Predictors of stunting, wasting, and underweight among Tanzanian children born to HIV-infected women

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Abstract

Background—Children born to HIV-infected women are susceptible to undernutrition, but modifiable risk factors and the time course of the development of undernutrition have not been well characterized.

Objective—To identify maternal, socioeconomic, and child characteristics that are associated with stunting, wasting, and underweight among Tanzanian children born to HIV-infected mothers, followed from 6 weeks for 24 months.

Methods—Maternal and socioeconomic characteristics were recorded during pregnancy, data pertaining to the infant's birth were collected immediately after delivery, morbidity histories and anthropometric measurements were performed monthly. Multivariate Cox proportional hazards methods were used to assess the association between potential predictors and the time to first episode of stunting, wasting, and underweight.

Results—2387 infants (54.0% male) were enrolled and followed for a median duration of 21.2 months. The respective prevalence of prematurity (<37 weeks) and low birthweight (<2500g) was

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Conflict of Interest Statement

15.2% and 7.0%; 11.3% of infants were HIV-positive at 6 weeks. Median time to first episode of stunting, wasting, and underweight was 8.7, 7.2, and 7.0 months, respectively. Low maternal education, few household possessions, low infant birthweight, child HIV infection and male sex were all independent predictors of stunting, wasting, and underweight. In addition, preterm infants were more likely to become wasted and underweight, whereas those with a low Apgar score at birth were more likely to become stunted.

Conclusion—Interventions to improve maternal education and nutritional status, reduce mother-to-child transmission of HIV, and increase birth weight may lower the risk of undernutrition among children born to HIV-infected women.

Keywords

Child undernutrition; child growth; HIV

Introduction

One of the most common manifestations of HIV infection is undernutrition, and poor growth has been reported in as many as 50% of children with HIV (1). Although differences in weight and length between HIV-infected and uninfected infants may not be striking at birth (2), they often become apparent by three months of age, and tend to worsen over time (3, 4). In a recent review of growth patterns among HIV-infected children, 9 out of 10 studies conducted in resource-constrained countries reported negative associations between HIV infection and height-for-age, and all ten studies reported a negative association with weight gain (5).

While there is consistent evidence of impaired growth among HIV-infected children, fewer data are available on HIV-exposed, uninfected children (henceforth referred to as HIV-exposed children). The size of this sub-population of children is growing due to the increasing availability of anti-retroviral (ARV) therapy for the prophylaxis of mother-to-child transmission of HIV. Few studies have examined growth patterns of HIV-exposed (4, 5), and risk factors for undernutrition among this vulnerable population have not been well characterized. Children born to HIV-infected women are at risk of deficiencies in multiple micronutrients that play an important role in child growth and development (6–8). Furthermore, poor socioeconomic conditions in resource-limited settings may limit the quality of care the child receives, resulting in impaired growth and health (9).

The objective of this study was to identify the maternal, socioeconomic and child predictors of stunting, wasting, and underweight among Tanzanian children born to HIV-infected women who were followed from 6 weeks of age for 24 months.

Subjects and Methods

Subjects included in this analysis were part of a randomized, double-blind, placebo-controlled trial designed to determine whether the daily administration of multiple micronutrients (vitamins B, C, and E) to infants born to HIV-infected women reduced the risk of mortality and infectious disease morbidity, compared with placebo. Women   18

years who tested HIV-positive at the 32nd week of gestation or earlier in one of eight antenatal clinics in Dar es Salaam, Tanzania were invited to participate. Written informed consent for participation was obtained from all women. Maternal and socioeconomic characteristics were assessed prior to delivery. Eligibility for infant participation in the trial included: 1) singleton birth and; 2) 5–7 weeks of age at randomization. Infants with serious congenital anomalies or other conditions that would have interfered with study procedures were excluded. Infants were then randomly assigned to receive a daily oral dose of multivitamins or placebo for 24 months after enrollment.

Mothers and children were asked to return to the study clinics for monthly follow-up visits. As part of standard medical care, all children received growth monitoring, immunizations, routine medical care for illnesses, and large periodic doses of vitamin A. Mothers were counseled on the risks and benefits of exclusive breastfeeding. Nevirapine prophylaxis for mother-to-child transmission of HIV was provided to the mother at the onset of labor and to the child within 72 hours of birth. Part way through the trial, the availability of ARV medication increased and mothers and children in the study were screened for ARV eligibility and treated according to Tanzanian Ministry of Health guidelines. The standard first line regimen was stavudine (d4T), lamivudine (3TC), and nevirapine (NVP) for mothers and zidovudine (AZT), 3TC, and NVP for children. All children were tested for HIV infection at six weeks of age using Amplicor HIV-1 DNA PCR assay version 1.5 (Roche Molecular Systems, Branchburg, NJ, USA), and then again at 18 months using ELISAs. If a child tested positive at 18 months, his or her blood samples were back-tested to estimate the time of transmission, which was defined as the mid-point between the last negative and first positive HIV test. Children who remained HIV-negative throughout the follow-up period were considered HIV-exposed. A complete blood count was also obtained at 6 weeks of age and every six months thereafter.

Data pertaining to the infant's birth were collected immediately after delivery. At each monthly follow-up visit, a study nurse conducted a morbidity assessment, which was supported by a pictorial diary that mothers were asked to complete at home to record when their child had certain symptoms. Diarrhea was defined as the presence of three or more loose or watery stools in the prior 24 hours. Body temperature, measured using a digital thermometer to the nearest 0.1°C, and respiratory rate, measured for 1 min using a stopwatch, were recorded on the day of the clinic visit. Rapid respiratory rate was defined as 50 breaths/min for infants and 40 breaths/min for children over 12 months. Respiratory conditions were defined as follows: the occurrence of cough alone; cough and fever; or cough plus one or more of these events: difficulty breathing; rapid respiratory rate; refusal to eat, breastfeed or drink liquids. At each monthly follow-up visit, the study nurse inquired about infant feeding in the past seven days. Exclusive breastfeeding was defined as feeding a child with breast milk only and no additional foods. We calculated the duration of exclusive breastfeeding as the mean infant age at which the last time the mother reported the child was still exclusively breastfeeding and the first time the mother reported the child was given other foods in addition to breast milk. The study nurse also performed anthropometric measurements at each monthly clinic visit. Weight was measured to the nearest 10 g using a digital infant balance (TANITA) and length was measured to the nearest 1 mm using a rigid

length board with a movable foot piece (Shorr Productions). Anthropometric equipment was calibrated on a regular basis.

