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Reduced Mortality Associated With Breast-Feeding–Acquired HIV Infection and Breast-Feeding Among HIV-Infected Children in Zambia

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Abstract

Objectives—In developing countries, where mother-to-child transmission of HIV through breast-feeding is common, little is known about the impact of postpartum transmission on child survival. This study assessed whether children infected postpartum have longer survival from time of infection versus those infected during gestation or delivery.

Design—We used a prospective cohort study to analyze data from 213 HIV-infected children enrolled in a breast-feeding intervention trial in Lusaka, Zambia (2001 to 2004).

Methods—We compared mortality 1 year after HIV infection in children stratified by age of infection: 0 to 3 days (intrauterine [IU] group), 4 to 40 days (intrapartum/early postpartum [IP/EPP] group), and >40 days (postpartum [PP] group).

Results—A total of 61, 71, and 81 children were infected in the IU, IP/EPP, and PP groups, respectively. Children with intrauterine or intrapartum/early postpartum transmission had higher mortality over the first 12 months after infection than children with postpartum transmission ($P = 0.001$ and $P = 0.006$, respectively); no differences were detected between children with intrauterine and intrapartum/early postpartum transmission. Nearly 20% of the IU and IP/EPP groups died by 100 days after infection, whereas nearly 10% of the PP group had died by this time. After adjusting for birth weight, maternal CD4 cell count, breast-feeding, and maternal death, children infected postpartum had one quarter the mortality rate (hazard ratio [HR] = 0.27, 95% confidence interval [CI]: 0.15 to 0.50) of those infected in utero. Stopping breast-feeding increased mortality in infected children (HR = 3.1, 95% CI: 1.8 to 5.3).

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Conclusions—This study demonstrates a survival benefit among children infected postpartum versus children infected during pregnancy or delivery and a benefit to increased breast-feeding duration among infected children. Testing children for HIV early may provide a means to allow for earlier intervention.

Keywords

Africa; breast-feeding; HIV; infant mortality; mother-to-child transmission; pediatric HIV

Interventions to prevent mother-to-child transmission (MTCT) of HIV have reduced transmission to as low as 2% in developed countries,¹ although in developing areas, transmission remains between 20% and 45%.²⁻⁵ Children can be infected before birth (in utero), at birth (intrapartum), or after birth (postpartum) through breast-feeding. Evidence from developed countries, where postpartum transmission is rare, has shown that children infected in utero have faster disease progression than children infected at birth.^{6,7} The reasons for this progression are poorly defined but are presumed to be attributable to the immaturity of the immune system of the developing fetus and/or inoculum size. In developing countries, breast-feeding transmission is still common,⁸ yet little is known about the impact of postpartum breast-feeding transmission on child survival.

Differences in disease progression by timing of infection may have implications for early infant testing algorithms and the development of antiretroviral (ARV) treatment guidelines among children infected at different developmental periods. If children infected through breast-feeding do survive longer from the time of infection compared with children infected at birth or in utero, reductions of in utero and intrapartum transmission through ARV therapy may also be accompanied by a shift to longer average survival among infected children simply because a greater proportion of all infections occur through breast-feeding. Slower disease progression may also provide more opportunities to intervene.

Several studies in sub-Saharan Africa have examined the survival of children infected through breast-feeding.⁹⁻¹⁴ Most reports have found increased survival among children infected postpartum compared with children infected in utero¹⁰⁻¹³; however, for most studies, small sample sizes have limited the ability to compare intrapartum and postpartum transmission. A recent pooled analysis¹³ has shown a 25% reduction in mortality for children infected after 4 weeks of age compared with those infected before but found no difference between children infected at birth and those infected shortly after.

