

Maternal Disease Stage and Child Undernutrition in Relation to Mortality Among Children Born to HIV-Infected Women in Tanzania

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Objective: To examine whether maternal HIV disease stage during pregnancy and child malnutrition are associated with child mortality.

Design: Prospective cohort study in Tanzania.

Methods: Indicators of disease stage were assessed for 939 HIV-infected women during pregnancy and at delivery, and children's anthropometric status was obtained at scheduled monthly clinic visits after delivery. Children were followed up for survival status until 24 months after birth.

Results: Advanced maternal HIV disease during pregnancy (CD4 count <350 vs. ≥350 cells/mm³) was associated with increased risk of child mortality through 24 months of age (hazard ratio [HR] = 1.74, 95% confidence interval [CI]: 1.32 to 2.30). CD4 count <350 cells/mm³ was also associated with an increased risk of death among children who remained HIV-negative during follow-up (HR = 2.00, 95% CI: 1.36 to 2.94). Low maternal hemoglobin concentration and child undernutrition were related to an increased risk of mortality in this cohort of children.

Conclusions: Low maternal CD4 cell count during pregnancy is related to increased risk of mortality in children born to HIV-infected women. Care and treatment for HIV disease, including highly active antiretroviral therapy to pregnant women, could improve child survival. Prevention and treatment of undernutrition in children remain critical interventions in settings with high HIV prevalence.

Key Words: CD4, child mortality, HIV, sub-Saharan Africa, undernutrition

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There has been a disproportionate rise in HIV infection rates among women compared with men, and this is most evident in sub-Saharan Africa, where 77% of all HIV-positive women live.¹ In 2003, 57% of total prevalent HIV infections in sub-Saharan Africa were among women aged 15 to 49 years as compared with 1985, when the numbers of HIV-infected women and men in this region were equal.¹ This has resulted in an increased number of HIV infections among children.² In 2005, there were 700,000 new HIV infections among children younger than 15 years of age and 570,000 deaths attributable to HIV/AIDS in the same age group. Even though AIDS is a major cause of mortality in vertically infected children, there is evidence that maternal health status during pregnancy is also an independent predictor of death in these children.^{3–8} Advanced clinical disease,³ lower CD4 cell counts,^{4–7} and higher HIV RNA viral loads⁸ in HIV-infected mothers have been associated with disease progression or death in their HIV-infected children. The increased risks of morbidity and mortality attributable to these maternal factors may also be present in children who remain uninfected with HIV.^{7,9} Most of the studies published to date had relatively small sample sizes and a short duration of follow-up for child mortality, however, although some of them were conducted in developed countries, where child mortality rates are low, the causes of child mortality are different, and treatment for AIDS is more readily available. Also, none of the studies had data on immunologic status of the mother in the second trimester of pregnancy, when most women in developing country settings visit antenatal clinics for the first time.

More than half of the deaths among preschool children in developing countries are attributable to the underlying effects of malnutrition on disease.^{10,11} Most prospective studies have examined this association in settings with low HIV prevalence.^{12,13} Little is known about the relation between undernutrition and mortality among children exposed to HIV infection in utero or after birth through breast-feeding in developing countries with a high burden of HIV infection. Nutritional surveillance of children born to HIV-infected women in regions with high HIV prevalence is a simple and inexpensive tool that has the potential of identifying children at increased risk of mortality so that appropriate interventions can be instituted.

We examined the associations between HIV disease stage and nutritional status of HIV-infected women during pregnancy on mortality of HIV-infected and uninfected

children. We also investigated the association of child undernutrition with mortality through 24 months of age.

METHODS

Study Design and Population

This prospective study was conducted within the setting of a randomized, double-blind, placebo-controlled trial to study the effects of vitamin supplementation of HIV-infected women during pregnancy and lactation on maternal and child health outcomes. Details of the trial have been published elsewhere.¹⁴ Enrollment occurred at 4 antenatal clinics in Dar es Salaam, Tanzania; eligible women were between 12 and 27 weeks of gestation, HIV-infected, and residents of Dar es Salaam. Maternal HIV infection was diagnosed at baseline on the basis of a positive enzyme-linked immunosorbent assay (ELISA) confirmed by a Western blot test. After giving informed consent, women were randomized in a double-blind factorial design to 4 arms: vitamin A, vitamin A and multivitamins, multivitamins excluding vitamin A, or placebo. All women received standard antenatal care as per the guidelines of the Ministry of Health of Tanzania, which included daily supplementation with iron and folic acid and weekly doses of chloroquine phosphate. Women in the vitamin A arm received another high dose of vitamin A at delivery.

