

Child mortality in relation to HIV infection, nutritional status, and socio-economic background

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Background The aims of this study were to examine the impact of child HIV infection on mortality and to identify nutritional and sociodemographic factors that increase the risk of child mortality independent of human immunodeficiency virus (HIV) infection.

Methods We conducted a prospective study in Dar es Salaam, Tanzania, among 687 children 6–60 months of age who were admitted to hospital with pneumonia. After discharge, children were followed up every 2 weeks during the first year and every 4 months thereafter. Sociodemographic characteristics were determined at baseline, and HIV status, haemoglobin, and malaria infection were assessed from a blood sample. During the first year of follow-up, we measured height, weight, and mid-upper arm circumference (MUAC) monthly. We estimated the risk of mortality according to HIV status and socio-economic characteristics using Cox proportional hazards models. Nutritional status variables (wasting and stunting) were examined as time-varying risk factors.

Results Mean age at enrolment was 18 months. A total of 90 children died during an average 24.7 months of follow-up. HIV infection was associated with an adjusted 4-fold higher risk of mortality [relative risk (RR) = 3.92, 95% confidence interval (CI) 2.34–6.55, $P < 0.0001$]. Other risk factors included child's age <24 months, stunting, low MUAC, anaemia, and lack of water supply in the household. In models with time-varying covariates, stunting and wasting during the previous month were both significant and independently related to increased risk of death. HIV infection appeared to be a stronger predictor of mortality among children who were wasted than among those who were not (P for interaction = 0.05).

Conclusions HIV infection is a strong predictor of death among children who have been hospitalized with pneumonia. Preventable conditions including inadequate water supply, child undernutrition, and anaemia contribute significantly to infant and child mortality independent of HIV infection.

Keywords Child mortality, infant mortality, HIV, stunting, wasting, anaemia, water

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The increasing incidence of human immunodeficiency virus (HIV) infection in sub-Saharan Africa is being matched by a rise in mortality from AIDS.¹ Among children, the epidemic threatens to set back the significant reductions in infant and child mortality that the region had achieved during the past decades.² In Tanzania, for example, child mortality is reported to have risen from 137 per 1000 in 1992–1996 to 147 per 1000 in 1995–1999.³

Although the relative importance of HIV infection on the risk of child death was recognized early in the epidemic,⁴ few

studies have quantified the impact of child-HIV status on infant and child mortality in Africa. Mortality before 2–3 years of age has been reported to be between 7 and 18 times higher for HIV-infected than HIV-uninfected infants,^{5–8} whereas mortality by the age of 5 can be up to 21 times higher for HIV-infected compared with HIV-uninfected children.⁹ Some of these estimates, however, are not adjusted for other highly prevalent risk factors of child death which at the same time may worsen the course of untreated HIV infection.

It is unclear to what extent previously known predictors of child survival, including sanitation, maternal education, socio-economic conditions, and the child's nutritional status, still constitute risk factors for child mortality in settings where HIV infection has become a substantial contributing cause to the incidence of child deaths and specific antiretroviral treatment is not widely available yet. The study of risk factors for child mortality in the era of HIV could help identify preventable conditions to improve child survival.

Using data from a vitamin A supplementation trial, we examined the risk factors for mortality in a cohort of Tanzanian children 6–60 months of age at recruitment, who were followed up for an average 2 years.

Methods

The vitamin A trial was conducted between 1993 and 1997 among 687 children admitted with pneumonia to the Muhimbili Medical Center in Dar es Salaam, with the purpose of determining the effect of vitamin A on severity of infection during hospital stay. Children were followed up after discharge from the hospital to assess the effect of supplements on mortality, morbidity, and growth endpoints. Details of the study have been published elsewhere.¹⁰ In brief, children 6–60 months of age who were admitted with pneumonia and who were free of signs and symptoms of vitamin A deficiency were randomly assigned to receive placebo or one oral dose of 200 000 IU (100 000 if ≤ 12 months) vitamin A on the day of admission, a second dose the following day, and a third and fourth dose at 4 and 8 months, respectively, after discharge from the hospital. Children with baseline weight-for-age $< 60\%$ of the World Health Organization median, those who had measles, pulmonary tuberculosis, whooping cough, or xerophthalmia, or those who had received vitamin A supplements in the preceding 4 months were excluded. Verbal informed consent was sought from the mother or primary caregiver of the child for participation in the study.