Interpretation of previous studies has been complicated by several factors. First, determining the time of MTCT is not possible when a blood sample is not taken at birth; in this case, in utero and intrapartum transmission cannot be separated. Second, duration of breast-feeding, a potentially important confounder of the relation between time of transmission and infant survival, has not been included in many of the analyses. This is typically done because breast-feeding is near universal in the countries in which these studies have been conducted. As new breast-feeding interventions are developed to try to reduce MTCT,¹⁵⁻¹⁸ however, knowledge of the impact of timing of transmission in a population with limited breast-feeding is crucial.

This study set out to determine if children infected postpartum have longer survival from time of infection compared with those infected during gestation or delivery. The analysis was conducted among a cohort of children enrolled in a completed study of a breast-feeding intervention for the prevention of MTCT of HIV; therefore, we were able to control tightly for confounding by breast-feeding.

METHODS

Study Design and Study Population

The current study population is a subset of participants who were enrolled in the Zambia Exclusive Breast-Feeding Study (ZEBS); the ZEBS was designed to determine whether exclusive breast-feeding, along with abrupt weaning at 4 months, could reduce the amount of transmission of HIV from mother to child. Details of the study design, enrollment, and data collection have been described previously.¹⁸ Briefly, between May 2001 and September 2004, 1435 HIV-infected pregnant women at 2 clinics in Lusaka, Zambia were enrolled at antenatal visits. All women enrolled in the study were intensively counseled to breast-feed their children exclusively through 4 months of age. At 1 month after delivery, all women whose children remained enrolled were randomized to (1) abrupt cessation of breast-feeding at 4 months or (2) exclusive breast-feeding through 6 months with weaning as they normally would and the duration of all breast-feeding based on the mother's informed choice. At the time of this study, highly active antiretroviral therapy (HAART) was not yet available in Zambia; all children were given cotrimoxazole prophylaxis from 6 weeks to 12 months of age.

The current analysis includes all live-born singleton children enrolled in the ZEBS who tested HIV-positive during follow-up. The ZEBS study was approved by Institutional Review Boards at Boston University, Childrens Hospital of Los Angeles, Columbia University, and the University of Zambia Research Ethics Committee.

Analytic Variables

We assessed the association between time of HIV transmission and subsequent child mortality over 1 year from the time of infection. The primary outcome was time to child death. The circumstances of all child deaths were elicited from the mother or family members and hospital records when available.

The primary exposure variable was time of HIV transmission. To assess time of transmission, dried blood heel-stick samples were obtained for each child at each visit and extracted DNA was tested for HIV by polymerase chain reaction (PCR).¹⁹⁻²¹ Clinic or home follow-up visits were scheduled for birth, 1 week, 1 month, monthly through 6 months, and then every 3 months through 2 years. Time of HIV infection was considered to be the midpoint between birth or the last negative test result and the first positive test result. Although this method can produce some bias, the bias is minimal in most cases.²²

Presumed time of transmission (as defined by the midpoint) was categorized into the following time of transmission groups: positive between 0 and 3 days (intrauterine [IU]), positive between 4 and 40 days (mostly intrapartum but may include some early postpartum [IP/EPP]), and positive after 40 days (postpartum [PP]). Using 40 days as a cutoff would include most children with a last negative test result at 1 month and a first positive test result at 2 months (midpoint = 45 days) in the late transmission group. There were 20 subjects who could be classified into a group based on their midpoint but could not be classified according to working group definitions²³ because data were missing. Of these 20 subjects, 8 were missing a birth sample, 3 were missing a 1-week visit sample, and 1 was missing both. The impact of these potential misclassifications is explored in a sensitivity analysis (see Supplemental Appendix; Supplemental materials are available via the Article Plus feature at www.jaids.com. You may locate this article, and then click on the Article Plus link on the right).

Person-time was accrued from the estimated time of infection (midpoint between birth or the last negative test result and the first positive test result) through the date of the earliest occurrence of (1) completion of 1 year of follow-up beyond the estimated time of HIV infection (2) determination of lost to follow-up (LTF) status, or (3) death.