At the time of enrollment and during monthly visits to the clinic during and after pregnancy, women underwent a complete physical examination by a research physician and provided a detailed medical history and information on sociodemographic characteristics. World Health Organization (WHO) staging criteria in use at that time were used to determine HIV disease stage.¹⁵ Children born to women enrolled in the trial were followed from birth through monthly visits to the study clinic; home visits were made in the event that a scheduled clinic visit was missed, and neighbors and relatives were contacted to obtain information on survival status of the mother and child. The first postnatal clinic visit was at 6 weeks after birth. During visits to the clinic, children underwent a complete physical examination by a study physician, trained research nurses measured weight to the nearest 100 g using calibrated beam balances (model 725; Seca, Hamburg, Germany) and recumbent length to the nearest 0.1 cm with an infant length board (locally manufactured according to WHO recommendations), and mothers provided a detailed history of their child's illness and breast-feeding status since the last clinic visit.

Laboratory Methods

At baseline (median = 21 weeks of gestation, range: 12 to 27 weeks), 6 weeks postpartum, and every 6 months thereafter, mothers were requested to provide a blood sample for measurement of absolute counts of CD4 T cells (using the FACSscan and FACSCount system; Becton-Dickinson, San Jose, CA); a complete blood cell count, including hemoglobin concentration, using a CBC5 Coulter counter (Coulter Corporation, Miami, FL) or the cyanmethemoglobin method using a Colorimeter (Corning, Corning, NY); and an erythrocyte sedimentation rate (ESR) using the Westergren method. Viral load assessment was done on a randomly selected subset

of 387 women at baseline and during delivery (using the Roche Amplicor assay; Roche Diagnostics, Branchburg, NJ). Children were scheduled to provide a blood sample at birth, 6 weeks of age, and every 3 months thereafter for assessment of HIV infection and at birth and every 6 months thereafter for measurement of absolute CD4 T-cell counts. HIV-1 infection was diagnosed in the children on the basis of a positive peripheral mononuclear cell (PBMC) specimen by polymerase chain reaction (PCR) before 18 months of age (using the Amplicor HIV-1 detection kit; Roche Diagnostics) or a positive ELISA confirmed by a Western Blot test at or after 18 months of age.

Data Analyses

We examined the associations between maternal disease stage variables and child mortality and also the association between child undernutrition and mortality. Of the 1078 HIV-infected women enrolled in the trial, 3 were not pregnant, 6 died before delivery, and pregnancy outcome was not known for 28. Overall, 984 children were born alive. Because twins have an increased risk of mortality, we excluded them from the analyses, and the study population consisted of the 939 liveborn singletons. We examined the relation of maternal HIV disease stage at baseline and at delivery as measured by CD4 cell counts, WHO HIV disease stage, viral load, and other proxy indicators of maternal health status, namely, hemoglobin concentration, ESR, and history of genital ulcer disease. Univariate and multivariate Cox proportional hazard models were fitted, and a counting process data structure was used to stratify analyses for the mortality endpoint by HIV-infected and uninfected person-time over the 24 months of follow-up.^{16,17} Each covariate was entered into a separate univariate proportional hazards model. All covariates with $P \leq 0.20$ in the univariate models were entered into multivariate proportional hazards models. For the subgroups stratified by HIV status, additional multivariate models, which included all the variables significant at the $P = 0.20$ level in the unstratified analysis, gave similar results (details not shown). All multivariate models were adjusted for time-varying child HIV infection status (infected/not infected), with the time of infection designated as the midpoint between the last negative and first positive HIV test result, maternal trial regimen (multivitamins: yes/no, vitamin A: yes/no) and maternal education (none/some). Continuous risk factors were categorized using conventional cutoffs: CD4 counts (<350 vs. ≥ 350 cells/mm³), viral load ($\geq 50,000$ vs. $<50,000$ copies/mL), hemoglobin (<8.5 vs. ≥ 8.5 g/dL), or the highest quartile ESR (≥ 81 vs. <81 mm/h). Time of diagnosis of HIV infection in the child was also categorized to distinguish intrapartum and early postnatal infections (0 to 49 days) from late postnatal infections (after 49 days). The missing indicator method was used for covariates with missing data.¹⁸

Cox models were also fitted to examine the association between child undernutrition and mortality through 24 months of age. Time-dependent indicators of undernutrition updated every month included underweight (weight-for-age z-score < -2 according to the National Center for Health Statistics [NCHS]/WHO reference),¹⁹ stunting (height-for-age z-score < -2), and wasting (weight-for-height z-score < -2).