Statistical Analyses

For this analysis, we included all infants enrolled in the trial who were not stunted, wasted, or underweight at the time of enrollment (i.e. 6 weeks of age) and who had at least one additional set of anthropometric measurements taken after enrollment and before 24 months of age. Length-for-age (LAZ), weight-for-length (WLZ), and weight-for-age (WAZ) Z scores were calculated using the 2006 WHO Child Growth Standards (10). Stunting, wasting, and underweight were defined as binary outcomes using a cut-off of <-2 SD.

Descriptive statistics were used to summarize the baseline characteristics of the study population. Hazard ratios and 95% CI for each of the potential predictors were obtained from separate Cox proportional hazards models, with time to first episode of stunting, wasting, or underweight as the outcome and age in months as the time metameter. The mother's vital status and the child's HIV status, exclusive breastfeeding, anemia, and morbidity history varied over the course of follow-up; therefore, we included all available time-updated data on these variables. Time-varying data was carried forward until the next observation except for hemoglobin concentrations, which were carried forward for a maximum of six months. Given the well-known inter-relationship between undernutrition and infection (11) and the potential for a child's declining nutritional status to influence acute morbidity, we stopped updating the time-varying morbidity variables 8 weeks before the end of each time interval of analysis.

Each outcome was modeled separately, and the first time the child reached a score of <-2 SD signified an "event". Follow-up time was censored at the time of event, or time of last anthropometric assessment. First, we ran separate univariate models between each potential predictor and the time to each event. We then constructed multivariate models that included all predictors that were significant at p <0.10 in univariate analyses. A priori, we decided to retain child sex, time-varying HIV status, and assigned study treatment regimen in the multivariate models, regardless of their significance, since these variables are important from a biological perspective. We used missing indicator variables in the multivariate models for covariates with missing data.

We constructed curves that depicted all subjects' LAZ, WLZ, and WAZ, by age, over the entire follow-up period, and stratified these by HIV status at 6 weeks using unadjusted, restricted cubic spline models (12). Automated stepwise selection with entry and retain criteria of p<0.20 was used for the placement of 10 knots in each curve (13). We used the likelihood ratio test to test for non-linearity, comparing the model with only the linear term to the model with the linear and restricted cubic spline terms.

All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). Institutional review board approval was granted by the Harvard School of Public Health Human Subjects Committee, and the Muhimbili University of Health and Allied Sciences Senate Research and Publications Committee.

Results

Study population

Between August 2004 and November 2007, 2387 infants were enrolled. Table 1 shows baseline characteristics of this study population. Of the 2,387 infants who were enrolled in the parent study, 206 were excluded from the stunting analysis, 183 from the wasting analysis, and 217 from the underweight analysis because they had the outcome at six weeks or did not have at least one additional anthropometric measurement over follow-up. The remaining infants contributed a total of 31,040; 30,531; and 31,564 person-months of follow-up to the analysis of stunting, wasting, and underweight, respectively.

Predictors of stunting

The median age at which the first episode of stunting occurred among the 666 (30.5%) infants who became stunted was 8.7 months. Maternal education and height, as well as more household possessions were inversely independently associated with the risk of child stunting (Table 2). The risk of becoming stunted was 28% greater among males vs. females (HR = 1.28; 95% CI=1.09, 1.49; p=0.002) and 49% greater among infants with a low Apgar score (HR = 1.49; 95% CI = 1.04, 2.13; p=0.03). Low birthweight infants were 2.5 times more likely to become stunted than those with a birth weight 2500 g (HR=2.50; 95% CI=1.80, 3.47; p<0.0001). Infants who were HIV-positive had more than 2.5 times the risk of stunting than those who were HIV-negative (HR=2.79; 95% CI: 2.29, 3.40; p<0.0001). The number of cumulative episodes of diarrhea, fever, common cold, vomiting, loss of appetite, and cough were not significantly associated with the risk of stunting.

Predictors of wasting

The median age at first episode of wasting among the 705 (32.0%) infants who became wasted was 7.2 months. In the multivariate analysis, maternal education and MUAC were inversely associated with the risk of wasting (Table 3). The risk of wasting was also elevated among infants whose mothers had a more advanced HIV disease stage and were taking ARVs during pregnancy. The effect of ARVs remained when the analyses were restricted to children who were HIV negative at 6 weeks (HR=1.29; 95% CI=1.05, 1.57; p=0.02). The ARV effect also retained significance (HR=1.25; 95% CI=1.03, 1.51; p=0.03) after additionally adjusting for maternal CD4 count during pregnancy.

The risk of wasting was lower among children born to families owning more household possessions. Child sex, birth weight, gestational age at birth, and current HIV status were all significantly independently associated with the risk of wasting. The HR of wasting among males vs. females, infants with a birth weight < 2500 g vs. 2500 g, and those born at < 37 weeks vs. 37 weeks gestational age were 1.40 (95% CI = 1.20, 1.63; p<0.0001), 1.49 (95% CI=1.20, 1.63; p=0.003), and 1.28 (95% CI=1.05, 1.57; p=0.02), respectively. HIV-infected infants were more than twice as likely to become wasted than HIV-uninfected infants, and those with more diarrhea episodes were slightly less likely to become wasted.

Predictors of underweight

The median age at which the first episode of underweight occurred among the 649 (29.9%) infants who became underweight was 7.0 months. As with stunting, the risk of underweight was lower in the multivariate analysis among infants born to mothers with more education and whose height was above the median value (Table 4). Ownership of more household assets was protective against underweight. Male sex, low birthweight, preterm birth, and HIV-infection were associated with a significant independent increased risk of underweight.

Figures 1–3 all highlight a deterioration in nutritional status over time; however, the magnitude of the decline is noticeably greater among HIV-infected infants. In all three curves, the association between age and Z-score among HIV-infected and HIV-uninfected children was non-linear ($p<0.0001$). There was a steep decline in LAZ immediately after enrollment among HIV-infected children and mean LAZ reached its lowest level at approximately 92 weeks in both groups of children (Figure 1). Mean WLZ decreased after 6 weeks of age among HIV-infected and HIV-uninfected children; however, the rate of decline was more precipitous among HIV-infected children (Figure 2). Mean WAZ declined gradually over the course of follow-up among HIV-uninfected children, reaching its lowest level at approximately 60 weeks of age (Figure 3).

Discussion

We assessed predictors of stunting, wasting, and underweight in a cohort of 2,387 Tanzanian infants born to HIV-infected women who were followed from 6 weeks of age for 24 months. Our study population is the largest reported cohort of young children born to HIV-infected women in sub-Saharan Africa with longitudinal anthropometric measurements to-date. Our ability to perform repeated anthropometric measurements at frequent, monthly intervals enabled precise time-to-event analysis and the construction of curves that plotted nutritional status over time. We not only identified several important biological and socioeconomic correlates that were independently associated with the risk of child undernutrition, but also quantified the magnitude of the risk that was associated with each characteristic. A particular novel finding was the increased risk of stunting, wasting, and underweight experienced by male vs. female children.

