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Maternal Antiretroviral Therapy Is Associated with Lower Risk of Diarrhea in Early Childhood

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Abstract

Objectives—To identify risk factors, including maternal antiretroviral therapy (ART), for diarrhea in Tanzanian children exposed to HIV during the first 2 years of life.

Study design—Using generalized estimating equations, we analyzed data from a cohort of 2387 Tanzanian children exposed to HIV from age 6 weeks to 2 years, as well as data from their mothers, to determine risk factors for diarrhea in children. Mothers recorded diarrhea in a diary and reported results at visits scheduled every four weeks.

Results—Body mass index was 18.5 in 95.6% of mothers. World Health Organization HIV stage was 1/2 for 1255 (87.8%) mothers. ART was received by 24.3% of mothers, most initiating ART during pregnancy. At baseline (6 weeks of age) 264 (11.3%) children were infected with HIV. In children whose mothers received ART, the relative risk of diarrhea in children was 0.79 (95% CI 0.68–0.92), after we adjusted for multiple factors, including child HIV status and exclusive breastfeeding duration. Exclusive breastfeeding (relative risk 0.67, 95% CI 0.56–0.80) also was protective.

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Conclusion—Our results provide additional support to increase ART coverage for all pregnant mothers, to control clinical HIV progression, reduce perinatal HIV infection, but also to reduce the risk of a major cause of death and morbidity in young children worldwide.

Trial registration—ClinicalTrials.gov: NCT00197730.

Diarrhea in children younger than 5 years of age is a major global health problem, causing an estimated 760 000 deaths annually, and accounts for almost 10% of postnatal child deaths¹ and up to 17% of child deaths in Tanzania.² Diarrhea episodes in the first 2 years of life may have many effects, including negatively impacting adult height, IQ, and school attendance.^{3–5} Every 5 episodes of diarrhea during childhood may stunt a child by 13%.³ Stunting remains a measure of poor nutritional status. Furthermore, multiple episodes of diarrhea also lead to impaired catch-up growth.³ Poor nutritional status and impaired growth are associated with poor neurocognitive outcomes, immune deficiencies, and greater risk of death in children.⁶ In addition, most child deaths from diarrhea occur in the world's poorest regions, with about 90% of related deaths in sub-Saharan Africa and South Asia.⁷ The incidence of diarrhea is most prevalent in areas also heavily impacted by HIV, including sub-Saharan Africa.

Antiretroviral therapy (ART) is lifesaving therapy for people infected with HIV, including pregnant women and mothers. The effects of ART for mothers may include improved nutritional status, greater hemoglobin, and improved economic status.⁸ In children, ART for mothers reduces the rate of HIV transmission,⁹ but there is controversy about the benefits of ART on other child outcomes such as birth weight¹⁰ and prematurity in children exposed to HIV.^{8,11,12} These are critical questions, given the size of the affected population. In 2013, 16 million women were infected with HIV, and 240 000 children were newly infected with HIV,¹³ and with mother-to-child HIV transmission rates as low as 5%,⁹ many hundreds of thousands more were exposed to HIV.

Despite its evident public health importance and wide use in mothers with HIV, the potential for maternal ART to protect against infant infectious diseases including diarrhea has received little attention. Breastfeeding reduces diarrhea in children exposed to HIV^{14,15}; however, few other maternal factors that reduce diarrhea have been identified for children exposed to HIV. There has been very limited research that examines maternal predictors such as ART use on diarrhea in young children at risk of HIV infection.^{15,16} In areas with high burdens of infectious disease and high HIV prevalence, identifying factors that influence the incidence of diarrhea in the first 2 years of life could provide opportunities for intervention to reduce diarrhea and to prevent short- and longer-term diarrhea-associated morbidity and mortality. To better understand risk factors for diarrhea in children exposed to HIV early in life, we examined data from a cohort of Tanzanian mothers infected with HIV and children exposed to HIV followed prospectively from birth to 2 years of age.

Methods

The parent study for these analyses was a randomized, placebo-controlled clinical trial to determine the effects of micronutrient supplementation on morbidity and mortality in Tanzanian children exposed to HIV (ClinicalTrials.gov: NCT00197730). The methods and

main results have been documented in detail previously.¹⁷ In brief, pregnant mothers were enrolled before 32 weeks' gestation and children randomized to placebo or supplementation at 6 weeks of age. A total of 2387 infants were enrolled; 1193 were randomized to receive multivitamin and 1194 to receive placebo. As part of standard medical care, mothers were provided with micronutrient supplements, and all children received growth monitoring, immunizations, routine medical care for illnesses, and periodic high-dose vitamin A supplementation per Tanzanian Ministry of Health guideline (100 000 IU at 9 months and 200 000 IU at 15 and 21 months of age).