At baseline, study personnel obtained information from the child's caregiver on feeding practices, immunization, and sociodemographic variables such as parental age, education and occupation, quality of housing and water supply, and number and type of household possessions. A study physician conducted a complete clinical examination, and trained staff obtained anthropometric measurements using standardized procedures. We sought consent from the caregiver to obtain a blood sample at baseline and, from a subset of children, at 4 months and/or 8 months after discharge from the initial hospitalization. A complete blood count was done with standard techniques,¹¹ and malaria infection was assessed by thick and thin blood smears stained with Giemsa. After the end of follow-up, the latest blood specimen available for each child was anonymously

tested for HIV antibodies using enzyme-linked immunosorbent assay (Murex Biotech Ltd, Dartford, United Kingdom) and confirmed by Western blot (Biorad Laboratories, Ltd, Hertfordshire, United Kingdom). HIV status of children who were younger than 15 months and had positive or indeterminate results was also tested using amplified heat-denatured HIV-p24 antigen assays with confirmatory neutralization assays (DuPont, Wilmington, DE). In a previous study conducted in Tanzania, this heat-denatured assay had a sensitivity of 98.7% and a specificity of 100% for detecting HIV infection in infant specimens, including children who were older than 6 months of age, when compared with polymerase chain reaction tests.¹² HIV status was known for 648 of the 687 children enrolled. Antiretroviral therapy was not available in this setting at the time of the study.

Survival status was assessed during monthly visits to the clinic by the child and caregiver, and home visits by research staff 2 weeks after each clinic visit. At every clinic visit, a trained study nurse obtained anthropometric measurements using standardized procedures and a study physician carried out a complete medical examination. Mothers were asked whether the child was being breastfed, and the time of cessation since the previous visit for those who indicated that the child was not being breastfed. After one year into the study, follow-up was conducted through home visits every 4 months. The mean duration of follow-up was 24.7 months (SD = 12.3, median = 28.2). In June 1996, survival status was known for 611 children. Of the remaining 76 from the 687 enrolled, 18 discharged themselves from hospital and could not be traced and 58 moved out of the study area or within the city and their new address was not known.

We examined predictors of total mortality that included HIV infection and other baseline characteristics, breastfeeding, and anthropometric indicators of the nutritional status during follow-up. Baseline predictors included the child's sex, age in months (6–11, 12–23, or ≥ 24), stunting (height-for-age z-score < -2 according to the NCHS/WHO reference¹³), wasting (weight-for-height z-score < -2), low mid-upper arm circumference (MUAC, < 25 th percentile of the age-specific population distribution), haemoglobin concentration, lymphocytes count, and erythrocyte sedimentation rate (quartiles), and malaria infection (presence of parasites in blood film). We also examined as independent covariates the duration of exclusive breastfeeding ($>$ or ≤ 4 months), mother's age, education, occupation (housewife or working outside home), parity, and whether she cohabited with a partner, the type of water supply in the household, whether there was electricity at home, the number of household amenities from a list including car, refrigerator, radio, bicycle, and television, whether the child slept under a bednet, and whether the episode of pneumonia on admission to hospital was a severe one (either of: respiratory rate $> 60/\text{min}$, high fever $\geq 39^\circ\text{C}$, or severe hypoxaemia $< 90\%$ ^{14,15}). We estimated the proportion of child deaths within levels of each predictor, and used Cox proportional hazards models to examine the associations between each predictor and time-to-death.¹⁶ A multivariable adjusted model was fitted with the predictors that were statistically significant at $P \leq 0.10$ in univariate analyses; however, only those that remained significant at $P \leq 0.05$ were retained in the final model. We have reported that vitamin A supplementation

significantly reduced mortality;¹⁷ therefore, regimen assignment (vitamin A or placebo) was also included in the multivariable model.

Time-dependent predictors updated every month included indicators of the nutritional status (stunting, wasting, and low weight-for-age) and breastfeeding status (yes/no). Hazard ratios and 95% confidence intervals (CIs) for each time-dependent predictor were obtained from multivariable Cox models that included the same adjusting variables as the model for baseline covariates. For nutritional indicators and breastfeeding, the interval between two consecutive visits for each child defined a risk set. The exposure (i.e. stunting) was evaluated at the beginning of each risk set and the outcome (death or censored) at the end. Given that information on time-varying breastfeeding and nutritional indicators was available only during the first year of follow-up, we examined their associations with mortality during the whole follow-up period as well as during the first year only. Finally, we examined whether the association between HIV infection and mortality was modified by any of the other risk factors. We also assessed potential interactions between baseline covariates and breastfeeding status as a time-varying covariate evaluated at the beginning of each risk set on the risk of death. A partial likelihood ratio test was used to assess the statistical significance of interactions. Data were analysed with Statistical Analyses System software (SAS Institute Inc. Cary, NC).

