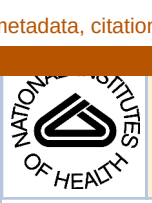

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Predictors for mortality and loss to follow-up among children receiving anti-retroviral therapy in Lilongwe, Malawi

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Summary

OBJECTIVES—To determine predictors of mortality in children on anti-retroviral therapy (ART) who attended the Paediatric HIV Clinic at Kamuzu Central Hospital in Lilongwe, Malawi.

METHODS—Retrospective case cohort study by chart review of children who had started ART between October 2004 and May 2006. Bivariable and multivariable analysis were performed with and without defaulters to evaluate associations according to vital status and to identify independent predictors of mortality.

RESULTS—Forty-one of 258 children (15.9%) were deceased, 185 (71.7%) were alive, and 32 (12.4%) had defaulted: 51% were female, 7% were under 18 months, 26% were 18 months to 5 years, and 54% were >5 years of age. Most were WHO stage III or IV (56% and 37%, respectively). On multivariate analysis, factors most strongly associated with mortality and defaulting were age <18 months [hazards ratio (HR) 2.11 (95% CI 1.0–4.51)] and WHO stage IV [HR 2.00 (95% CI 1.07–3.76)].

CONCLUSIONS—To improve outcomes of HIV-positive children, they must be identified and treated early, specifically children under 18 months of age. Access to infant diagnostic procedures must be improved to allow effective initiation of ART in infants at higher risk of death.

Keywords

Malawi; HIV/AIDS; paediatrics; mortality; anti-retroviral therapy

Introduction

Malawi is a nation of more than 13.5 million people, where more than 14% of young adults are infected with HIV (United States Central Intelligence Agency 2007). Up to 90 000 of the

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approximately 1 million HIV-infected individuals in Malawi are children (UNAIDS 2006), who become infected prenatally, perinatally during delivery, or postnatally via breast milk. In Malawi, HIV/AIDS has reduced the life expectancy at birth to 43 years (United States Central Intelligence Agency 2007).

Anti-retroviral therapy (ART) can drastically improve survival of HIV-infected individuals, even in poor settings (Mocroft *et al*. 1998; Egger *et al*. 2002; Eley *et al*. 2006; Little *et al*. 2007; Walker *et al*. 2007). The Malawian Ministry of Health has greatly increased ART distribution since June 2004 through a free anti-retroviral drug provision programme. Distribution to adults has progressed well: 146 856 individuals were receiving therapy by December 2007 (Lowrance *et al*. 2007). But treatment of children has lagged behind: only 8% of the total ART distribution is given to children under 13 years of age, although children comprise 10–15% of cases, according to national estimates (Makombe *et al*. 2006; MoH Malawi 2007). As of December 2007, 11 865 children had been started on ART (MoH Malawi 2007).

Mortality remains relatively high in Malawians receiving ART. Approximately 10–15% of individuals die within 15 months of ART initiation, most within the first 3 months (Etard *et al*. 2006; Zachariah *et al*. 2006; Zijlstra & van Oosterhout 2006; Callens *et al*. 2009). Among adults on ART, anaemia, low body mass index, low CD4 count (<50) or advanced WHO staging (IV), and Kaposi's sarcoma predict mortality (Zachariah *et al*. 2006; Boyd & Cooper 2007; Walker *et al*. 2007). In children younger than 15 years, WHO stage IV, severe wasting, low total lymphocyte count, and low CD4 count and percentage appear to contribute to early mortality (HIV Paediatric Prognostic Markers Collaborative Study 2005; Bolton-Moore *et al*. 2007; Bong *et al*. 2007; Kiboneka *et al*. 2008). Demographic factors may also play an important role in children's survival (Ntozi *et al*. 1997). There is not enough information on HIV care and clinical outcomes in children, mainly because relatively few children receive ART. Hence our aim was to examine the characteristics of HIV-infected children receiving ART in Lilongwe, Malawi and to determine factors associated with mortality.

Materials and methods

Study design

We conducted a retrospective case cohort study using data from the paper medical record system in the Paediatric HIV Clinic at Kamuzu Central Hospital (KCH). In a case cohort design, a sample of the entire available cohort is selected. This subcohort serves as the control population and is representative of the entire cohort. All cases are evaluated, including those that occur from within the subcohort and those that were not included in the subcohort (Rothman & Greenland 1998). The case cohort design provides a direct estimate of the risk ratio while reducing the number of ‘controls’ requiring evaluation. In our study, the subcohort (controls) comprised a 65% sample of all HIV-infected children in the clinic (n = 400), regardless of mortality status. All HIV-infected children who died or defaulted (cases) in the clinic were included in the study population. Data were entered and stored in Microsoft Office Access (Microsoft Corp., Redmond, WA, USA). The study was approved by the University of North Carolina Institutional Review Board and the Malawi National Health Science Research Committee.