All antiretroviral medications were prescribed according to Tanzanian Ministry of Health national guidelines. Nevirapine was given as single dose to the mother at the onset of labor and also to the infant within 72 hours of birth. In July 2005 the availability of ART expanded as the result of funding from HIV treatment support programs such as the US President's Emergency Plan for AIDS Relief.¹⁸ During the study period, ART eligibility included mothers with World Health Organization (WHO) stage 3 HIV disease or CD4+ cell count <350 cells/ μ L and children with WHO stage 3 HIV.¹⁹ Children age <18 months were eligible for ART with CD4+% <20, or if age $\geq$ 18 months, with CD4+% <15. First-line therapy for mothers included stavudine or zidovudine, lamivudine, and nevirapine, and for children included zidovudine, lamivudine, and nevirapine. Once started, ART was not stopped. Alternative drugs were available as needed.

Documentation of child morbidities, including diarrhea, was performed via a nurse visit of mothers and their children every 4 weeks at a central clinic site on the campus of Muhimbili University of Health and Allied Sciences. At these visits, mothers and nurses reviewed the data in a symptom diary from the previous 4 weeks that was collected via pictorial representations of symptoms of common morbidities including diarrhea. Nurse visits occurred every 4 weeks and physician visits occurred every 12 weeks or when requested for sick child visit. Acute diarrhea was defined as 3 or more loose or watery stools within 24 hours with or without blood or mucus. Persistent diarrhea was defined as watery or loose stools for more than 14 sequential days. Dysentery was defined as any diarrhea with blood, pus, or mucous. A positive report for any of these definitions was used as the primary outcome in our analysis. Diarrhea reports within 14 days of a previous report were counted as a single episode to avoid multiple counting of diarrhea events. In breastfed infants more than 12 weeks postnatal age who commonly have several loose stools per day at baseline, diarrhea was defined as a change in stool pattern according to the mother. Children with illnesses (including diarrhea) unable to be managed by nurses were referred to a study physician, where additional clinical data were collected.

Exclusive breastfeeding was defined as feeding a child with breast milk only, without supplemental foods. HIV treatment was provided to all participants according to standard of care per the Tanzania Ministry of Health. Written informed consent was obtained from all subjects at enrollment. All procedures were approved by institutional review boards at both Muhimbili University of Health and Allied Sciences and Harvard T.H. Chan School of Public Health.

Statistical Analyses

Examination of associations of potential risk factors with incident diarrhea was performed with the use of generalized estimating equations in the GENMOD procedure of the Statistical Analysis Systems statistical software package, version 9.2 (SAS Institute Inc, Cary, North Carolina). The binomial distribution with the log link function and a working exchangeable covariance structure was specified for repeated diarrhea episodes. A data structure with one record per child-visit was used to facilitate the handling of time-varying covariates.

For inclusion in the model, we considered potential risk factors for diarrhea from a list of known^{14,20} and suspected risk factors. These variables were categorized as follows: maternal age (<25, 25 years), education level (none, 1–7, 8 + years), employment (housewife without income, housewife with income, others), daily food expenditure (500, >500 Tanzanian Shillings), marital status (single, married/living with partner), number of previous pregnancies (0, 1–3, 4+), maternal WHO HIV stage (1/2, 3/4), time-varying ART (yes/no), maternal body mass index (BMI <18.5, 18.5 to <25.0, 25.0 to <30, 30+ kg/m²), maternal hemoglobin level (<11.0, 11.0 g/dL), maternal CD4+ counts (<350, 350 cells/μL), child sex (male/female), birth weight (<2500, 2500 g), preterm birth (<37, 37 weeks), time-varying exclusive breastfeeding (yes/no), time-varying breastfeeding (yes/no), and child time-varying HIV status (yes/no). Exposure to the treatment arm of the parent study was included in the multivariate models. Relative risks (RRs) and their corresponding 95% CIs are used to estimate their associations with incident diarrhea. Variables with *P* value <.2 in univariate analysis were selected for multivariate analysis. The significance tests were 2-sided, and differences were considered significant at *P* < .05.