The strength and consistency of the association between maternal education and each form of child undernutrition deserves special note. Our findings are consistent with studies of similar populations in sub-Saharan Africa. Villamor et al. (14) reported that a low level of maternal education predicted linear growth retardation among infants under 12 months of age who were born to HIV-infected women in Tanzania. Similarly, Webb et al. (15) found that greater maternal schooling significantly reduced the deterioration in LAZ and WLZ scores from birth to 24 months, and McGrath et al. found higher maternal education to decrease the risk of stunting and underweight among HIV-exposed children (16). In an analysis of Demographic and Health Survey data from six countries in sub-Saharan Africa, maternal secondary education was positively associated with WAZ in Ghana, Nigeria, and Tanzania (17). Mothers with higher levels of formal education may possess greater knowledge of proper hygiene practices and optimal child caring and feeding practices, which could be particularly important in the context of HIV.

Our findings also highlight the importance of maternal nutritional status in predicting the risk of undernutrition in her offspring, which is in agreement with results from several other studies (4, 16–20). While the influence of maternal height on the risk of child stunting may partially reflect genetic potential, MUAC may act as a proxy of many factors that could indirectly affect the risk of child wasting. A mother with a low MUAC may have more advanced HIV disease stage or be co-infected with other diseases which could lower her nutritional status and overall health, consequently impairing her ability to properly care for her child (21, 22). A low maternal MUAC could also reflect household food insecurity, which might adversely affect complementary feeding the child receives (23). We also found that the risk of wasting was elevated among children whose mothers had a more advanced HIV disease stage and who took ARVs during pregnancy. However, the effect of ARVs must be interpreted with caution, since a standardized protocol for ARV therapy was implemented only part way through the study.

We found a consistent association between child sex and each nutritional outcome. Male children were 28%, 40%, and 28% more likely to become stunted, wasted, and underweight, respectively, in comparison to females. Similar observations were made in a study from Andhra Pradesh, India, which reported that male children were twice and 50% more likely than females to be wasted and underweight, after controlling for multiple other risk factors in the respective analyses (24). Moreover, in a meta-analysis from 10 countries in sub-Saharan Africa, Wamani et al. reported a higher prevalence of stunting in males vs. females (25). To our knowledge, our study is the first to identify an increased risk or stunting, wasting, and underweight among male children born to HIV-infected women. Although the mechanism behind this association has not been fully explored, possible explanations include preferential treatment towards girls in terms of healthcare-seeking behavior or dietary consumption.

The magnitude of the effect of the infant's HIV status on stunting, wasting, and underweight was also striking (Figures 1–3). This observation has been made in several other studies including the European Collaborative Study of children born to HIV-infected women in Europe, which reported that although there were no differences in length or weight between HIV-infected and HIV-uninfected infants at birth, between 6 and 12 months of age, uninfected infants grew an estimated 1.6% faster in height and 6.2% faster in weight, and between 8 and 10 years age, these figures reached 16% and 44%, respectively (3). Such findings emphasize the importance of early diagnosis of HIV infection and timely delivery of supportive interventions to this vulnerable group. We found that low birth weight infants were more likely to become stunted, wasted, and underweight, which is consistent with previous reports (9, 15, 17, 18, 20, 27, 28), and underscores the importance of optimal prenatal care (29).

Although the link between infection and nutrition is well-established (11), epidemiological analyses that have assessed the effect of various morbidities on the subsequent risk of stunting, wasting, and underweight have produced mixed results. In a study of HIV-infected and uninfected children, Villamor et al. found no association between the incidence of diarrhea overall and attained weight after 1 year, or episodes of respiratory infection and height or weight gain (14). Webb et al. found that episodes of diarrhea or respiratory

infections were related to lower WLZ, but not LAZ in a HIV-exposed children (15). On the other hand, Bailey et al. reported that prolonged diarrhea was risk factor for stunting among a population of HIV-uninfected, -exposed, and -infected children in the Democratic Republic of the Congo (4) and McGrath et al. found a positive association between diarrhea morbidity and risk of wasting among HIV-exposed infants in Kenya (16). In the current study, we were aware of the potential for reverse causation between morbidity and undernutrition (i.e. the risk of morbidity may increase with declining nutritional status) and attempted to capture the effect of chronic morbidity by ending the updating of the child's morbidity history 8 weeks prior to the end of each time interval. Using this approach, diarrhea was inversely associated with the risk of wasting, but not stunting or underweight.

Our study has both strengths and limitations. We were able to obtain repeated anthropometric measures at monthly intervals on a large sample of infants born to HIV-infected women. We also collected data on a comprehensive set of predictors including demographic, socioeconomic, anemia, and morbidity indicators. We used statistical techniques to account for the time-varying nature of certain predictors. Although our analysis does not include a comparison group of HIV-uninfected infants born to HIV-uninfected women, WHO Z scores provide this comparison. Although we considered a comprehensive set of variables in our analyses, residual confounding from unmeasured covariates cannot be ruled out. Finally, a standardized ARV therapy protocol for mothers was implemented part way through the study, which makes it difficult to interpret the true effect of maternal ARV therapy on the risk of child undernutrition.

In conclusion, maternal education and nutritional status, as well as child HIV status, sex, and birth weight were significant, independent predictors of stunting, wasting, and underweight among infants born to HIV-infected women in Tanzania. Strategies to promote female education, improve maternal nutritional status, increase socioeconomic status, reduce low birth weight, and lower the transmission of mother-to-child transmission of HIV could all help to lower the burden of child undernutrion among HIV-exposed infants.