Separate univariate and multivariate models were fit for each of the anthropometric indicators. The risk interval was defined as the interval between 2 scheduled monthly visits, with the exposure updated at the beginning of each interval and the outcome assessed at the end of the interval. Multivariate models were adjusted for maternal trial regimen, maternal education, maternal CD4 cell count during pregnancy, and time-varying indicators for child's breast-feeding status lagged (breast-feeding status 3 months preceding the anthropometric measurement) by 3 months (breast-feeding: yes/no), child's CD4 count (age <12 months: <750 vs. ≥ 750 cells/mm³, age ≥ 12 months: <500 vs. ≥ 500 cells/mm³), and child's HIV status (infected/not infected).

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

RESULTS

There were 228 child deaths during 17,568 child-months of follow-up, and 257 children were known to be infected with HIV during follow-up. The median maternal CD4 count at baseline was 402 cells/mm³ (interquartile range [IQR]: 278 to 529 cells/mm³). At baseline, 38% of women had a CD4 count <350 cells/mm³ and 20% were in WHO HIV disease stage 2 or more. Viral load measurement was available for a random subset of 387 women at baseline and 177 women at delivery, with 49% of those with a viral load measurement at baseline having a viral load $\geq 50,000$ copies/mL. Mothers of 38 children died during the period of follow-up.

Children whose mothers' baseline CD4 count was <350 cells/mm³ had a 1.74 times (95% confidence interval [CI]: 1.32 to 2.30) higher risk of mortality through 24 months than children whose mothers' baseline CD4 count was ≥ 350 cells/mm³ (Table 1). The relative risk (RR) was higher in children who were not infected with HIV (hazard ratio [HR] = 2.00, 95% CI: 1.36 to 2.94; Table 2) than in those who were infected with HIV (HR = 1.38, 95% CI: 0.94 to 2.03; Table 3). Maternal CD4 cell count <350 cells/mm³ at delivery was associated with a 62% increased risk of child death (HR = 1.62, 95% CI: 1.18 to 2.22; see Table 1). Higher maternal viral load was also associated with increased risk of child mortality (see Table 1), especially among infants not known to be infected with HIV. Advanced maternal HIV stage at baseline was associated with a borderline statistically significant increased risk of child mortality in the subgroup of HIV-uninfected children (although not in the HIV-infected children) (HR = 1.51, 95% CI: 0.98 to 2.32; $P = 0.06$; see Table 2).

Other proxy indicators of poor maternal health and nutritional status were also associated with risk of child death, namely, low maternal hemoglobin concentration at delivery (HR = 1.53, 95% CI: 1.04 to 2.24) and increased ESR at delivery (HR = 1.44, 95% CI: 0.97 to 2.14; $P = 0.07$) (see Table 1). Among HIV-infected children, increased ESR in the mothers at baseline was associated with a borderline statistically significant increased risk of child death (see Table 3).

HIV infection in the child was significantly associated with an increased risk of death, and the magnitude of risk varied depending on the time of diagnosis of HIV infection (see Table 1). Compared with those who were not known to be infected with HIV, children diagnosed within 49 days of birth had a nearly 6-fold increased risk of mortality (HR = 6.23, 95% CI: 4.43 to 8.76), whereas those diagnosed after 49 days of birth had a nearly 3-fold increased risk of death (HR = 2.83, 95% CI: 1.95 to 4.11) (see Table 1).

We next examined the association between child undernutrition as a time-varying predictor and mortality. We modeled anthropometric indices at each clinic visit in relation to the risk of mortality over the next month and also assessed the associations when the measurements were lagged by 3 months. The lag was used as an approach to separate out the effect of malnutrition from that of any acute illness that might have immediately preceded death in these children. Being underweight (weight-for-age z-score < -2) at a previous clinic visit was associated with a high RR of mortality (HR = 3.88, 95% CI: 2.66 to 5.66), and the association was attenuated when examining weight for age lagged by 3 months (HR = 2.23, 95% CI: 1.30 to 3.85) (Table 4). Wasting (weight-for-height z-score < -2) was associated with an even higher RR of mortality (HR = 5.35, 95% CI: 3.38 to 8.48), with a weight-for-height z-score lagged by 3 months associated with a lower RR (HR = 2.45, 95% CI: 1.13 to 5.31). Children who were stunted (height-for-age z-score < -2) were also at a significantly higher risk of mortality, and the strength of association was attenuated slightly when the assessment was lagged by 3 months.