Results

Enrollment and follow-up occurred between August 2004 and May 2008. Baseline characteristics of mothers and children at 6 weeks postpartum are shown in Table I. There were 2387 mothers and children enrolled. Case report forms without identifiable answers (eg, through failure to answer or misplaced form) were not included in the analysis. At baseline, more than two-thirds of mothers had less than 8 years of education, and two-thirds had no income. Mothers were generally not first-time mothers, with more than three-quarters of mothers having a previous pregnancy. Daily food expenditure was equally split between above and below 500 Tanzanian Shillings.

The majority of mothers (87.8%) had WHO HIV disease stage 1 or 2, and 24.3% of them received ART during pregnancy or after delivery. The primary regimens used include 3TC and nevirapine plus either stavudine or zidovudine. More than 95% of mothers had BMI 18.5 kg/m² at 6 weeks' postpartum. Only 7% of mothers had a mid-upper arm circumference below 22 cm.

At baseline (6 weeks' postpartum), 264 of 2345 children (11.3%) tested were infected with HIV (Table I). Subsequently another 91 children tested positive for HIV after baseline. Among infants at baseline, only 7% had low birth weight and 15% were born before 37 weeks' gestation. Mean weight at baseline was 4.4 kg (SD 0.7). Less than 10% of children

had a weight for age z score <-2 . More than 40% of children had hemoglobin <10 g/dL at 6 weeks of age, but mean hemoglobin was 11.5 g/dL (SD 1.4).

There were 1814 diarrhea episodes in 41 308 nurse observations. The Figure shows the incidence rate of diarrhea by age. Reports of diarrhea increased rapidly in the first few months of life and decreased after reaching the peak diarrhea incidence at 6–9 months of age.

Table II shows unadjusted and adjusted RRs for the associations between maternal and child characteristics and child diarrhea in our cohort. Maternal ART was a significant protective factor for child diarrhea, with RR of 0.79 (95% CI 0.68–0.92, $P = .002$), after we adjusted for multiple factors, including child HIV status and exclusive breastfeeding duration. This 21% reduction in the risk of child diarrhea was one of the strongest protective factors identified. There was no significant difference among the 4 ART regimens ($P = .14$). In univariate analysis, more advanced maternal disease stage increased diarrhea risk in children but lost significance in multivariate analysis ($P = .13$). Maternal CD4+ T-cell count was not significantly associated with child diarrhea.

Other factors associated with reduction in risk of diarrhea were child age ≥ 18 months compared with age <6 months (57% reduction), exclusive breastfeeding (33% reduction), and mean daily food expenditure >500 Tanzanian Shillings (33% reduction). Other characteristics with significant association with increased diarrhea risk include HIV infection in the child (29% increase), and 4 or more previous pregnancies (23% increase, compared with no previous pregnancies). Neither markers of maternal nutritional status (hemoglobin, low mid-upper arm circumference, BMI), nor markers of child nutritional status (low birth weight, underweight, or wasting at baseline) were associated with risk of diarrhea.

Discussion

In a large cohort of Tanzanian children exposed to HIV, maternal ART was independently associated with a substantial and significant 21% lower risk of childhood diarrhea during the first 2 years of life. This association persisted after we adjusted for baseline maternal and baseline child nutritional status and most notably after adjustment for HIV infection and breastfeeding. We identified several other factors that reduced diarrhea risk independently, including longer breastfeeding (exclusive or any breastfeeding), increased maternal age, decreased parity, greater food expenditure, and older child age groups. In addition, HIV infection, whenever it occurred, increased the risk of subsequent diarrhea during the first 2 years of life.

There are limited previous data that examine the effect of ART on diarrhea. In a case-control study of children infected with HIV vs children without HIV in Botswana, investigators showed no protection of maternal highly active ART against diarrhea in children up to 6 months of age; however, only 9 of 588 women received ART during the 6 months postpartum.¹⁵ A study from Zimbabwe focused on postpartum HIV transmission examined 2250 children exposed to HIV, with 35.7% of their mothers receiving postpartum ART.