Potential Confounders

Candidate confounders were those believed to be potentially associated with the exposure and independent risk factors for the outcome. Information on potential demographic, medical, and obstetric confounders was collected at enrollment. At each visit, data on all mothers' height and weight were recorded. Baseline laboratory testing for all enrolled mothers consisted of HIV RNA quantitation (Roche Amplicor, version 1.5; Roche, Branchburg, NJ), CD4 T-cell lymphocyte counts (FACSCount system; BD Immunocytometry Systems, San Jose, CA), and hemoglobin (Hgb) level (Hemocue system; Hemocue, Lake Forest, CA).

Particular attention was paid to the role of breast-feeding cessation as a confounder. Detailed information on breast-feeding behavior was collected by structured questionnaire at each visit by study personnel not associated with the intervention. We coded mothers to have stopped breast-feeding at the exact date the mother first reported stopping all breast-feeding. Children who died were assumed to have been breast-fed up to their date of death unless records specifically reported that breast-feeding had stopped before the start of illness that immediately preceded the child's death.

Statistical Analyses

We calculated mortality rates per 1000 person-years within each HIV time of transmission group. Crude comparisons between groups were done using Cox proportional hazards and are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). These models are presented along-side adjusted models for comparison. We also computed the probability of survival from time of infection using life table analysis and Kaplan-Meier curves. Crude comparisons were made using the log-rank statistic.

We included maternal CD4 cell count, low birth weight, and maternal mortality (as a time-dependent covariate) as predictors in all models. To identify additional confounders, we first compared the rate of child deaths within each level of the potential confounder. These are compared using crude HRs and 95% CIs. For each variable, we computed a *P* value for its association with child mortality based on a χ^2 test.

To create a multivariable model, variables with a *P* value <0.2 in crude analyses were singly added to a proportional hazards model with child mortality as the dependent variable and time of transmission groups as the independent variable, adjusted only for maternal mortality and low birth weight. The covariate with the largest percent change >10% was retained, and a new percent change was calculated with each remaining variable. This continued until no variable remained whose addition resulted in a change in HR >10%.

Because the neonatal period is a period of high mortality even in the absence of HIV, we conducted a second analysis in which we compared HIV infection groups conditional on survival to 40 days (excluded 8 children who died and 5 who were LTF).

RESULTS

Cohort Description

There were 1087 live-born singleton children who met the eligibility criteria for the current analysis. Of these, 47 were excluded because they had no HIV data (21 died and 26 LTF). Another 17 children were excluded who were LTF at birth. This left 1023 mother-child pairs eligible for the current analysis.

Among the 213 HIV-infected subjects, 61 (29%) were estimated to be infected between 0 and 3 days (IU group), 71 (33%) between 4 and 40 days (IP/EPP group), and 81 (38%) after 40

days (PP group). Median follow-up time was 183 days for the 0- to 3-day group, 276 days for the 4- to 40-day group, and 365 days for the >40-day group. Just more than 50% of the children were male, and nearly 16% of the children had a low birth weight (<2500 g).

Among mothers of HIV-infected children, maternal disease stage was quite advanced, with 60% having a viral load >100,000 copies/mL, 43% having a CD4 count <200 cells/ μ L (cohort median = 223 cells/ μ L), and 67% having significant anemia (Hgb <11.0 g/dL). In total, 6% of the mothers died over the year since the child's infection and while their child was alive (8.2%, 2.8%, and 6.2% of mothers died in the IU, IP/EPP, and LP groups, respectively).

Descriptive Analyses by Time of Transmission Groups

There were 81 child deaths over the year since infection. The probability of death from time of infection varied greatly between the HIV time of transmission groups. By life table analysis, 56% of children infected between 0 and 3 days, 51% infected by 4 to 40 days, and 27% infected after 40 days died by 1 year of follow-up after infection.