Acknowledgments

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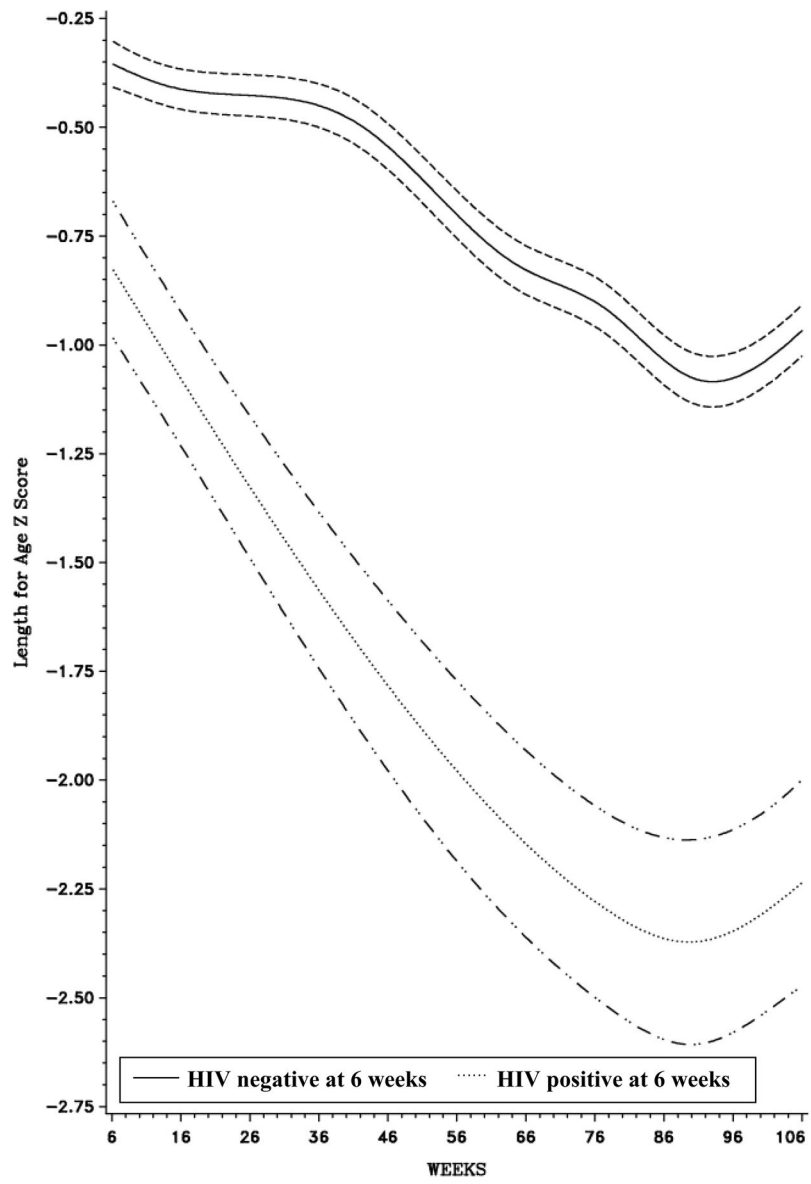
Figure 1.

Length-for-Age Z-Scores, by age (weeks), stratified by HIV status at 6 weeks[1]

[1] Bands represent 95% Confidence Intervals (CI)
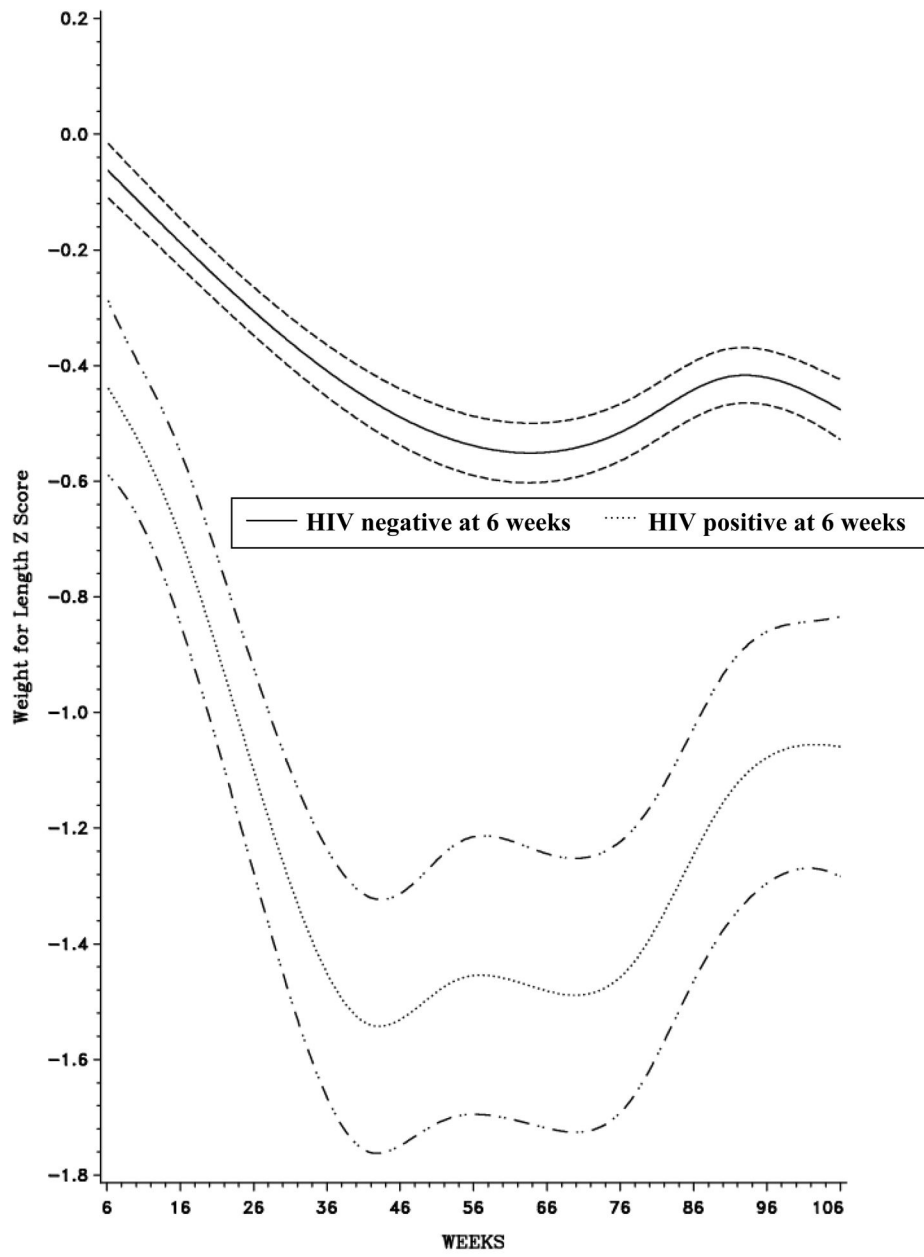
Figure 2.
Weight-for-Length Z-Scores, by age (weeks), stratified by HIV status at 6 weeks[1]
[1]Bands represent 95% Confidence Intervals (CI)
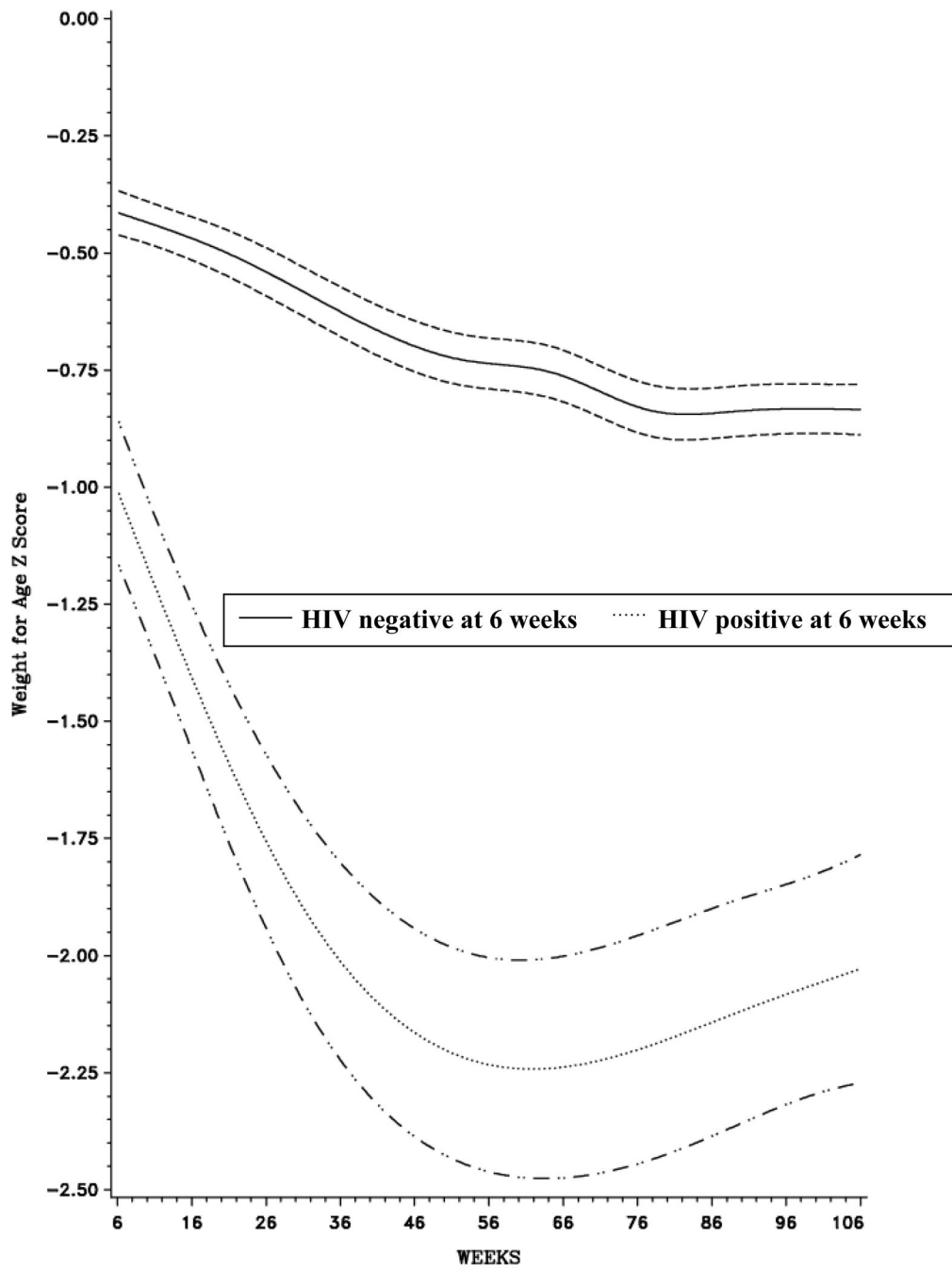
Figure 3.
Weight-for-Age Z-Score, by age (weeks), stratified by baseline HIV status[1]
[1] Bands represent 95% Confidence Intervals (CI)