Compared with children whose mother did not receive ART, there was no difference in the joint outcome of diarrhea/growth faltering by 48 weeks of age (hazard ratio [HR], $P = .92$).¹⁶ In addition, investigators followed children only to age 48 weeks, not 2 years, as in our study. One additional study suggested that certain ART medications in mothers may not improve postnatal outcomes such as growth, but this study did not examine diarrhea as an outcome.²¹

Although many studies have examined breastfeeding's effect on diarrhea, few have focused on children exposed to HIV.^{14,21} There is some evidence that children exposed to but not infected with HIV may be at greater risk of infectious morbidity compared with infants who were not exposed.^{15,22} South African investigators examined the effect of breastfeeding on diarrhea in children exposed to HIV up to 6 months of age. No breastfeeding increased the risk of diarrhea up to 6 months of age (HR 1.35 [adjusted HR 1.17–1.53]), but the effect of maternal ART on diarrhea was not examined. Unlike our cohort, this study did not include children up to 2 years of life,¹⁴ the age to which the WHO recommends to continue breastfeeding.²³ In our study, exclusive breastfeeding substantially reduced diarrhea (RR 0.67 [95% CI 0.56–0.80]). Data from South Africa¹⁴ showed mixed feeding was not protective against diarrhea; however, this finding contrasts with our finding in which any breastfeeding including mixed feeding was also protective against diarrhea (RR 0.66 [95% CI 0.56–0.77]).

We confirmed several other factors that were associated with a lower incidence of diarrhea. In our study, household daily food expenditure of 500 or more Tanzanian Shillings reduced diarrhea risk by 33%. Greater food expenditure has been associated with lower rates of malnutrition²⁴ but not specifically with the incidence of diarrhea. Older children experienced less diarrhea in our study. This has been seen previously in children aged 0–5 years²⁵ but is not a universal outcome.²⁶ HIV infection was a predictor of diarrhea in our cohort up to 2 years of age (RR 1.29 [95% CI 1.10–1.50]), but the effect size was lower than that for perinatal (HR 1.43 [95% CI 1.18–1.72]) or postnatal infection (HR 1.76 [95% CI 1.15–2.69]) in South Africa.¹⁴ In addition, we determined that having an older mother (age 25+ years) with fewer children (lower parity) protected children from diarrhea, and in South Africa maternal age and parity had no effect on the risk of diarrhea.¹⁴ Interestingly, malnutrition defined by low weight-for-age z score (underweight) at 6 weeks of age was not associated with increased risk of diarrhea, even when modeled independently from other baseline anthropometric measurements to avoid collinearity. This finding was surprising, given that the cycle of malnutrition and diarrheal diseases is well established.⁴ Even low baseline maternal mid-upper arm circumference (<22 cm), a summary measure of nutritional status in pregnant mothers, was not associated with incidence of diarrhea ($P = .46$).

We documented the peak of the rate of incidence of diarrhea between 6–9 months of age (Figure). In children exposed to HIV, a peak rate of incidence of diarrhea near age 6 months has been documented previously.²⁰ In our study, peak rate of incidence of diarrhea was within the first 9 months of life (Figure), a period during which breastfeeding mothers are returning to clinic regularly for HIV care and treatment. This confluence of child disease and health care visits offers opportunities for intervention, including initiating mothers and/or breastfeeding children onto ART.

Our study had several limitations. This was an observational study design and has the known limitations of available data. We may have slightly undercounted acute diarrhea episodes because multiple reports within 14 days were counted as one episode in our analysis. The study was not designed specifically to examine maternal ART effect on diarrhea. Our study was large, however, and included many variables reflecting nutritional status and HIV status. We did not track maternal adherence to ART, which improves health outcomes in patients with HIV^{27,28}; however, we pooled all those who initiated ART during the study period, including those who may not have been adherent. This pooling would tend to result in a smaller effect size. Another common therapy used in HIV care is cotrimoxazole, which also can be used to treat diarrhea^{16,29} and other infections.¹⁶ Although cotrimoxazole was used as standard of care in mothers with HIV, its use in children was not tracked. We did not measure serum levels of micronutrients, whose intake may impact risk and severity of diarrhea^{30,31}; however, vitamin A routinely was provided for children in Tanzania during the study. Notably, routine zinc supplementation for acute diarrhea was not widely available during the study period. Finally, rotavirus vaccines were not generally available during the study period, and their current availability may affect the generalizability of our findings.

Our study is unique in identifying direct benefit of maternal ART to reduce an important child morbidity. Aside from the choice to exclusively breastfeed, few other maternally determined factors have been shown independently to protect children from diarrhea morbidity.^{14,15} Our findings support use of ART in all mothers with HIV to reduce child diarrhea. Many women with HIV are enrolled in HIV care before or during pregnancy. Despite goals to expand care to pregnant mothers, many women do not have access to ART during pregnancy or may not qualify for treatment based on local guidelines. Although coverage of ART for pregnant women in low- and middle-income countries continues to expand, in 2010 it was only 48%.³² Several challenges to initiating patients with HIV such as pregnant women on ART include appropriate guidelines for initiating ART, recruitment strategies, program capability, and patient motivation.³³ If maternal ART reduces diarrhea in offspring, this is an obvious opportunity to address effectively 2 diseases in 2 individuals with one therapy.