The protocol was approved by the Research and Publications Committee of Muhimbili University College of Health Sciences, the Research and Ethics Committee of Tanzania Food and Nutrition Center, and the Human Subjects Committee of the Harvard School of Public Health.

Results

Mean age at enrolment was 17.6 months (SD = 12.1, median = 13.0) with 42% <12 months; 46% of children were female. Among the 624 children with known nutritional status at baseline, 29% were stunted and 18% were wasted; also, 25% were severely anaemic (haemoglobin concentration ≤ 7 g/dl), and 26% had positive blood smears for malaria. The majority came from households without tap water (83%) and with less than two amenities from a list that included car, refrigerator, radio, bicycle, and television (77%). 87% of the children's mothers had completed secondary education. The prevalence of breastfeeding at recruitment was 98%, 84%, and 10% for the age groups 6–11, 12–23, and ≥ 24 months, respectively. All children had been introduced to complementary foods. Of the 648 children for whom HIV status was known, 58 (9%) were infected.

Among the 687 children enrolled, there were 90 deaths over an average 24.7 months of follow-up. The majority ($n = 76$) occurred during the first year after recruitment, and 21 of them during the initial hospitalization for pneumonia. HIV infection was the strongest predictor of child mortality in this population (Table 1); HIV-infected children had a 4-fold higher risk of death compared with those uninfected ($P < 0.0001$), after adjusting for a number of potential confounders. In the same multivariable model, mortality decreased significantly with age: compared with children ≥ 24 months of age, the adjusted risk of death was 3.7 times higher for infants ($P < 0.001$) and 3.1 times higher for

children 12–23 months ($P = 0.004$). Baseline stunting and low MUAC were independently related to 2.1- and 1.9-fold increased risk of death, respectively. There were significant inverse trends in mortality by categories of haemoglobin concentration at baseline (P , test for trend = 0.02), and by the quality of water supply in the household (P , test for trend = 0.006); mortality was three times higher among children living in houses with water from public wells, compared with children with running water at home. Higher maternal education was significantly related to decreased mortality risk only in univariate analysis. Baseline characteristics that were not significantly associated with child mortality included wasting (low weight-for-height), lymphocyte count, erythrocyte sedimentation rate, malaria infection, duration of exclusive breastfeeding, mother's age, parity, or whether she cohabited with a partner, whether there was electricity at home, and whether the child slept under a bednet.

We next examined the associations between indicators of the nutritional status as time-varying characteristics during the first year of follow-up and the risk of death during both the first year and the whole follow-up period (Table 2). During the first year of follow-up, the adjusted risk of death among children who were stunted at the previous clinic visit (33 days before, on average) was 2.3 times higher than that of children who were not stunted ($P = 0.003$). The association was slightly attenuated after further adjustment for wasting (low weight-for-height) at the previous clinic visit [relative risk (RR) = 1.83; 95% CI 1.03–3.25; $P = 0.04$]. When the whole follow-up period was considered including deaths that occurred after the first year, stunting at the last visit during the first year was associated with a significant 2-fold increased risk of death. Wasting at the previous clinic visit was associated with a 2.5 increased adjusted risk of death during the first year of follow-up ($P = 0.0002$). After further adjustment for stunting, the independent RR for wasting was 1.94 (95% CI 1.16–3.25; $P = 0.01$). The risk of death during the whole follow-up period was 2.9 times higher for children who had been wasted during the first year, compared with children who were not wasted. Low weight-for-age was not significantly related to child mortality in this population.

Cessation of breastfeeding was also examined in relation to child mortality as a time-varying covariate. In multivariable analysis there was a 2.3-fold increased risk of death associated with cessation of breastfeeding before or at the time of the previous clinic visit (RR = 2.33; 95% CI 0.98–5.52; $P = 0.06$). Breastfeeding appeared to modify the association between the quality of water supply and child mortality (P , test for interaction = 0.05). Among breastfed children, lack of water in the household was not associated with mortality (RR = 1.11; 95% CI 0.48–2.55); in contrast, it was related to a significant 5-fold increased risk of death among children who had stopped breastfeeding (RR = 5.24; 95% CI 1.16–23.5) after controlling for other risk factors.