Table 1

Baseline characteristics

Maternal characteristics	N[1] (%) or Mean ± SD
Age at delivery (years)	
<20	83 (3.6)
20–24	540 (23.6)
25	1666 (72.8)
Marital status	
Single/Widowed/Divorced/Other	310 (13.1)
Married	2051 (86.9)
Number of prior pregnancies	
0	539 (22.8)
1–3	1632 (69.1)
4	191 (8.1)
Formal education (years)	
0	158 (6.7)
1–7	1700 (71.9)
8	507 (21.4)
Occupation	
Housewife without income	1528 (66.5)
Housewife with income	200 (8.7)
Business woman	130 (5.7)
Other	440 (19.2)
Mid-Upper Arm Circumference during pregnancy (cm)	25.9 ± 3.2
Height (cm)	155.2 ± 6.1
WHO HIV disease stage	
1	1040 (72.8)
2	215 (15.1)
3	174 (12.2)
Received ARVs during pregnancy[2]	429 (20.2)
Socioeconomic characteristics	
Daily food expenditure per person in household <500 TShs	304 (13.6)
Household possessions[3]	
0	339 (14.4)
1–2	1091 (46.2)
3–4	931 (39.4)
Child characteristics	
Female sex	1098 (46.0)
Low birthweight (<2,500 g)	161 (7.0)
Preterm birth (gestational age < 37 weeks)	357 (15.2)
Place of birth	

Maternal characteristics	N^1 (%) or Mean ± SD
Home	50 (2.2)
Hospital/clinic	2233 (97.8)
Apgar score 7 at 5 min	87 (4.1)
Child fed colostrum at birth	1861 (90.3)
Child received BCG immunization as a newborn	1859 (90.2)
HIV-positive at 6 weeks	264 (11.3)

[1] Total N=2387

[2] The standard first line regimen for mothers was stavudine, lamivudine, and nevirapine

[3] From a list that includes fan, refrigerator, sofa, radio/television

Table 2

Maternal, socioeconomic and child risk factors for time to stunting

	N[1]	Events	Univariate		Multivariate	
			HR (95% CI)[2]	p	HR (95% CI)[2],[3]	p
Maternal Characteristics						
Age at delivery (years)						
<20	72	24	1.00	0.12		
20–24	498	162	1.01 (0.66, 1.54)			
25	1477	453	0.87 (0.58, 1.31)			
Marital status						
Single/Widowed/Divorced/Other	280	96	1.00	0.17		
Married	1831	564	0.86 (0.69, 1.07)			
Number of prior pregnancies						
0	490	131	1.00	0.61		
1–3	1460	486	1.21 (1.00, 1.47)			
4	162	41	0.90 (0.63, 1.27)			
Formal education (years)						
0	139	53	1.00	<0.0001	1.00	0.04
1–7	1521	509	0.92 (0.69, 1.22)		1.01 (0.75, 1.34)	
8	455	98	0.55 (0.40, 0.77)		0.77 (0.54, 1.08)	
Occupation						
Housewife without income	1377	444	1.00			
Housewife with income	175	54	0.90 (0.68, 1.20)	0.31		
Business woman	118	28	0.72 (0.49, 1.05)			
Other	388	121	0.94 (0.77, 1.15)			
Mid-Upper Arm Circumference during pregnancy (cm)						
< 22.0	135	53	1.00	0.06	1.00	0.72
22.0	1976	606	0.76 (0.58, 1.01)		0.95 (0.71, 1.26)	
Height (cm)						
< 155.0	1027	410	1.00	<0.0001	1.00	<0.0001
155.0	1107	255	0.51 (0.43, 0.59)		0.52 (0.45, 0.61)	