The IU (0 to 3 days) and IP/EPP (4 to 40 days) transmission groups exhibited an initial high mortality rate during the first 3 months of follow-up after infection compared with children infected after 40 days (log-rank $P = 0.001$ and 0.005 , respectively); no differences were detected between the IU (0 to 3 days) and IP/EPP (4 to 40 day) groups (log-rank $P = 0.50$) (Fig. 1). Nearly 20% of the IU and IP/EPP groups died by 100 days after infection, whereas approximately 10% of the PP group died by 100 days after infection. Differences between the IU (0 to 3 days) and IP/EPP (4 to 40 days) groups compared with the PP (>40 days) group increased even more sharply after 200 days.

In unadjusted analyses, most (low CD4 cell count and maternal mortality) but not all (high viral load) indicators of maternal disease stage predicted child mortality, although the associations had wide CIs (Table 1). Low birth weight and breast-feeding cessation were also predictive of child death.

Among HIV-infected subjects, children infected after 40 days (PP group) had less than half the crude mortality rate (HR = 0.39, 95% CI: 0.22 to 0.70) over 1 year compared with those infected by day 3 (IU group) (Table 2). Those infected between 4 and 40 days (IP/EPP group) of life, however, had no significant decreased mortality compared with those infected by 3 days (IU group). After adjusting for low birth weight, low maternal CD4 cell count, cessation of breast-feeding, and maternal death (see Table 2), the protective association on child mortality comparing postpartum transmission (>40 days) with intrauterine (0 to 3 days) transmission was even greater (HR = 0.27, 95% CI: 0.15 to 0.50), suggesting that the crude relation was negatively confounded. When we excluded the 20 subjects who could not be classified according to working group definitions, the adjusted HR was nearly identical (HR = 0.29, 95% CI: 0.16 to 0.54). In a probabilistic sensitivity analysis (see Supplemental Appendix) accounting for misclassification of time of transmission and loss to follow-up, the median estimate of effect moved toward the null (HR = 0.42; 95% simulation interval (SI): 0.23 to 0.74). We found no difference between the IP/EPP group (4 to 40 days) compared with the IU group (0 to 3 days) (HR = 1.1, 95% CI: 0.61 to 1.8) even after adjustment.

We also observed harmful associations between child mortality and breast-feeding cessation (HR = 3.1, 95% CI: 1.8 to 5.3), low birth weight (HR = 3.7, 95% CI: 2.1 to 6.5), and maternal death (HR = 3.1, 95% CI: 1.4 to 6.9). All 3 associations were strengthened after adjusting for other predictors of child mortality. When the analysis was conditioned on survival to 40 days (Table 3), results differed little from the previous models, although the overall effect of maternal death was reduced.

DISCUSSION

This analysis of a well-defined cohort of HIV-infected children in Zambia supports earlier work¹³ indicating that timing of MTCT has a large effect on early childhood mortality. In this cohort, children likely infected in the intrauterine or intrapartum period had substantially increased mortality compared with children infected in the postpartum period, even when limiting the analysis to children who survived at least 40 days to account for the increased mortality in this period. Thus, although children are at constant risk of infection throughout the breast-feeding period,⁸ children infected by means of this route seem to have decreased mortality compared with those infected earlier. In addition, we found that breast-feeding was strongly protective against mortality among HIV-infected children. Even after adjusting for the timing of infection and maternal death, we found that children who were not breast-fed were 3 times as likely to die over the first year after infection compared with children who were breast-fed. This suggests that increasing the duration of breast-feeding among HIV-infected children could prolong life.

The reasons for decreased mortality among the PP group are not known but may be explained in part by infection at a more mature immunologic stage in the child. Some of the differences may be attributable to inherent differences in age (ie, children infected later are, by definition, older and have survived a period of high mortality); however, we continued to find strong differences even after conditioning on surviving the first 40 days of life. Additionally, because postpartum transmission through breast milk occurs by a different route, the actual dose of virus that a child receives is likely to be different and may lead to different long-term patterns of mortality for children infected through different routes.