DISCUSSION

Health status of HIV-infected women during pregnancy and around the time of delivery is known to influence the rate of disease progression in their HIV-infected offspring.²⁻⁸ A small study from Thailand with only 12 child deaths during follow-up found a more than 4-fold increased risk of death through 1 year among HIV-infected children if the maternal CD4 count at delivery was <400 cells/ μ L.⁶ Two studies from the United States reported an association between maternal CD4 cell count at delivery and mortality in HIV-infected children, although the association was not significant in one of the studies after adjusting for HIV RNA level and Centers for Disease Control and Prevention (CDC) HIV disease category.^{4,5} The association between maternal CD4 cell count and mortality among HIV-uninfected children reported by us is similar to that reported from a study in Zambia with 4 months of follow-up for child mortality.⁹

We present evidence of increased risk of mortality among HIV-infected and uninfected children born to HIV-infected women who are at an advanced stage of HIV disease during pregnancy. There was a nearly 2-fold increase in risk of total child mortality through 24 months of age if maternal CD4 count during pregnancy was <350 cells/mm³. A study pooling the results of 7 clinical trials in sub-Saharan Africa found an increased risk of death among children born to HIV-infected women if the mother's CD4 cell count at delivery was low. In that study, the excess risk of mortality was quite similar for HIV-infected and uninfected children (HIV-infected

TABLE 1. Association of Maternal HIV Disease Stage During Pregnancy With Child Mortality

Predictors	No. at Risk	No. Deaths (%)	HR* (95% CI) (Univariate)	P*	HR† (95% CI) (Adjusted)	P†
CD4 count at baseline (cells/mm ³)						
<350	332	113 (34%)	2.03 (1.55 to 2.65)	<0.0001	1.74 (1.32 to 2.30)	<0.0001
≥350	552	102 (18%)	1.00		1.00	
CD4 count at delivery (cells/mm ³)						
<350	161	59 (37%)	1.80 (1.34 to 2.43)	<0.0001	1.62 (1.18 to 2.22)	0.003
≥350	778	169 (22%)	1.00		1.00	
Viral load at baseline (copies/mL)						
≥50,000	190	90 (47%)	3.13 (2.12 to 4.63)	<0.0001	1.43 (0.93 to 2.18)	0.10
<50,000	197	35 (18%)	1.00		1.00	
Viral load at delivery (copies/mL)						
≥50,000	70	31 (44%)	4.01 (2.17 to 7.44)	<0.0001	2.47 (1.22 to 5.02)	0.01
<50,000	107	15 (14%)	1.00		1.00	
HIV stage at baseline						
2+	185	57 (31%)	1.46 (1.08 to 1.97)	0.01	1.07 (0.79 to 1.47)	0.66
1	753	171 (23%)	1.00		1.00	
Genital ulcer at baseline						
Yes	60	22 (37%)	1.75 (1.12 to 2.72)	0.01	1.39 (0.88 to 2.18)	0.15
No	837	190 (23%)	1.00		1.00	
Hemoglobin at baseline (g/dL)						
<8.5	248	69 (28%)	1.33 (1.00 to 1.76)	0.05	1.26 (0.94 to 1.70)	0.12
≥8.5	675	152 (23%)	1.00		1.00	
Hemoglobin at delivery (g/dL)						
<8.5	81	32 (40%)	1.86 (1.28 to 2.71)	0.001	1.53 (1.04 to 2.24)	0.03
≥8.5	858	196 (23%)	1.00		1.00	
ESR at baseline (mm/h)						
≥81	217	64 (29%)	1.41 (1.05 to 1.89)	0.02	1.13 (0.83 to 1.53)	0.43
<81	634	142 (22%)	1.00		1.00	
ESR at delivery (mm/h)						
≥81	88	30 (34%)	1.47 (1.00 to 2.16)	0.05	1.44 (0.97 to 2.14)	0.07
<81	851	198 (23%)	1.00		1.00	
Time of diagnosis of HIV infection in the child						
After 49 d	134	49 (37%)	3.24 (2.24 to 4.67)	<0.0001	2.83 (1.95 to 4.11)	<0.0001
0 to 49 d	123	70 (57%)	6.71 (4.80 to 9.37)	<0.0001	6.23 (4.43 to 8.76)	<0.0001
Not known if HIV infected	600	69 (12%)	1.00		1.00	

*From separate univariate Cox proportional hazards models.