	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
WHO HIV disease stage						
1	947	288	1.00	0.41		
2	195	65	1.15 (0.88, 1.50)			
3	152	49	1.08 (0.80, 1.47)			
Received ARVs during pregnancy[4]						
No	1549	511	1.00	0.46		
Yes	376	115	0.93 (0.76, 1.14)			
Vital status[5]						
Alive	30914	665	1.00	0.44		
Dead	126	1	0.44 (0.06, 3.11)			
Socioeconomic Characteristics						
Household food expenditure (TShs/person/day)						
< 500	276	109	1.00	0.005	1.00	0.08
500	1725	516	0.74 (0.60, 0.91)		0.32 (0.67, 1.02)	
Household possessions[6]						
0	292	117	1.00	<0.0001	1.00	0.002
1–2	977	327	0.82 (0.66, 1.01)		0.91 (0.73, 1.13)	
3–4	843	215	0.59 (0.47, 0.73)		0.71 (0.56, 0.90)	
Child Characteristics						
Sex						
Female	987	284	1.00	0.02	1.00	0.002
Male	1148	382	1.20 (1.03, 1.40)		1.28 (1.09, 1.49)	
Birth weight (g)						
2,500	1988	598	1.00	<0.0001	1.00	<0.0001
< 2,500	71	40	2.76 (2.00, 3.80)		2.50 (1.80, 3.47)	
Gestational age at birth (weeks)						
37	1830	556	1.00	0.03	1.00	0.15
< 37	272	98	1.26 (1.02, 1.56)		1.18 (0.94, 1.46)	

	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
Place of birth				0.39		
Home	39	13	1.00			
Hospital/clinic	2010	625	0.79 (0.45, 1.36)			
Apgar score at 5 min				0.02		0.03
>7	1848	561	1.00		1.00	
7	74	32	1.52 (1.07, 2.17)		1.49 (1.04, 2.13)	
Child fed colostrum				0.99		
Yes	1680	524	1.00			
No	173	53	1.00 (0.76, 1.33)			
Child received BCG immunization as a newborn				0.18		
Yes	1682	517	1.00			
No	171	60	1.20 (0.92, 1.57)			
Exclusively breastfed[5]				0.01		0.05
No	25,054	477	1.00		1.00	
Yes	5,866	187	1.39 (1.07, 1.80)		1.29 (1.00, 1.67)	
Anemia (Hb <11 g/dL)[5]				0.12		
No	5,789	118	1.00			
Yes	23,970	523	1.18 (0.96, 1.44)			
Cotrimoxazole consumption last month[5]				0.15		
0	1,848	47	1.00			
1–20 times	3,235	74	0.94 (0.64, 1.37)			
21 times	16,296	325	0.82 (0.60, 1.14)			
HIV status[5]				<0.0001		<0.0001
Negative	28,533	537	1.00		1.00	
Positive	2,472	126	2.65 (2.19, 3.22)		2.79 (2.29, 3.40)	
Cumulative morbidity episodes[5,7]						
Diarrhea				0.53		
0	23,200	519	1.00			
1–2	6,930	128	1.01 (0.82, 1.25)			

	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
3	909	18	1.26 (0.78, 2.02)			
Fever						
0	17,837	422	1.00			
1–2	9,991	182	0.94 (0.77, 1.15)	0.83		
3–4	2,370	49	1.17 (0.84, 1.62)			
5	840	13	0.95 (0.53, 1.70)			
Common cold						
0	9,436	260	1.00			
1–2	11,646	220	0.81 (0.66, 0.98)	0.95		
3–4	5,599	99	0.85 (0.64, 1.13)			
5	4,358	87	1.05 (0.77, 1.44)			
Vomiting						
0	27,975	605	1.00			
1	2,493	52	1.17 (0.87, 1.57)	0.58		
2	571	9	0.92 (0.47, 1.79)			
Refusal to eat, drink or breastfeed						
0	26,962	603	1.00			
1	3,025	47	0.83 (0.611.12)	0.22		
2	1,052	16	0.84 (0.51, 1.40)			
Cough alone						
0	10,660	292	1.00			
1–2	9,912	178	0.77 (0.62, 0.96)	0.24		
3–4	5,154	113	1.00 (0.75, 1.33)			
5	5,312	83	0.77 (0.55, 1.06)			
Cough and fever						
0	21,808	496	1.00			
1–2	7,845	140	0.96 (0.78, 1.18)	0.63		
3	1,386	30	1.28 (0.87, 1.89)			
Cough plus difficulty breathing, rapid respiratory rate or refusal to eat						
0	26,916	582	1.00	0.27		

	N[1]	Events	Univariate		Multivariate	
			HR (95% CI)[2]	p	HR (95% CI)[2],[3]	p
1	4,123	84	1.14 (0.90, 1.46)			

[1] N represents the number of children for time-fixed predictors, and number of person-months for time-varying predictors

[2] Hazard Ratios (HR) and 95% Confidence Intervals (CI) were obtained from Cox proportional hazards models

[3] Multivariate results additionally adjusted for parent study treatment regimen

[4] The standard first line regimen for mothers was stavudine, lamivudine, and nevirapine

[5] Time-updated variable; N refers to person-months

[6] From a list that includes fan, refrigerator, sofa, radio/television

[7] An episode was defined if the symptom was reported during the 4 weeks prior to the visit

