning was calculated on the basis of the exact age at which all breast-feeding stopped. The maternal report provided at the first clinic visit after weaning was used. Children who died were assumed to have been breast-fed up to their date of death unless study records specifically reported that breast-feeding ceased prior to the start of the illness immediately preceding the child's death. Curves to display survival probabilities by different weaning ages using the time-dependent covariate for weaning were generated with Cox models. Piecewise time-dependent covariates for weaning age were introduced to examine whether the effects of weaning on mortality were constant across child age. Confounding was investigated by examining whether the inclusion of each putative confounder changed the magnitude of the weaning association by >10%. Any factor that modified the primary relationship in this way or which was significantly associated with mortality was included in the final model. Effect modification was investigated through stratification and multiplicative interaction terms in the Cox model. To compare characteristics between groups, differences in categorical parameters were tested using χ^2 tests, normally distributed continuous variables were tested using Student t tests, and non-normal continuous variables were tested using Wilcoxon rank-sum tests. Analyses were done using SAS (SAS Institute).

RESULTS

Mortality rates. Of 958 mother-child pairs randomized in the study, 749 had a last PCR test result that was negative. The mortality rate among uninfected children was 2.8% (21 deaths) by 4 months, 9.4% (65 deaths) by 12 months, and 13.6% (91 deaths) by 24 months of age. The median time between the last negative PCR result and death was 31 days (interquartile range [IQR], 16–53 days). The early mortality rate in the randomized cohort is an under-estimate, because the study aimed only to randomize mother-child pairs in which the child survived to 1 month of age. To generate estimates of mortality among children <2 years of age that do not under-represent neonatal mortality, we examined neonatal mortality in the

larger cohort of 1002 live-births, including those excluded prior to randomization and censoring those who had test results positive for HIV before 28 days of age. In this birth cohort, neonatal mortality was 4.4%.

Maternal, household, and infant characteristics of the surviving and deceased uninfected children are displayed in Table 1. Children who died were more likely to have mothers with low $CD4^+$ cell counts and high viral loads, to have had mothers who died, to have lived in households reporting food insecurity and with >1 other child <5 years of age, to have been of low birth weight, and to have weaned earlier.

Diarrhea was the leading cause of death, contributing to 61.5% of deaths among children 6–24 months of age, but it was not a major cause of mortality for those <6 months of age. Pneumonia was the second major cause of death contributing to deaths across all age categories (42.9% of deaths overall). If sepsis and pneumonia were combined into a single category, they became the leading cause of death, contributing to 84.6% of deaths among children <6 months of age and to 41.5% of deaths among children 6–24 months of age (Table 2).

Weaning and mortality. Weaning was associated with a >2-fold increase (hazard ratio [HR], 2.56; 95% CI, 1.53–4.28) in mortality over the full period from birth through 24 months of age. Mortality among children <2 years of age in the cohort of children who did not stop breast-feeding before 18 months of age was 9.7%, and it was 17.4% in the cohort of children who stopped breast-feeding at 5 months of age (Figure 1).

To investigate whether weaning became safer as children became older, we examined the effects of weaning before 4 months of age and at 4–5 months, 6–11 months, and 12–18 months of age, using 4 time-dependent covariates for these periods with those who weaned at ages older than 18 months as the comparison. Elevated risks of mortality among uninfected children persisted through 18 months of age. Weaning at 4–5 months of age, which is the period encouraged in the intervention group and especially supported with additional nutritional interventions, was associated with a significant 2.03-fold increase in mortality (95% CI, 1.13–3.65-fold increase), albeit slightly lower than that observed for other age groups. Weaning at 6–11 months of age was associated with a 3.54-fold increase (95% CI, 1.68–7.46-fold increase), and weaning at 12–18 months of age was associated with a 4.22-fold increase (95% CI, 1.59–11.24-fold increase) in uninfected child mortality, compared with those children weaning at ages older than 18 months (Table 3). The adverse effects of weaning were not confined to the period immediately after breast-feeding ended. Among children who stopped breast-feeding at 4 months, the absence of breast milk was associated with significantly increased mortality in the period 2 months after weaning (HR, 2.17; 95% CI, 1.13–4.16). In the acute period (within the first 2 months after weaning), weaning-related mortality was not as elevated (HR, 1.61; 95% CI, 0.48–5.42).