†From multivariate Cox proportional hazards models. The basic multivariate model included the following variables, with indicator variables for individuals missing data on a particular variable: CD4 cell count at baseline, WHO HIV disease stage at baseline, genital ulcer at baseline, hemoglobin at baseline, ESR at baseline, maternal education, maternal trial regimen, and time-varying child HIV status. In separate models, CD4 cell count at delivery replaced CD4 cell count at baseline, hemoglobin at delivery replaced hemoglobin at baseline, ESR at delivery replaced ESR at baseline, and time of diagnosis of HIV infection (0 to 49 days, >50 days) replaced time-varying child HIV status. Estimates for viral load were obtained by adding viral load to the basic multivariate model and only using subjects who had viral load measurements.

children: RR = 1.86, HIV-uninfected children: RR = 1.72; comparing CD4 count <200 vs. ≥500 cells/μL), but the estimate for the uninfected children was not statistically significant. Our results are in contrast to those from a smaller study from West Africa, which reported no association between maternal CD4 cell counts during pregnancy on 15-month child mortality.²⁰ That study had limited statistical power to detect an association between maternal health status and child mortality, however.

We also noted that high maternal viral load was associated with increased risk of child mortality. Our estimates are higher than those obtained from a meta-analysis that examined the association among HIV-infected children.⁸ This is possibly

attributable to the fact that the meta-analysis included studies among populations in Europe and North America, where the nature of the association is likely to be different because of different morbidity profiles and causes of mortality among children. In our study, raised ESR was probably associated with other opportunistic infections in these HIV-infected women and the presence of genital ulcers was also associated with increased risk of child death. These variables probably reflect advanced disease stage in these HIV-infected women. Maternal anemia during pregnancy has been shown to be associated with infant mortality among HIV-infected and uninfected children in sub-Saharan Africa.^{9,21,22} Maternal hemoglobin <8.5 g/dL at delivery was associated with

TABLE 2. Association of Maternal HIV Disease Stage During Pregnancy With Mortality Among Children not Known to Be Infected With HIV

Maternal Predictors	Child-Months at Risk	No. Deaths	HR* (95% CI) (Univariate)	P*	HR† (95% CI) (Adjusted)	P†
CD4 count at baseline (cells/mm ³)						
<350	4423	55	2.05 (1.40 to 3.01)	0.0002	2.00 (1.36 to 2.94)	0.0004
≥350	9195	51	1.00			
CD4 count at delivery (cells/mm ³)						
<350	1951	20	1.26 (0.78 to 2.06)	0.34	—	—
≥350	12,454	89	1.00			
Viral load at baseline (copies/mL)						
≥50,000	1308	11	1.20 (0.54 to 2.65)	0.66	—	—
<50,000	3177	15	1.00			
Viral load at delivery (copies/mL)						
≥50,000 copies	606	13	7.52 (2.43 to 23.27)	0.0005	7.49 (2.36 to 23.71)	0.0006
<50,000 copies	1881	4	1.00			
HIV stage at baseline						
2+	2409	29	1.66 (1.09 to 2.55)	0.02	1.51 (0.98 to 2.32)	0.06
1	11,876	80	1.00			
Genital ulcer at baseline						
Yes	797	10	1.79 (0.93 to 3.44)	0.08	1.43 (0.74 to 2.80)	0.26
No	13,139	86	1.00			
Hemoglobin at baseline (g/dL)						
<8.5	3506	28	1.11 (0.72 to 1.71)	0.64	—	—
≥8.5	10,792	75	1.00			
Hemoglobin at delivery (g/dL)						
<8.5	995	12	1.51 (0.83 to 2.75)	0.18	1.39 (0.76 to 2.54)	0.29
≥8.5	13,410	97	1.00		1.00	
ESR at baseline (mm/h)						
≥81	3176	28	1.23 (0.80 to 1.91)	0.35	—	—
<81	10,025	71	1.00			
ESR at delivery (mm/h)						
≥81	1235	11	1.12 (0.60 to 2.09)	0.73	—	—
<81	13,170	98	1.00			

*From separate univariate Cox proportional hazards models.