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Table 3

Maternal, socioeconomic and child risk factors of time to wasting

Maternal Characteristics	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
Age at delivery (years)						
<20	72	25	1.00	0.99		
20–24	488	150	0.87 (0.57, 1.33)			
25	1513	497	0.90 (0.61, 1.35)			
Marital status						
Single/Widowed/Divorced/Other	275	92	1.00	0.50		
Married	1858	606	0.93 (0.74, 1.15)			
Number of prior pregnancies						
0	472	148	1.00	0.88		
1–3	1487	492	1.03 (0.85, 1.23)			
4	175	57	1.01 (0.74, 1.37)			
Formal education (years)						
0	143	54	1.00	<0.0001	1.00	0.005
1–7	1539	539	0.98 (0.74, 1.29)		0.99 (0.75, 1.32)	
8	455	105	0.59 (0.43, 0.83)		0.70 (0.50, 0.98)	
Occupation						
Housewife without income	1393	469	1.00	0.77		
Housewife with income	181	61	0.99 (0.76, 1.29)			
Business woman	123	27	0.62 (0.42, 0.92)			
Other	383	131	1.04 (0.86, 1.26)			
Mid-Upper Arm Circumference during pregnancy (cm)						
< 22.0	143	68	1.00	<0.0001	1.00	0.006
22.0	1989	630	0.60 (0.47, 0.77)		0.70 (0.54, 0.90)	
Height (cm)						
< 155.0	1076	360	1.00	0.39		
155.0	1077	344	0.94 (0.81, 1.09)			

	N^1	Events	Univariate		Multivariate	
			HR (95% CI)[2]	p	HR (95% CI)[2,3]	p
WHO Stage						
1	975	292	1.00	<0.0001	1.00	0.003
2	194	78	1.42 (1.11, 1.82)		1.35 (1.05, 1.75)	
3	158	67	1.61 (1.23, 2.10)		1.40 (1.07, 1.84)	
Received ARVs during pregnancy[4]						
No	1561	495	1.00	0.003	1.00	0.008
Yes	393	157	1.31 (1.10, 1.57)		1.28 (1.07, 1.55)	
Vital status[5]						
Alive	3415	703	1.00	0.97		
Dead	116	2	0.97 (0.24, 3.90)			
Socioeconomic Characteristics						
Household food expenditure (TShs/person/day)						
< 500	269	103	1.00	0.18		
500	1759	564	0.87 (0.70, 1.07)			
Household possessions[6]						
0	390	151	1.00	<0.0001	1.00	0.004
1–2	1021	350	0.88 (0.71, 1.08)		0.92 (0.75, 1.14)	
3–4	723	197	0.66 (0.54, 0.84)		0.75 (0.60, 0.94)	
Child Characteristics						
Sex						
Female	986	284	1.00	0.0002	1.00	<0.0001
Male	1168	421	1.33 (1.15, 1.55)		1.40 (1.20, 1.63)	
Birth weight (g)						
2,500	1941	616	1.00	<0.0001	1.00	0.004
< 2,500	129	61	1.78 (1.37, 2.31)		1.49 (1.20, 1.63)	
Gestational age at birth (weeks)						
37	1816	572	1.00	0.002	1.00	0.02
< 37	308	122	1.37 (1.13, 1.67)		1.28 (1.05, 1.57)	

	N^1	Events	Univariate HR (95% CI)^2	p	Multivariate HR (95% CI)^{2,3}	p
Place of birth						
Home	40	10	1.00			
Hospital/clinic	2022	667	1.30 (0.69, 2.42)	0.42		
Child fed colostrum						
Yes	1686	543	1.00			
No	170	55	0.99 (0.75, 1.31)	0.94		
Child received BCG immunization as a newborn						
Yes	1685	540	1.00			
No	171	58	1.04 (0.79, 1.37)	0.77		
Exclusively breastfed[5]						
No	24,432	516	1.00			
Yes	6,021	185	1.04 (0.82, 1.31)	0.76		
Anemia (Hb <11 g/dL)[5]						
No	5,423	132	1.00			
Yes	23,769	543	1.03 (0.85, 1.25)	0.79		
Cotrimoxazole consumption last month[5]						
0	1,822	45	1.00			
1–20 times	3,025	68	0.88 (0.59, 1.29)			
21 times	15,952	334	0.82 (0.59, 1.14)	0.23		
HIV status[5]						
Negative	27,975	573	1.00		1.00	
Positive	2,521	128	2.39 (1.98, 2.90)	<0.0001	2.26 (1.86, 2.74)	<0.0001
Cumulative morbidity episodes[5,7]						
Diarrhea						
0	23,117	601	1.00		1.00	
1–2	6,596	94	0.76 (0.60, 0.96)	0.03	0.78 (0.61, 0.98)	0.04
3	818	10	0.82 (0.43, 1.55)		0.80 (0.42, 1.52)	
Fever						
0	17,950	480	1.00			

	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
1–2	9,645	184	1.03 (0.85, 1.25)	0.93		
3–4	2,241	37	1.21 (0.84, 1.75)			
5	694	4	0.49 (0.18, 1.35)			
Common Cold						
0	9,667	273	1.00	0.61		
1–2	11,400	298	1.11 (0.92, 1.32)			
3–4	5,304	87	0.95 (0.72, 1.27)			
5	4,159	47	0.86 (0.59, 1.25)			
Vomiting						
0	27,821	664	1.00	0.58		
1	2,235	37	1.01 (0.72, 1.42)			
2	473	4	0.63 (0.23, 1.58)			
Refusal to eat, drink or breastfeed						
0	26,725	656	1.00	0.12		
1	2,874	42	0.90 (0.65, 1.25)			
2	931	7	0.54 (0.25, 1.15)			
Cough and fever						
0	21,725	551	1.00	0.52		
1–2	7,581	136	1.05 (0.86, 1.29)			
3	1,224	18	1.14 (0.70, 1.86)			
Cough plus difficulty breathing, rapid respiratory rate or refusal to eat						
0	26,590	641	1.00	0.84		
1	3,941	64	0.97 (0.74, 1.27)			

[1] N represents the number of children for time-fixed predictors, and number of person-months for time-varying

[2] Hazard Ratios (HR) and 95% Confidence Intervals (CI) were obtained from Cox proportional hazards models

[3] Multivariate results additionally adjusted for parent study treatment regimen

[4] The standard first line regimen for mothers was stavudine, lamivudine, and nevirapine

[5] Time-updated variable; N refers to person-months

[6] From a list that includes fan, refrigerator, sofa, radio/television

[7] An episode was defined if the symptom was reported during the 4 weeks prior to the visit