Finally, we examined the association between HIV infection and mortality within levels of potential effect modifiers (Table 3). The increased risk in mortality attributable to HIV infection appeared to be higher among wasted children compared with those who were not wasted (P , test for interaction = 0.05), after adjusting for potential confounders. Mortality associated with HIV infection also appeared to be

Table 1 Child mortality according to baseline characteristics

Characteristic	N at risk ^a	Number of deaths (%)	Unadjusted hazard ratio (95% CI) ^b	Adjusted hazard ratio (95% CI) ^c	Adjusted <i>P</i> ^c
HIV status					
Negative	590	57 (9.7)	1.00	1.00	
Positive	58	23 (39.7)	4.61 (2.84–7.49)	3.92 (2.34–6.55)	<0.0001
Child's sex					
Female	313	42 (13.4)	1.00	—	—
Male	371	47 (12.7)	0.98 (0.65–1.48)	—	—
Child's age (months)					
6–11	287	48 (16.7)	3.61 (1.71, 7.63)	3.70 (1.72–7.95)*	<0.001
12–23	237	34 (14.3)	3.12 (1.44–6.73)	3.14 (1.44–6.88)	0.004
≥24	163	8 (4.9)	1.00	1.00	
Stunted at baseline^d					
No	443	42 (9.5)	1.00	1.00	
Yes	181	35 (19.3)	2.12 (1.35–3.32)	2.12 (1.31–3.42)	0.002
Low MUAC at baseline^e					
No	416	35 (8.4)	1.00	1.00	
Yes	212	43 (20.3)	2.53 (1.62–3.95)	1.88 (1.16–3.03)	0.01
Haemoglobin concentration (g/dl)					
≤7.00	156	27 (17.3)	3.93 (1.78–8.64)	2.55 (1.13–5.77)**	0.02
7.01–8.50	142	25 (17.6)	3.88 (1.75–8.61)	2.81 (1.24–6.37)	0.01
8.51–10.00	154	18 (11.7)	2.48 (1.08–5.71)	1.76 (0.75–4.10)	0.19
>10.00	164	8 (4.9)	1.00	1.00	
Severe pneumonia on admission^f					
No	416	33 (7.9)	1.00	1.00	
Yes	266	55 (20.7)	2.61 (1.71–3.98)	2.47 (1.59–3.85)	<0.0001
Quality of water supply					
Tap in house	114	7 (6.1)	1.00	1.00	
Tap in compound	191	24 (12.6)	2.02 (0.87–4.69)	1.40 (0.60–3.29)	0.44
Tap outside compound	346	51 (14.7)	2.45 (1.11–5.39)	2.27 (1.02–5.03)	0.04
Public well	35	8 (22.9)	3.76 (1.36–10.4)	2.92 (1.03–8.30)***	0.04
Mother's level of education					
None/illiterate	91	14 (15.4)	1.00	—	—
Elementary	551	74 (13.4)	0.84 (0.48–1.49)	—	—
Secondary or higher	44	2 (4.5)	0.27 (0.06–1.17)	—	—
Mother works outside home					
No	500	73 (14.6)	1.00	—	—
Yes	186	17 (9.1)	0.61 (0.36–1.03)	—	—
Mother lives with partner					
Yes	564	67 (11.9)	1.00	—	—
No	122	23 (18.9)	1.60 (1.00–2.57)	—	—
Number of household amenities^g					
None	98	18 (18.4)	1.58 (0.92–2.69)	—	—
1	430	53 (12.3)	1.00	—	—
≤2	158	19 (12.0)	0.95 (0.56–1.60)	—	—

^a Totals may not add up to 687 due to missing values.^b From individual univariate Cox proportional hazards models with time-to-death as the outcome and indicator variables for each level of exposure. CI, confidence intervals.^c From a multivariable Cox proportional-hazards model with time-to-death as the outcome and the following indicator variables as predictors: child's age (2 indicators), stunted (1 for stunted and 1 for missing), MUAC (1 for low MUAC and 1 for missing), haemoglobin concentrations (3 indicators and 1 for missing), severe pneumonia (1 indicator), HIV status (1 indicator for HIV-positive and 1 for missing), quality of water supply (3 indicators), and vitamin A supplementation (1 indicator). Adjusted *P*-value, test for trend, when the variable is introduced into the multivariable model as continuous: *0.001, **0.002, ***0.006.^d Stunted children were <−2 z-scores (NCHS/WHO reference) in height-for-age. Wasted children were <−2 z-scores in weight-for-height.^e MUAC <25th percentile of the population age-specific distribution.^f Severe pneumonia was defined as having either rapid respiratory rate (>60/min), high fever (≥39°C), or severe hypoxaemia (oxygen saturation <90%) on admission.^g From a list of five items: car, refrigerator, radio, bicycle, and television.