†From multivariate Cox proportional hazards models. The basic multivariate model included the following variables, with indicator variables for individuals missing data on a particular variable: CD4 cell count at baseline, HIV stage at baseline, genital ulcer at baseline, hemoglobin at delivery, maternal trial regimen, and maternal education. Estimates for viral load were obtained by adding viral load to the basic multivariate model and only using subjects who had viral load measurements.

increased risk of child mortality. This is in agreement with studies from Kenya and Tanzania^{21,22} but differs from the results reported from the Zambian study,⁹ which had child follow-up only through 4 months of age and reported a significantly increased risk of mortality only in HIV-negative children. This could reflect a reduction in the risk of child mortality attributable to maternal anemia beyond early infancy in our analysis through 24 months of follow-up.

In this study, early transmission of HIV from mother to child was associated with an increased risk of death as compared with later transmission, in accord with other studies from sub-Saharan Africa,^{23–25} including a study that was based on data from the same cohort as this, which showed an increased risk of death in the first year of life if the child was diagnosed as being infected with HIV by 49 days as compared with after 49 days.²⁶ This report demonstrates that the increased risk of mortality persists beyond infancy into the second year of life.

There are several potential mechanisms for the association between maternal disease stage and child mortality. It

is possible that the children born to women with advanced HIV disease are infected from their mothers with a virulent strain of the virus and/or inherit a genetic vulnerability to disease progression because of immunologic insufficiency.^{27–29} Higher viral load in the mother exposes the child to a higher infective inoculum, which could cause rapid development of disease and death in the child.⁴ Coinfections with other pathogens are likely in women with more advanced disease, and these may be transmitted to their offspring.^{30–36} Transfer of passive immunity from mother to child in utero and through breast milk may be deficient in women with advanced disease.^{37,38} Additionally, ability to care and nurture the child is likely to be lacking in women at an advanced disease stage and has an adverse impact on child survival.

We found child undernutrition, as measured by wasting, stunting, or underweight, to be strongly associated with mortality in children born to HIV-infected women. When the anthropometric assessment was lagged by 3 months, there was attenuation of the adverse relation, but these measurements

TABLE 3. Association of Maternal HIV Disease Stage During Pregnancy With Mortality Among HIV-Infected Children

Maternal Predictors	Child-Months at Risk	No. Deaths	HR* (95% CI) (Univariate)	P*	HR† (95% CI) (Adjusted)	P†
CD4 count at baseline (cells/mm ³)						
<350	1313	58	1.45 (0.99 to 2.11)	0.06	1.38 (0.94 to 2.03)	0.09
≥350	1692	51	1.00		1.00	
CD4 count at delivery (cells/mm ³)						
<350	820	39	1.43 (0.98 to 2.10)	0.07	1.45 (0.98 to 2.14)	0.07
≥350	2368	80	1.00		1.00	
Viral load at baseline (copies/mL)						
≥50,000	1843	79	1.73 (1.06 to 2.82)	0.03	1.67 (1.01 to 2.76)	0.04
<50,000	804	20	1.00		1.00	
Viral load at delivery (copies/mL)						
≥50,000	495	18	1.21 (0.57 to 2.58)	0.62	—	—
<50,000	366	11	1.00			
HIV stage at baseline						
2+	761	28	0.97 (0.63 to 1.48)	0.87	—	—
1	2426	91	1.00			
Genital ulcer at baseline						
Yes	237	12	1.45 (0.80 to 2.63)	0.23	—	—
No	2919	104	1.00			
Hemoglobin at baseline (g/dL)						
<8.5	882	41	1.32 (0.90 to 1.93)	0.15	1.31 (0.88 to 1.94)	0.18
≥8.5	2236	77	1.00		1.00	
Hemoglobin at delivery (g/dL)						
<8.5	370	20	1.47 (0.91 to 2.38)	0.11	1.39 (0.85 to 2.27)	0.19
≥8.5	2818	99	1.00		1.00	
ESR at baseline (mm/h)						
≥81	652	36	1.55 (1.04 to 2.32)	0.03	1.46 (0.97 to 2.20)	0.07
<81	2110	71	1.00			
ESR at delivery (mm/h)						
≥1	377	19	1.44 (0.88 to 2.35)	0.15	1.30 (0.79 to 2.15)	0.31
<81	2810	100	1.00		1.00	

*From separate univariate Cox proportional hazards models.