This finding of reduced mortality among those infected postpartum is consistent with previous studies that found relative associations of 0.10¹⁰ and 0.74¹³ comparing mortality among late versus early infection, depending on the definition of time of infection and variables adjusted for in the analysis. Direct comparisons between our study and previous work are difficult, because the definitions of time of transmission groups used differ slightly. Our results are similar to but more pronounced than findings from the pooled analysis,¹³ which found later infection (at or after 4 weeks) to be associated with a 26% decrease in mortality (HR = 0.74, 95% CI: 0.55 to 0.99) compared with early infection (before 4 weeks) but found no difference between in utero and intrapartum infections. Their analysis was somewhat different in that they required a negative HIV test result at 4 weeks to be included in the late transmission group, whereas we used categorization based on the midpoint between the last negative and first positive test results. Our results are similar to a recent finding in a cohort of children in Zimbabwe that found similar mortality rates in children infected in utero compared with those infected intrapartum but a strongly reduced risk of mortality in children infected postpartum compared with those infected in utero.¹⁴

In our analysis, approximately 20% of children infected before 40 days of life died by 100 days after infection; those infected after 40 days had only reached approximately 10% mortality by that time, leaving more time to intervene. Because this analysis was conducted in a population in which half of the mothers were counseled to wean their children abruptly at 4 months, this study demonstrates that earlier findings of increased mortality associated with intrauterine transmission also hold true in the context of a breast-feeding intervention to prevent MTCT and further demonstrates the need for early detection of HIV so as to intervene as soon as possible.

Unlike our analysis, previous studies on the topic have not examined or have had insufficient variability to examine associations between breast-feeding and mortality in HIV-infected children. Because this analysis was conducted within a population of children involved in a

trial of a breast-feeding intervention, detailed data were kept on mothers' breast-feeding practices. Because HIV transmission can occur after birth through breast milk, children who are breast-fed longer are at increased risk of later HIV infection throughout the lactation period simply because of the prolonged exposure.⁸ Children who are breast-fed longer have reduced mortality compared with children who are breast-fed for a shorter period, however, making this a potentially strong confounder.

In the pooled analysis¹³ in which breast-feeding behavior was adjusted for, the authors found no difference in mortality between breast-fed and non-breast-fed children (HR = 1.1, 95% CI: 0.70 to 1.7). There may be residual confounding, however, because their analysis only compares children ever breast-fed with children never breast-fed; 80% of the women had some breast-feeding, which would tend to bias the association of breast-feeding and child death toward the null. Others, however, using time-dependent measures of breast-feeding as we have, have found a protective effect of breast-feeding duration among children born to HIV-infected mothers, even when the child is also infected.²⁴ We found a strong increased risk of death associated with cessation of breast-feeding even after adjustment for maternal mortality, maternal disease stage, and low birth weight; further, addition of breast-feeding cessation to our multivariable model increased the effect of postpartum versus in utero transmission on child mortality, demonstrating the confounding effects of breast-feeding. Having detailed data on breast-feeding allowed us to adjust for changes in breast-feeding over time.

As with some^{9,13,14} but not all^{11,12} of the previous studies on this topic that attempted to separate intrapartum or early postpartum transmission from intrauterine transmission, we did not find important or robust differences between children likely infected in utero and children infected in the intrapartum or early postpartum period, even among children who survived to 40 days. This suggests that patterns of mortality in children infected near birth may require similar intervention strategies as those in children infected before birth.

Our study has several limitations that should be considered when interpreting the results. First, following a cohort of children is difficult and LTFs are inevitable. Among the HIV-infected subjects, the risk of LTF was 16% (30 of 187 subjects); LTF was highest among the earliest transmission group (24% in IU group, 13% in IP/EPP group, and 12% in PP group). We consider it unlikely that children in one of the time of transmission groups who were lost to follow-up would be more likely to have been lost because they were closer to death compared with any other group. If those who were lost were more likely to have died compared with others in their group, overall estimates of mortality would likely be underestimated and differences between the groups might be larger than what we observed.