Table 4

Maternal, socioeconomic and child risk factors of time to underweight

			Univariate		Multivariate	
Maternal Characteristics	N[1]	Events	HR (95% CI)[2]	p	HR (95% CI)[2],[3]	p
Age at delivery (years)				0.12		
<20	71	24	1.00			
20–24	498	156	0.93 (0.61, 1.43)			
25	1476	438	0.82 (0.55, 1.24)			
Marital status				0.93		
Single/Widowed/Divorced/Other	274	82	1.00			
Married	1834	562	0.99 (0.79, 1.25)			
Number of prior pregnancies				0.62		
0	477	132	1.00			
1–3	1467	461	1.09 (0.90, 1.32)			
4	165	49	1.03 (0.74, 1.42)			
Formal education (years)				<0.0001		0.02
0	141	55	1.00		1.00	
1–7	1519	494	0.86 (0.65, 1.14)		0.94 (0.71, 1.25)	
8	452	95	0.52 (0.37, 0.72)		0.72 (0.51, 1.01)	
Occupation				0.33		
Housewife without income	1370	437	1.00			
Housewife with income	175	49	0.85 (0.64, 1.15)			
Business woman	118	24	0.61 (0.40, 0.92)			
Other	393	121	0.97 (0.79, 1.19)			
Mid-Upper Arm Circumference during pregnancy (cm)				<0.0001		0.07
< 22.0	132	58	1.00		1.00	
22.0	1976	587	0.64 (0.49, 0.84)		0.77 (0.59, 1.02)	
Height (cm)				<0.0001		<0.0001
< 155.0	1038	371	1.00		1.00	
155.0	1091	278	0.65 (0.55, 0.75)		0.67 (0.58, 0.79)	

	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
WHO HIV disease stage						
1	955	268	1.00			
2	193	56	1.07 (0.80, 1.42)			
3	147	51	1.30 (0.97, 1.76)	0.10		
Received ARVs during pregnancy[4]						
No	1552	473	1.00			
Yes	380	119	1.06 (0.87, 1.30)	0.57		
Vital status[5]						
Alive	31459	648	1.00			
Dead	104	1	0.58 (0.08, 4.12)	0.59		
Socioeconomic Characteristics						
Household food expenditure (TShs/person/day)						
< 500	271	96	1.00			
500	1729	521	0.87 (0.70, 1.08)	0.19		
Household possessions[6]						
0	296	116	1.00		1.00	
1–2	967	321	0.82 (0.67, 1.02)		0.86 (0.69, 1.07)	
3	846	206	0.57 (0.45, 0.72)	<0.0001	0.62 (0.49, 0.79)	<0.0001
Child Characteristics						
Sex						
Female	985	280	1.00		1.00	
Male	1145	369	1.18 (1.01, 1.38)	0.03	1.28 (1.09, 1.50)	0.003
Birth weight (g)						
2,500	1977	577	1.00		1.00	
< 2,500	73	37	2.16 (1.55, 3.02)	<0.0001	1.81 (1.29, 2.55)	0.0006
Gestational age at birth (weeks)						
37	1825	535	1.00		1.00	
< 37	275	106	1.42 (1.15, 1.75)	0.001	1.30 (1.05, 1.61)	0.02

	N[1]	Events	Univariate		Multivariate	
			HR (95% CI)[2]	p	HR (95% CI)[2,3]	p
Place of birth				0.10		
Home	43	16	1.00			
Hospital/clinic	1997	600	0.66 (0.40, 1.08)			
Child fed colostrum				0.93		
Yes	1667	495	1.00			
No	179	51	0.99 (0.74, 1.32)			
Child received BCG immunization as a newborn				0.08		0.78
Yes	1665	484	1.00		1.00	
No	179	62	1.26 (0.97, 1.65)		1.04 (0.79, 1.37)	
Exclusively breastfed[5]				0.04		0.30
No	25,463	477	1.00		1.00	
Yes	6,003	171	1.29 (1.01, 1.64)		1.14 (0.89, 1.44)	
Anemia (Hb <11 g/dL)[5]				0.40		
No	5,674	117	1.00			
Yes	24,553	499	1.09 (0.89, 1.34)			
Cotrimoxazole consumption last month[5]				0.91		
0	1,788	37	1.00			
1–20 times	3,211	75	1.06 (0.71, 1.58)			
21 times	16,759	324	0.88 (0.62, 1.26)			
HIV status[5]				<0.0001		<0.0001
Negative	29,065	509	1.00		1.00	
Positive	2,463	138	3.13 (2.59, 3.78)		3.21 (2.65, 3.89)	
Cumulative morbidity episodes[5,7]						
Diarrhea				0.06		0.42
0	23,580	536	1.00		1.00	
1–2	7,011	105	0.87 (0.69, 1.09)		0.98 (0.78, 1.24)	
3	971	8	0.55 (0.27, 1.12)		0.65 (0.31, 1.34)	
Fever						
0	18,281	435	1.00			

	N[1]	Events	Univariate HR (95% CI)[2]	p	Multivariate HR (95% CI)[2,3]	p
1–2	10,019	165	0.95 (0.78, 1.17)	0.75		
3–4	2,395	43	1.25 (0.88, 1.78)			
5	866	6	0.52 (0.22, 1.18)			
Common Cold						
0	9,702	238	1.00			
1–2	11,603	272	1.12 (0.92, 1.35)	0.54		
3–4	5,695	84	0.94 (0.70, 1.27)			
5	4,562	55	0.86 (0.60, 1.24)			
Vomiting						
0	28,552	609	1.00			
1	2,431	37	0.95 (0.68, 1.34)	0.14		
2	610	3	0.35 (0.11, 1.08)			
Refusal to eat, drink or breastfeed						
0	27,487	609	1.00	0.003	1.00	0.07
1	2,939	33	0.69 (0.48, 0.99)		0.83 (0.56, 1.23)	
2	1,137	7	0.40 (0.19, 0.86)		0.51 (0.23, 1.13)	
Cough alone						
0	10,905	273	1.00			
1–2	9,967	231	1.14 (0.93, 1.38)	0.47		
3–4	5,263	83	1.01 (0.74, 1.37)			
5	5,426	62	0.81 (0.56, 1.17)			
Cough and fever						
0	22,315	499	1.00			
1–2	7,854	131	1.05 (0.85, 1.30)	0.75		
3	1,394	19	1.01 (0.62, 1.64)			
Cough plus difficulty breathing, rapid respiratory rate or refusal to eat						
0	27,363	599	1.00	0.03	1.00	0.19
1	4,199	50	0.72 (0.53, 0.97)		0.80 (0.32, 1.97)	

[1] N represents the number of children for time-fixed predictors, and number of person-months for time-varying

[2]Hazard Ratios (HR) and 95% Confidence Intervals (CI) were obtained from Cox proportional hazards models

[3]Multivariate results additionally adjusted for parent study treatment regimen

[4]The standard first line regimen for mothers was stavudine, lamivudine, and nevirapine

[5]Time-updated variable; N refers to person-months

[6]From a list that includes fan, refrigerator, sofa, radio/television

[7]An episode was defined if the symptom was reported during the 4 weeks prior to the visit