Table 2 Risk of child mortality according to anthropometric status during follow-up

Anthropometric indicator ^a	No. of child-months	No. of deaths	Unadjusted hazard ratio (95% CI) ^b	Adjusted hazard ratio (95% CI) ^c	Adjusted <i>P</i>
Height-for-age					
First year of follow-up					
Not stunted	3095	30	1.00	1.00	0.003
Stunted	1824	34	2.28 (1.39–3.74)	2.25 (1.32–3.84)	
Total follow-up period					
Not stunted	8704	33	1.00	1.00	0.005
Stunted	6257	41	2.31 (1.45–3.67)	2.00 (1.23–3.26)	
Weight-for-height					
First year of follow-up					
Not wasted	4135	34	1.00	1.00	0.0002
Wasted	1428	38	2.84 (1.78–4.52)	2.47 (1.53–3.98)	
Total follow-up period					
Not wasted	12 691	37	1.00	1.00	<0.0001
Wasted	3841	46	3.38 (2.18–5.22)	2.89 (1.84–4.53)	
Weight-for-age					
First year of follow-up					
Not underweight	4516	47	1.00	1.00	0.08
Underweight	309	13	2.42 (1.26–4.64)	1.80 (0.92–3.51)	
Total follow-up period					
Not underweight	13 966	57	1.00	1.00	0.17
Underweight	676	13	2.19 (1.17–4.11)	1.57 (0.82–3.00)	

^a Stunted children were <-2 z-scores (NCHS/WHO reference) in height-for-age. Wasted children were <-2 z-scores in weight-for-height. Underweight children were <-2 z-scores in weight-for-age.

^b From individual univariate Cox proportional hazards models: outcome variable is time-to-death and time metameter is number of days between visits. The exposure (stunting, wasting, or underweight) is time-dependent; assessed at the beginning of each time interval. Average time between visits is 90 days when total time of follow-up is considered, and 33 days when the first year of follow-up is considered. CI, confidence intervals.

^c From multivariable Cox proportional hazards models (one for each anthropometric indicator): outcome variable is time-to-death and time metameter is number of days between visits. In addition to the anthropometric exposure (stunting, wasting, or underweight), indicator variables for the following adjusting predictors are included: child's age (2 indicators), MUAC (1 for low MUAC and 1 for missing), haemoglobin concentrations (3 indicators and 1 for missing), severe pneumonia (1 indicator), HIV status (1 indicator for HIV-positive and 1 for missing), quality of water supply (3 indicators), and vitamin A supplementation (1 indicator). MUAC indicators were excluded from the models for wasting and underweight.

higher among infants compared with children ≥ 1 year of age and among children with severe anaemia compared with those with haemoglobin >7 g/dl; however, the interaction terms were not statistically significant. Stunting, cessation of breastfeeding, and indicators of poor socio-economic status did not modify the association between HIV status and the risk of child death.

Discussion

We characterized risk factors for mortality in a cohort of 687 Tanzanian children who had been hospitalized with pneumonia and who were followed up for an average 2 years after discharge from hospital. The strongest predictor of mortality in this population was HIV infection. Other predictors included the child's age, stunting and wasting, poor quality of water supply, low haemoglobin concentrations, and cessation of breastfeeding.

Our crude relative hazard estimate for the association between HIV infection and child mortality in children 6–60 months of age (RR = 4.6) is lower than the estimates reported

from other studies in Africa, including a birth cohort followed up to 36 months in Zaire (RR = 7.3),⁵ one in Kenya among children born to HIV-positive mothers who were followed up to 24 months (RR = 9.0),⁷ a study in Malawi among children followed up from 1 to 3 years of age (RR = 9.2),⁶ a trial of mother-to-child transmission prevention in Côte d'Ivoire and Burkina Faso among children followed up from birth up to 18 months (RR = 18.1 for infection <12 days of age and 7.6 for infection ≥ 13 days),⁸ and a study in Rwandan children followed from birth to 60 months of age (RR = 20.7).⁹