Second, it is possible that some selection bias occurred through children who were excluded because they had no HIV data or because they were lost to follow-up at birth. It is possible that these children were excluded because they were more likely to be HIV infected at birth and that they had higher mortality than those children who were HIV infected in utero and were included in the study. Omitting these children would likely underestimate the effect of later versus early transmission on mortality, and perhaps obscure differences between intrauterine and intrapartum or early postpartum transmission.

In conclusion, this study demonstrates a clear survival benefit among children infected postpartum through breast-feeding transmission compared with children infected in utero or intrapartum, whereas no differences were detected between children infected intrapartum versus those infected in utero. Those who acquire infection at a younger age are at increased risk for mortality. Thus, the window for intervention in children infected earlier may be shorter. Testing children for HIV early in life (ie, at 4 to 6 weeks), as is recommended by current HIV

diagnosis algorithms, provides a means for identifying those children most at risk of rapidly succumbing to their HIV infection risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Predictors of Mortality Among 213 HIV-Infected Children Enrolled in a Breast-Feeding Intervention Trial in Zambia Between May 2001 and September 2004

TABLE 1

Factor	Level	Deaths/Total	Total PYs	Rate per 1000 PYs	HR (95% CI)
Time of transmission group	HIV ⁺ 0 to 3 d	29/61	35.0	828.6	1
	HIV ⁺ 4 to 40 d	33/71	47.1	700.6	0.85 (0.52 to 1.4)
	HIV ⁺ >40 d	19/81	59.8	317.7	0.39 (0.22 to 0.70)
Mother died*	No	73/213	151.3	482.3	1
	Yes	8/12	2.9	2733.4	5.2 (2.5 to 10.9)
Viral load	≤100,000	29/82	56.4	514.2	1
	>100,000	48/121	78.3	613.0	1.2 (0.76 to 1.9)
Maternal baseline CD4 count (cells/μL)	≥200	39/120	81.4	479.1	1
	<200	42/93	60.4	695.4	1.5 (0.94 to 2.2)
Mother had anemia	No	27/69	45.4	594.7	1
	Yes	54/140	93.6	576.9	0.97 (0.61 to 1.5)
Number of SES factors [†]	0	13/30	21	619.0	1
	>0	68/183	120.9	562.4	0.91 (0.50 to 1.7)
Mother employed (full time)	No	72/195	130.2	553.0	1
	Yes	9/18	11.7	769.2	1.4 (0.69 to 2.8)
Has a tap in house	No	74/198	131.5	562.7	1
	Yes	7/15	10.3	679.6	1.2 (0.54 to 2.6)
Has electricity in home	No	51/126	84.7	602.1	1
	Yes	30/87	57.2	524.5	0.87 (0.55 to 1.4)
Ran out of food in previous month	No	63/168	109.7	574.3	1
	Yes	18/45	32.2	559.0	0.97 (0.57 to 1.6)
Mother's highest school grade	<8	49/120	79.1	619.5	1
	8 to 9	19/58	38.8	489.7	0.79 (0.47 to 1.3)
Number of previous pregnancies	<9	13/35	24.0	541.7	0.87 (0.47 to 1.6)
	0	9/26	15.7	573.2	1
	1 to 3	43/135	94.3	456.0	0.80 (0.39 to 1.6)
	>3	29/52	31.9	909.1	1.6 (0.75 to 3.4)
Mother's age baseline (y)	<20	6/16	10.5	571.4	1

Factor	Level	Deaths/Total	Total PYs	Rate per 1000 PYs	HR (95% CI)
Low birth weight [‡]	20 to 24.9	22/68	46.2	476.2	0.84 (0.34 to 2.1)
	25 to 29.9	26/75	51.9	501.0	0.88 (0.36 to 2.1)
	30 to 34.9	23/44	27.1	848.7	1.5 (0.61 to 3.7)
	35+	4/10	6.1	655.7	1.2 (0.33 to 4.2)
Male child	No	59/175	122.7	480.8	1
	Yes	20/34	16.8	1190.5	2.5 (1.5 to 4.2)
	No	31/105	74.1	418.4	1
	Yes	50/108	67.8	737.5	1.8 (1.1 to 2.8)
Stopped breast-feeding*	No	41/196	96.7	424.2	1
	Yes	40/106	45.2	884.3	2.2 (1.4 to 3.6)

PY indicates person-years; SES, socioeconomic status.