†From multivariate Cox proportional hazards models. The basic multivariate model included the following variables, with indicator variables for individuals missing data on a particular variable: maternal trial regimen, maternal education, CD4 cell count at baseline, hemoglobin at baseline, and ESR at baseline. In separate models, CD4 cell count at delivery replaced CD4 cell count at baseline, maternal hemoglobin at delivery replaced hemoglobin at baseline, and ESR at delivery replaced ESR at baseline. Estimates for viral load were obtained by adding viral load to the basic multivariate model and only using subjects who had viral load measurements.

remained strong predictors of mortality. Wasting and stunting were significant predictors of mortality in a smaller study among children in Tanzania.³⁹ A study from the Philippines reported weight-for-age z-scores between -2 and -3 to be associated with a 3- to 15-fold increased risk of mortality depending on the child's age, and similar results were obtained in another study from Sudan.^{12,13} In a study among HIV-infected children from Uganda, an average weight-for-age z-score < -1.5 in the first year of life was associated with a nearly 5-fold (odds ratio [OR] = 4.87, 95% CI: 1.27 to 18.67) increased risk of death by 25 months.⁴⁰ Undernutrition increases the risk of child mortality as a result of infectious causes, which are responsible for the major burden of childhood mortality in developing countries; a recent analysis reported that 52.5% of young childhood deaths were attributable to undernutrition as measured by low weight for age.¹¹

The findings of this study have important public health implications for countries with a high burden of HIV infection among women of reproductive age. Many of these countries

also have high rates of child mortality and have to make major efforts to achieve the millennium development goal (MDG) of reduction of mortality in children younger than 5 years of age by two thirds by the year 2015. Programs for prevention of mother-to-child transmission (PMTCT) of HIV are increasingly becoming available, along with highly active antiretroviral therapy (HAART) for treatment of AIDS, although major gaps in coverage still remain. This highlights the urgent need to prioritize the provision of HAART and treatment of anemia to HIV-infected pregnant women who need them as part of comprehensive antenatal care. The benefits of these interventions should accrue far beyond the interruption of vertical transmission of HIV and could potentially have a significant impact on child mortality.

The findings underline the need for integrating other maternal and child health interventions with programs for treatment and care of HIV-infected women and children to have a maximum impact on child survival in regions with high HIV prevalence. These interventions include comprehensive

TABLE 4. Association of Child Malnutrition With Mortality

Child Predictors	Child-Months at Risk	No. Deaths	HR* (95% CI) (Univariate)	HR† (95% CI) (Adjusted)	P† (Adjusted)
Underweight					
Yes	1927	46	7.22 (5.01 to 10.41)	3.88 (2.66 to 5.66)	<0.0001
No	15,641	179	1.00	1.00	
Underweight (lagged by 3 mo)					
Yes	1225	21	3.84 (2.24 to 6.59)	2.23 (1.30 to 3.85)	0.004
No	16,343	204	1.00	1.00	
Stunted					
Yes	2064	39	5.21 (3.57 to 7.61)	3.00 (2.04 to 4.40)	<0.0001
No	15,504	186	1.00	1.00	
Stunted (lagged by 3 mo)					
Yes	1225	22	3.72 (2.19 to 6.34)	2.21 (1.29 to 3.77)	0.004
No	16,344	203	1.00	1.00	
Wasted					
Yes	561	24	8.40 (5.41 to 13.05)	5.35 (3.38 to 8.48)	<0.0001
No	17,008	201	1.00	1.00	
Wasted (lagged by 3 mo)					
Yes	309	8	3.54 (1.65 to 7.58)	2.45 (1.13 to 5.31)	0.02
No	17,259	217	1.00	1.00	

Underweight (weight-for-age z-score < -2), stunting (height-for-age z-score < -2) and wasting (weight-for-height z-score < -2).

*From separate univariate Cox proportional hazards models using time-varying anthropometric measurements.

†From separate multivariate Cox proportional hazards models using time-varying anthropometric measurements and adjusted for maternal CD4 cell count at baseline, maternal education, maternal trial regimen, and the following time-varying child variables: CD4 cell count, HIV status, and breast-feeding status (lagged by 3 months).

care and treatment for opportunistic infections and anemia during pregnancy and prevention and treatment of childhood malnutrition.

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