Some limitations in our study could partially explain the lower estimate we obtained. First, we only recruited children who were 6 months or older; some children who were infected with HIV prior to 6 months may have died before having the chance of becoming part of our study cohort. This would result in an underestimation of the association if their death was HIV related. Similarly, HIV-infected children recruited at older ages would represent only those who had survived by the time of enrolment. This possibility is consistent with the observed decline in the prevalence of HIV infection with age at

Table 3 Association between HIV infection and mortality within levels of potential effect modifiers

Potential modifier	HR (95% CI) ^a HIV(+)/HIV(-)	P, test for interaction ^b
Child's age (months) at baseline		0.26
<12	5.30 (2.68–10.5)	
≥12	2.92 (1.31–6.50)	
Haemoglobin concentration (g/dl) at baseline		0.20
≤7.00	7.62 (3.27–17.8)	
>7.00	3.73 (1.85–7.50)	
Wasting during follow-up		0.05
No	1.56 (0.53–4.57)	
Yes	5.16 (2.52–10.6)	
Breastfeeding status during follow-up		0.73
Weaned	5.69 (1.90–17.0)	
Not weaned	7.34 (2.97–18.2)	

^a Hazard ratios (HR) and 95% confidence intervals (95% CI) for the risk of death between HIV(+) and HIV(-) children, by levels of potential modifiers. One Cox proportional hazards model was fitted for each effect modifier with time-to-death as the outcome and predictors that included HIV status, the potential modifier, and their cross-product term. Wasting and breastfeeding during follow-up were treated as time-varying covariates updated at the beginning of each risk set in their corresponding models. All models were adjusted for child's age, stunting, haemoglobin concentration (except the model for anaemia), severity of pneumonia at baseline, quality of water supply, and vitamin A supplementation.

^b From a partial likelihood ratio test.

recruitment in this cohort: 36%, 40%, 10%, 7%, and 7% for recruitment age groups 6–11, 12–23, 24–35, 36–47, and ≥48 months, respectively. Second, we lacked an accurate estimate of age at HIV transmission and only tested the last available sample during follow-up (at 4 or 8 months after recruitment). In populations with prolonged breastfeeding, mother-to-child transmission of HIV may occur after 6 months of age.¹⁸ It is possible that some children who tested negative, especially the youngest at recruitment, may have become infected through breastfeeding during the follow-up period, after their last sample was collected; these children would have been treated in the analyses as uninfected, and the association between HIV status and mortality may have been biased towards the null value. Third, we examined the impact of HIV infection on all-cause mortality. The inclusion of deaths that could have not been directly attributed to HIV/AIDS (e.g. accidents) could result in an attenuation of the association. Fourth, confounding may be an important source of bias in observational studies, and we lacked information on some risk factors for child mortality that could have confounded some of the associations observed, including birth weight, HIV status of the mother, inter-pregnancy interval, and access and utilization of health services.^{19–21} Varying patterns of confounding across study populations might explain differences in the estimates of the association between HIV infection and child mortality.

Another limitation of our study is that children in this cohort were recruited during a pneumonia episode that required

hospitalization. On the one hand, these children's risk of death was probably higher than that of the general population of Tanzanian children. On the other hand, HIV infection and other risk factors for mortality could have predisposed children to the index episode of pneumonia that made them eligible for inclusion in the study cohort.

In settings where access to antiretroviral therapy is limited, it is relevant to account for factors that increase the risk of child death independent of HIV, since prevention and alleviation of those factors could improve health and survival in populations where HIV infection is a new competing cause of mortality. We found that lack of running water in the house or compound and haemoglobin ≤8.5 g/dl were significant and independent risk factors for mortality. There is a large body of evidence on the impact that interventions aimed at eliminating these factors could have in reducing child mortality in less-developed countries. Increasing access to safe water can result in up to 30% reductions in child mortality, possibly due to decreased rates of gastrointestinal infections.²² Prevention and treatment of the common causes of anaemia in children, such as low dietary intake of iron and other nutrients, malaria, and intestinal parasitoses are likely to decrease the burden of child mortality in sub-Saharan Africa. Available inexpensive interventions include the provision of impregnated mosquito nets to prevent malaria infection,²³ intermittent malaria prophylaxis and iron supplementation,²⁴ and periodic anthelmintic treatment.²⁵