Confounders and effect modifiers. We investigated whether any other factors, either alone or together, confounded the relationship between weaning and mortality. Low maternal $CD4^+$ cell count during pregnancy, maternal mortality, low birth weight, having >1 other child in the household <5 years of age, and reported food insecurity were each independently associated with significantly increased mortality among uninfected children in multivariate analysis but did not account for the relationship between weaning and mortality. After adjustment for these factors, the absence of breast-feeding continued to be associated with significantly increased risk of uninfected child mortality (Table 4). Weaning was associated with significantly increased risk of mortality in both the intervention group (HR, 3.19; 95% CI, 1.15–8.83) and the control group (HR, 2.84; 95% CI, 1.38–5.83) after adjusting for these same factors.

Maternal $CD4^+$ cell count measured during pregnancy was a significant effect modifier of the relationship between weaning and mortality. When maternal $CD4^+$ cell counts were high (>350 cells/μL), weaning was associated with >4-fold increased risk of death (HR, 4.16; 95% CI, 1.90–9.13) after adjusting for other confounders (Table 4). The weaning-mortality association was attenuated when maternal $CD4^+$ cell counts were low. Correspondingly, the association between low maternal $CD4^+$ cell counts and increased mortality among uninfected children was strongest among breast-fed infants (Figure 2 and Table 4). Taking into account this interaction, as well as adjusting for maternal mortality, birth weight, other children in the household, and food insecurity, the relative hazard of death associated with weaning before 6 months of age was 3.64 (95% CI, 1.63–8.14), with weaning at 6–11 months of age was 7.63 (95% CI, 2.84–20.45), and with weaning at 12–18 months of age was 8.96 (95% CI, 2.94–27.29).

There was no evidence that markers of a more beneficial socioeconomic position (eg, availability of electricity, domestic water source, maternal education, and cooking facilities) modified the association between weaning and mortality. None of the interaction terms were close to statistical significance. Further adjustment for maternal initiation of antiretroviral therapy or for the era when antiretroviral therapy became available had no appreciable effect on the results.

DISCUSSION

Premature truncation of the usual breast-feeding duration more than doubled the risk of death among uninfected children, and the increase was >4-fold if mothers were not yet immunocompromised. Weaning at older ages continued to confer elevated mortality risks, with 3- and 4-fold elevations associated with weaning between 6–11 months of age and 12–18 months of

age, respectively, relative to breast-feeding for longer than 18 months. Mortality elevations were >7-fold higher with weaning at 6–11 months of age and 12–18 months of age if mothers had $CD4^+$ cell counts >350 cells/μL. These sobering results are consistent with prior studies, which have observed that, among the general population, breast-feeding continues to protect against mortality even into the second year of life [5, 7, 12].

There was some evidence that the study interventions to support early weaning were beneficial. These interventions included counseling, education about preparation of replacement feeds and hygiene, growth monitoring (including nutritional supplementation of children manifesting signs of failure to thrive), trimethoprim-sulfamethoxazole, and provision of a 3-month supply of nutritionally replete replacement foods. Hazard ratios associated with weaning during the study-supported interval of 4–5 months were slightly lower than elevations observed at older ages. Despite these interventions, weaning was associated with a >2-fold higher risk of death, compared with that associated with continued breast-feeding. It is unclear what more could be added to make weaning safer than what was done as part of our study. It is possible that we have reached a biological threshold. Moreover, adverse effects of early weaning were not confined to the acute period immediately after weaning, suggesting that it is the absence of breast milk, rather than some temporary difficulty of the child adjusting to change, that is responsible for elevated mortality. It is likely that mortality associated with weaning will be greater in real-world program situations, where the extent of education and nutritional support is less than that provided by our trial. Higher mortality rates have been observed in program settings [13].