* Maternal death and breast-feeding are time-dependent variables; thus, children could contribute person-time to both groups. Maternal death is death during the child's follow-up time. An additional 17 mothers died after the child's follow-up ended.

[‡] SES is defined as the sum of owns a refrigerator, has electricity, completed >8 years of education, employed, and had food security for the previous month.

[‡] Low birth weight is defined as <2500 g.

TABLE 2

Analysis of Mortality From Time of Infection by HIV Timing Group in a Cohort of 213 HIV-Infected Children Born to Mothers Enrolled in a Breast-Feeding Intervention Trial in Zambia Between May 2001 and September 2004

Factor	Deaths/Total	Crude HR (95% CI)	Adjusted HR (95% CI)*
HIV+ 0 to 3 d	29/61	1.0	1.0
HIV+ 4 to 40 d	33/71	0.85 (0.52 to 1.4)	1.1 (0.61 to 1.8)
HIV+ >40 d	19/81	0.39 (0.22 to 0.70)	0.27 (0.15 to 0.50)
Mother alive [†]	73/201	1.0	1.0
Mother died	8/12	5.2 (2.5 to 10.9)	3.1 (1.4 to 6.9)
Normal birth weight	59/175	1.0	1.0
Low birth weight [‡]	20/34	2.5 (1.5 to 4.2)	3.7 (2.1 to 6.5)
CD4 count ≥200 cells/μL	39/120	1.0	1.0
CD4 count <200 cells/μL	42/93	1.5 (0.94 to 2.2)	1.1 (0.67 to 1.7)
Did not stop breast-feeding [†]	41/196	1.0	1.0
Stopped breast-feeding	40/106	2.2 (1.4 to 3.6)	3.1 (1.8 to 5.3)

* Adjusted model adjusted for all other variables in the model.

[†] Maternal death and breast-feeding are time-dependent variables; thus, children could contribute person-time to both groups. Maternal death is death during the child's follow-up time. An additional 17 mothers died after the child's follow-up ended.

[‡] Low birth weight is defined as <2500 g.

TABLE 3

Analysis of Mortality by HIV Timing Group Conditioned on Survival to 40 Days in a Cohort of 213 HIV-Infected Children Born to Mothers Enrolled in a Breast-Feeding Intervention Trial at 2 Clinics in Lusaka, Zambia Between May 2001 and September 2004

Factor	Crude HR (95% CI)	Adjusted HR (95% CI)
HIV ⁺ 0 to 3 d	1.0	1.0
HIV ⁺ 4 to 40 d	1.1 (0.62 to 1.8)	1.2 (0.66 to 2.1)
HIV ⁺ >40 d	0.50 (0.27 to 0.92)	0.32 (0.17 to 0.61)
Mother alive [*]	1.0	1.0
Mother died	3.3 (1.3 to 8.3)	2.2 (0.85 to 5.9)
Normal birth weight	1.0	1.0
Low birth weight [†]	2.0 (1.1 to 3.6)	3.0 (1.6 to 5.6)
CD4 count ≥200 cells/μL	1.0	1.0
CD4 count <200 cells/μL	1.5 (0.93 to 2.3)	1.2 (0.72 to 1.9)
Continued breast-feeding [*]	1.0	1.0
Not breast-feeding	2.2 (1.3 to 3.5)	3.0 (1.7 to 5.2)

^{*} Breast-feeding cessation and maternal death were time-dependent variables in crude and adjusted models.

[†] Low birth weight is defined as <2500 g.