The associations we found between stunting or wasting and child mortality are in agreement with the results from previous studies conducted in Africa and Asia.^{26,27} The impact of anthropometric indicators on mortality is augmented by the incidence of infections in a multiplicative synergistic manner,²⁸ and this interaction appears to be particularly strong for indicators of wasting.^{27–29} Although such synergism is well documented with diarrhoeal, respiratory, measles, and malaria infections; the evidence for paediatric HIV infection is scarce from longitudinal studies. Increased risk of death in relation to wasting has been reported in studies of HIV-positive children,^{6,30,31} but a formal interaction between wasting and HIV infection has not been tested to our knowledge. Our results suggest that such an interaction exists, since the excess risk of death attributable to HIV infection was higher among children who were wasted compared with those who were not wasted. Although we cannot determine whether wasting in our study was the consequence of HIV infection or whether it was present before transmission occurred, the existence of synergism between malnutrition and HIV on mortality suggests that the evaluation of nutritional interventions should be prioritized among HIV-infected children. Micronutrient supplementation could be one of those interventions, as it decreases the risk of wasting and disease progression among HIV-infected women.^{32,33} clinical trials evaluating the effect of micronutrients among HIV-infected children are currently ongoing. The potential effect of protein and energy supplementation also deserves evaluation.

Our study has several strengths. First, the rate of follow-up was high, and the median duration was long (>2 years). Second, we examined a large number of important predictors of death that had not been reported in previous longitudinal studies of child mortality in Africa. For some of the predictors studied, including the nutritional and breastfeeding status, we were able

to update the exposure status over time; this is particularly important for characteristics that would depend on each child's age at baseline and the duration of follow-up, such as breastfeeding. Third, although some estimates of the impact of HIV on child mortality in Africa exist in the literature, several of them were not adjusted for the potential confounding effects of nutritional and socio-economic characteristics; our estimate was adjusted for other important risk factors of mortality. Fourth, we were able to examine the interactions between nutritional and sociodemographic variables and HIV infection on child mortality. Finally, we studied a cohort that was relatively large in comparison with some of those studied previously.⁷⁻⁹

We conclude that HIV infection is a strong risk factor for mortality in Tanzania, among children who were hospitalized with pneumonia. Efforts towards prevention of mother-to-child transmission of HIV are likely to result in significant improvements in child survival. Previously recognized risk

factors for child mortality in sub-Saharan Africa continue to take a high toll, independent of HIV infection; well-known public health interventions, including improved water supply, alleviation of malnutrition, and treatment and prevention of anaemia could improve child survival even in HIV-endemic populations. The fact that these measures should be implemented in the whole population regardless of HIV infection does not exclude the importance of preventing HIV transmission and ensuring access to antiretroviral treatment for children who become infected.

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KEY MESSAGES

- HIV infection is a strong predictor of mortality in pre-school children from Tanzania.
- Preventable conditions including stunting, wasting, anaemia, and lack of safe water in the household continue to be important predictors of mortality, independent of HIV infection.
- The impact of child HIV infection on mortality is significantly greater among children who are wasted compared with those who are not.