We did not observe attenuation of the HRs associated with weaning among women with more-advantaged socioeconomic characteristics, but the numbers of women who met even crude indicators of socioeconomic advantage were small. Benefits of breast-feeding are demonstrated even in settings with high resources (eg, the United Kingdom, where breast-feeding was found to be associated with significantly reduced risks of severe diarrhea and pneumonia-related morbidity resulting in hospitalization) [14]. Our HRs may be biased towards the null by the nature of clinical research, which over-represents motivated and compliant participants and provides a health service safety net with easier access to medical care and medications.

It is intriguing that the benefits of breast-feeding were greatest among women with higher $CD4^+$ cell counts. Although some risks associated with weaning may be, in part, related to environmental factors, the effect modification by maternal immune status highlights the importance of the immunologically active components of breast milk [15, 16]. Our findings suggest that there may be some deficiencies in the breast milk of immunocompromised women, but these are yet to be identified [17].

Our results pertaining to the effects of early weaning on uninfected child mortality should be viewed in the context of HIV-free survival. The only reason to encourage early weaning is to reduce HIV transmission. Guidelines for uninfected women are unambiguous in their support for breast-feeding to 24 months of age or longer [18]. Our study was conducted largely prior to the availability of antiretroviral therapy for women. We have previously reported, in both an intent-to-treat analysis [8] and in analyses based on actual behavior [19], that early weaning resulted in no net benefit for HIV-free survival. Benefits for HIV reduction were off-set by elevations in uninfected child mortality. There are encouraging new data that antiretroviral drug regimens, when given as prophylaxis to the infant, can reduce post-natal HIV transmission [20, 21]. Mothers who receive effective antiretroviral therapeutic regimens also appear to be at low risk of HIV transmission [22, 23]. When antiretroviral drugs are given, the risks for mortality among uninfected children take on greater salience, because even small elevations can counterbalance the now-lessened HIV transmission risks. The balance also shifts among women who are at low risk of transmitting HIV, such as women with high $CD4^+$ cell counts. As we demonstrate here, women least likely to transmit HIV because of higher $CD4^+$ cell counts are also those for whom stopping breast-feeding confers the greatest dangers. As we have previously reported, even in the absence of antiretroviral therapy in women with higher $CD4^+$ cell counts, there is a net benefit in terms of HIV-free survival associated with longer breast-feeding [19].

There are limitations of our analysis. We aimed to reduce the risks of reverse causality by reviewing the clinical circumstances of each death to exclude deaths in cases where underlying illness was the motivation for weaning, but we acknowledge that we may not have had all necessary information in every case. Our observation that early weaning was associated with death in both the intervention and the control group, despite the vastly different reasons for early weaning in these 2 groups, strengthens our inference about the effects of early weaning on mortality. We also investigated possible confounding by several socioeconomic and clinical factors that are known to be associated with infant and young child death, and none of these factors accounted for the associations. Unmeasured confounders may play a role but, given the consistency of our results with biological plausibility and studies in uninfected populations, this is unlikely. One of the greatest strengths of our cohort is the degree of heterogeneity of feeding practice. Other studies tend to be conducted among HIV-infected women who are more homogenous in their feeding practices, thus limiting the comparisons possible. The fact that women in the intervention group were specifically encouraged to wean early also minimizes the usual reasons for early weaning and makes our associations less prone to the confounding factors that may dom-

inate in other studies and preclude sufficient variability for adequate statistical adjustment.

Support is needed for programs in low-resource settings to incorporate antiretroviral therapy for pregnant women with low $CD4^+$ cell counts and other strategies that address HIV transmission over the postnatal period, so that breast-feeding for a normal duration can be unambiguously supported. Our data, which are consistent with prior data for uninfected children, demonstrate that the survival of uninfected children born to HIV-infected mothers is compromised through the second year of life if breast-feeding is stopped early. Nutrition, education, and counseling interventions may reduce, but do not eliminate, this excess mortality.

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