In summary, our study suggests that maternal ART has benefit in reducing the risk of diarrhea in the first 2 years of childhood. These results provide additional support to increase ART coverage for all pregnant and lactating mothers, not only to control clinical progression and reduce perinatal HIV infection, but also to reduce the risk of a major cause of death and morbidity in young children worldwide.

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Glossary

ART	Antiretroviral therapy
BMI	Body mass index

HR	Hazard ratio
RR	Relative risk
WHO	World Health Organization

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Figure.
The incident rate of diarrhea by child age.

Table I

Maternal and child baseline characteristics

Characteristics	Mean (SD) or n (%)
Maternal	
Age, years (n = 2331)	28.2 (4.9)
Education (n = 2365)	
None	158 (6.7)
1–7 y	1700 (71.9)
8 + y	507 (21.4)
Employment (n = 2298)	
Housewife without income	1528 (66.5)
Housewife with income	330 (14.4)
Others	440 (29.1)
Marital status (n = 2361)	
Single	310 (13.1)
Married/living with partner	2051 (86.9)
Previous pregnancies (n = 2363)	
None	539 (22.8)
1–3	1632 (69.1)
4+	192 (8.1)
Daily food expenditure per person, TShs (n = 2242) *	
<500 Tanzanian Shillings	1163 (51.9)
500 Tanzanian Shillings	1079 (49.1)
Mid upper arm circumference, <22 cm (n = 2362) †	170 (7.2)
Hemoglobin level <11 g/dL (n = 2125) ‡	648 (30.5)
BMI group, kg/m ² (n = 2358)	
<18.5	104 (4.4)
18.5 to <25	1331 (56.5)
25.0 to <30	699 (29.6)
30	224 (9.5)
Time of ART initiation (n = 2387)	
None	1807 (75.7)
During pregnancy	429 (18.0)
After delivery	151 (6.3)
Antiretroviral regimen (n = 581)	
Stavudine + 3TC + nevirapine	274 (46.4)
Zidovudine + 3TC + nevirapine	228 (38.6)
Stavudine + 3TC + efavirenz	18 (3.0)
Zidovudine + 3TC + efavirenz	71 (12.0)
WHO HIV disease stage (n = 1429)	
1/2	1255 (87.8)
3/4	174 (12.2)

Characteristics	Mean (SD) or n (%)
CD4+ cell count (cells/ μ L) [†] (n = 2101)	
<350	619 (29.5)
350	1482 (70.5)
Gestational age at enrollment, wk	24.5 (5.5)
Child	
Male sex (n = 2387)	1289 (54.0)
Low birth weight <2500 g (n = 2289)	161 (7.0)
Prematurity, <37 wk (n = 2352)	357 (15.2)
HIV infected at baseline (n = 2345)	264 (11.3)
Weight at baseline, kg (n = 2355)	4.4 (0.7)
Length-for-age z score <-2 (n = 2348)	203 (8.7)
Weight-for-height z score <-2 (n = 2332)	181 (7.8)
Weight-for-age z score <-2 (n = 2355)	215 (9.1)
Duration of any breastfeeding, months (n = 2379)	4.4 (2.5)
Duration of exclusive breastfeeding, months (n = 2379)	3.5 (2.1)
Hemoglobin level at baseline 10 g/dL (n = 2276)	953 (41.9)

TShs, Tanzanian Shillings.

* 1250 Tanzanian Shilling = 1 USD at the time of the study.

[†] Maternal characteristics measured at 6 wk postpartum.