References

- UNAIDS. *AIDS Epidemic Update*. Geneva: UNAIDS, 2003.
- Ahmad OB, Lopez AD, Inoue M. The decline in child mortality: a reappraisal. *Bull World Health Organ* 2000;**78**:1175-91.
- Ng'weshemi J, Urassa M, Isingo R *et al*. HIV impact on mother and child mortality in rural Tanzania. *J Acquir Immune Defic Syndr* 2003;**33**:393-404.
- Mann JM, Francis H, Davachi F *et al*. Human immunodeficiency virus seroprevalence in pediatric patients 2 to 14 years of age at Mama Yemo Hospital, Kinshasa, Zaire. *Pediatrics* 1986;**78**:673-77.
- Ryder RW, Nsuami M, Nsa W *et al*. Mortality in HIV-1-seropositive women, their spouses and their newly born children during 36 months of follow-up in Kinshasa, Zaire. *AIDS* 1994;**8**:667-72.
- Taha TE, Kumwenda NI, Broadhead RL *et al*. Mortality after the first year of life among human immunodeficiency virus type 1-infected and uninfected children. *Pediatr Infect Dis J* 1999;**18**:689-94.
- Mbori-Ngacha D, Nduati R, John G *et al*. Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: A randomized clinical trial. *JAMA* 2001;**286**:2413-20.
- Dabis F, Elenga N, Meda N *et al*. 18-Month mortality and perinatal exposure to zidovudine in West Africa. *AIDS* 2001;**15**:771-79.
- Spira R, Lepage P, Msellati P *et al*. Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. *Pediatrics* 1999;**104**:e56.
- Fawzi WW, Mbise RL, Fataki MR *et al*. Vitamin A supplements and severity of pneumonia among children admitted to hospital in Dar es Salaam, Tanzania. *Am J Clin Nutr* 1998;**68**:187-92.
- Dacie JV, Lewis SM. *Practical Hematology*. London: Churchill-Livingstone, 1994.
- Lyamuya E, Bredberg-Raden U, Massawe A *et al*. Performance of a modified HIV-1 p24 antigen assay for early diagnosis of HIV-1 infection in infants and prediction of mother-to-infant transmission of HIV-1 in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;**12**:421-26.
- World Health Organization. *Measuring Change in Nutritional Status*. Geneva: WHO, 1983.
- English M, Berkley J, Mwangi I *et al*. Hypothetical performance of syndrome-based management of acute paediatric admissions of children aged more than 60 days in a Kenyan district hospital. *Bull World Health Organ* 2003;**81**:166-73.
- Djelantik IG, Gessner BD, Sutanto A *et al*. Case fatality proportions and predictive factors for mortality among children hospitalized with severe pneumonia in a rural developing country setting. *J Trop Pediatr* 2003;**49**:327-32.
- Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: Wiley, 1980.
- Fawzi WW, Mbise RL, Hertmark E *et al*. A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *Pediatr Infect Dis J* 1999;**18**:127-33.
- Fawzi W, Msamanga G, Spiegelman D *et al*. Transmission of HIV-1 through breastfeeding among women in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr* 2002;**31**:331-38.
- Nakiyingi JS, Bracher M, Whitworth JA *et al*. Child survival in relation to mother's HIV infection and survival: evidence from a Ugandan cohort study. *AIDS* 2003;**17**:1827-34.

- ²⁰ Bloland P, Slutsker L, Steketee RW, Wirima JJ, Heymann DL, Breman JG. Rates and risk factors for mortality during the first two years of life in rural Malawi. *Am J Trop Med Hyg* 1996;**55**:82–86.
- ²¹ Coodley GO, Coodley MK. A trial of testosterone therapy for HIV-associated weight loss. *AIDS* 1997;**11**:1347–52.
- ²² Esrey SA, Feachem RG, Hughes JM. Interventions for the control of diarrhoeal diseases among young children: improving water supplies and excreta disposal facilities. *Bull World Health Organ* 1985;**63**:757–72.
- ²³ Hawley WA, Phillips-Howard PA, ter Kuile FO *et al.* Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. *Am J Trop Med Hyg* 2003;**68**:121–27.
- ²⁴ Massaga JJ, Kitua AY, Lemnge MM *et al.* Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *Lancet* 2003;**361**:1853–60.
- ²⁵ Stoltzfus RJ, Chway HM, Montresor A *et al.* Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelmintic treatment improves growth, appetite and anemia in Zanzibari preschool children. *J Nutr* 2004;**134**:348–56.
- ²⁶ Pelletier DL. The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research. *J Nutr* 1994;**124**:2047S–81S.
- ²⁷ Fawzi WW, Herrera MG, Spiegelman DL, el Amin A, Nestel P, Mohamed KA. A prospective study of malnutrition in relation to child mortality in the Sudan. *Am J Clin Nutr* 1997;**65**:1062–69.
- ²⁸ Pelletier DL, Frongillo EA, Jr., Habicht JP. Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. *Am J Public Health* 1993;**83**:1130–33.
- ²⁹ Caulfield LE, de Onis M, Blossner M, Black RE. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. *Am J Clin Nutr* 2004;**80**:193–98.
- ³⁰ Berhane R, Bagenda D, Marum L *et al.* Growth failure as a prognostic indicator of mortality in pediatric HIV infection. *Pediatrics* 1997;**100**:E7.
- ³¹ Lepage P, Msellati P, Hitimana DG *et al.* Growth of human immunodeficiency type 1-infected and uninfected children: a prospective cohort study in Kigali, Rwanda, 1988 to 1993. *Pediatr Infect Dis J* 1996;**15**:479–85.
- ³² Villamor E, Msamanga G, Spiegelman D *et al.* Effect of multivitamin and vitamin A supplements on weight gain during pregnancy among HIV-1-infected women. *Am J Clin Nutr* 2002;**76**:1082–90.
- ³³ Fawzi WW, Msamanga GI, Spiegelman D *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004;**351**:23–32.