Table II

Predictors of diarrhea in children exposed to HIV in Tanzania

Characteristics	Univariate RR (95% CI)*	P value*	Multivariate RR (95% CI)*	P value*
Maternal age, y				
<25	Reference	.03	Reference	.005
25	0.90 (0.81–0.99)		0.82 (0.71–0.94)	
Education				
None	Reference	.97		
1–7 y	1.06 (0.88–1.27)			
8 + y	1.02 (0.83–1.24)			
Employment				
Housewife without income	Reference	<.001	Reference	.20
Housewife with income	0.83 (0.72–0.96)		0.98 (0.82–1.16)	
Others	1.13 (1.01–1.27)		1.16 (0.99–1.36)	
Marital status				
Single	Reference	.66		
Married/living with partner	0.97 (0.85–1.11)			
Previous pregnancies				
None	Reference	.04	Reference	.03
1–3	1.12 (1.00–1.25)		1.19 (1.02–1.38)	
4 +	1.18 (0.99–1.42)		1.23 (0.97–1.57)	
Daily food expenditure per person, Tanzanian Shillings [†]				
<500	Reference	<.001	Reference	<.001
500	0.67 (0.61–0.74)		0.67 (0.59–0.77)	
Hemoglobin level, g/dL				
11	Reference	.58		
<11	1.03 (0.93–1.14)			
BMI group, kg/m ²				
<18.5	0.89 (0.69–1.14)	.93		
18.5 to <25	Reference			
25 to <30	1.06 (0.96–1.18)			
>30	0.89 (0.75–1.05)			
MUAC, cm				
<22	1.11 (0.94–1.33)	.20	1.10 (0.87–1.38)	.45
22	Reference		Reference	
Received ART during pregnancy?				
No	Reference	<.001	Reference	.002
Yes	0.75 (0.67–0.86)		0.79 (0.68–0.92)	
ART use (time varying)				
No	Reference	<.001	Reference	<.001
Yes	0.73 (0.65–0.82)		0.77 (0.67–0.89)	
ART regimen				

Characteristics	Univariate RR (95% CI)*	P value*	Multivariate RR (95% CI)*	P value*
Stavudine + 3TC + nevirapine	Reference	<.001	Reference	.14
Zidovudine + 3TC + nevirapine	0.79 (0.66–0.95)		0.85 (0.68–1.07)	
Stavudine + 3TC + efavirenz	0.47 (0.24–0.91)		0.55 (0.27–1.10)	
Zidovudine + 3TC + efavirenz	0.83 (0.63–1.08)		0.83 (0.58–1.17)	
WHO disease stage				
1/2	Reference	.02	Reference	.13
3/4	1.22 (1.03–1.43)		1.18 (0.95–1.45)	
CD4+ count of mother, cells/μL				
350	Reference	.56		
<350	0.97 (0.87–1.08)			
Sex of child				
Female	Reference	.03	Reference	.06
Male	1.11 (1.01–1.21)		1.11 (0.99–1.25)	
Child age, mo				
Up to 6	Reference	<.001	Reference	<.001
6 to <18	1.11 (0.99–1.22)		0.91 (0.80–1.05)	
18	0.54 (0.47–0.62)		0.43 (0.36–0.52)	
Low birth weight <2500 g				
No	Reference	.27		
Yes	1.11 (0.92–1.32)			
HIV infected, time-varying				
No	Reference	<.001	Reference	.002
Yes	1.28 (1.12–1.47)		1.29 (1.10–1.50)	
Prematurity, <37 weeks				
No	Reference	.64		
Yes	1.04 (0.91–1.17)			
Exclusive breastfeeding, time-varying [†]				
No	Reference	.11	Reference	<.001
Yes	0.90 (0.80–1.02)		0.67 (0.56–0.80)	
Any breastfeeding, time-varying [†]				
No	Reference	.18	Reference	<.001
Yes	0.93 (0.83–1.04)		0.66 (0.56–0.77)	
Stunting, baseline				
No	Reference	.45		
Yes	0.94 (0.79–1.11)			
Underweight, baseline				
No	Reference	.27		
Yes	0.90 (0.76–1.08)			
Wasting, baseline				
No	Reference	.50		
Yes	1.06 (0.89–1.27)			
Multivitamin supplement to child				

Characteristics	Univariate RR (95% CI) [*]	<i>P</i> value [*]	Multivariate RR (95% CI) [*]	<i>P</i> value [*]
No	Reference	.46	Reference	.39
Yes	0.97 (0.88–1.06)		0.95 (0.85–1.06)	

MUAC, mid-upper arm circumference.

^{*}RRs, 95% CIs, and *P* values were obtained from generalized estimating equations with the binomial distribution, log link, and exchangeable covariance structure. Variables included in the multivariate model if *P* < .20 in the univariate model.

[†]Time-varying exclusive breastfeeding and time-varying any breastfeeding were assessed separately in the multivariate model to avoid collinearity.