Study setting

Kamuzu Central Hospital serves the central region of Malawi and is located in the capital city of Lilongwe. The KCH paediatric HIV clinic was established in October 2004. This clinic operated until November 2006, when the Malawi Baylor College of Medicine-Abbott Fund Children's Clinical Centre of Excellence opened its HIV clinic and assumed care of the children.

Study population

Subjects were all residents of Lilongwe or the central Malawi region. Children were eligible for the study if they were <18 years of age and confirmed HIV-1 positive by either ELISA antibody testing, HIV rapid tests, or DNA PCR. Patients were ART-naïve before referral to the Paediatric HIV clinic at KCH. Children had to have initiated ART in the clinic by 15 May 2006 and had to be receiving a regimen of ART or have received ART until the date of their death. The first-line anti-retroviral regimen in Malawi consists of a combination of nevirapine, stavudine and lamivudine, with zidovudine and efavirenz as alternatives in case of intolerance to first-line agents. The second-line regimen was not readily available at the time of this evaluation. These regimens were in accordance with WHO ART guidelines at the time (WHO 2004) and the Malawi National ART guidelines (MoH Malawi 2006).

Children >18 months of age were eligible for ART if they were HIV-seropositive, if their guardians understood the benefits and risks of ART, and if appropriate combinations of WHO clinical stage, total lymphocyte, and CD4 cell count criteria were met (WHO 2004;MoH Malawi 2006). Children <18 months of age were ART-eligible if they were HIV-seropositive, in WHO stage III with a CD4 lymphocyte count <20%, or if they suffered from a clinical condition (MoH Malawi 2006;Malawi Paediatric Anti-retroviral Treatment Group 2007). Subjects were seen every 1–2 months in the clinic at KCH for check-ups and medication refills, and as needed for acute illness. Care and management of these subjects was provided by paediatricians from KCH, the University of North Carolina School of Medicine, and from Baylor College of Medicine.

Data collection and measures

All subjects were enrolled at Kumuzu Central Hospital between October 2004 and May 2006. Data were collected in June and July 2006 with a standardized form. Outcomes were determined as of this date. Extracted data were entered into an MS Access database. The variables recorded comprised

- demographic information (age, gender, residence, and main caregiver's relation to child);
- health status at presentation, with ill at presentation defined as having one or more HIV-related symptoms at the initial visit;
- clinical history with relation to HIV [initial signs and symptoms of HIV, AIDS-defining illness, current or previous tuberculosis (TB) status, current medications, and prevention of mother to child transmission status defined by the mother and infant receiving prophylactic ART during pregnancy];
- family history (parents' HIV status, parents alive or dead, education status of parents, distance to KCH as per caregiver, and how many children in household)
- laboratory studies as performed by KCH or UNC facilities (CD4 count and RNA viral load pre- and post-ART)
- clinical staging of HIV in children and adolescents at ART initiation as defined by WHO (2004) ART guidelines
- treatment course (ART start dates, duration of ART, reason of first-line failure, drug allergies), and
- current status of the subject (alive, dead, cause of death, defaulter defined as having missed their most recent scheduled appointment by >3 months, transferred, and/or reason of transfer).

Variables were recorded as applicable to the subject.

Orphan status was inferred by the mother's vital status. Reliable information on the father's vital status was not typically documented, therefore mother's vital status was used as a proxy for orphan status of the child.

Statistical methods

Statistical analysis was performed in order to determine which recorded variables, if any, were associated with death or default among these patients. Our primary outcome was death or default, based on the similarity of these groups and previous studies that have suggested that the primary reason for a child to default was death (Hosseinipour *et al*. 2004; Brahmbhatt *et al*. 2006). We also conducted a sensitivity analysis with an alternative outcome of death only.

We described the study population with frequencies for demographics, clinical conditions and baseline laboratory values. We used $\alpha = 0.05$ for significance testing. All statistical analyses were performed using Stata 8.2 (Stata-Corp LP, College Station, TX, USA).

Cox proportional hazards modelling was used with the Prentice method to analyse these case cohort data (Barlow *et al*. 1999). The time axis was days on ART. Alive children were right-censored observations if death had not been reported by data review. Hazard ratios for bivariable analyses were calculated after ensuring that the proportional hazards assumption was not violated. For modelling purposes, only variables with fewer than 5% of values missing were included in the analyses. We included all variables in the multivariable model without further variable reduction.

Results

Characteristics of children on ART

From October 2004 to May 2006, 400 children were started on ART at Kumuzu Central Hospital. A total of 258 files were reviewed during the retrospective analysis. Of the 258 reviewed patients, 185 (72%) were alive, 41 (16%) were deceased, and 32 (12%) had defaulted. No children had transferred clinics.

The mean age of the cohort was 5.7 years; 79% were older than 18 months (Table 1). Thirteen subjects were older than 13 years and 49% were male. At the time of ART initiation, 55% had WHO stage III disease. The most common stage III conditions were pulmonary tuberculosis (66%), severe recurrent bacterial pneumonia (11%), moderate malnutrition/weight loss (9%) and oral thrush (8%). Among the stage IV conditions, severe failure to thrive or wasting (66%), extrapulmonary tuberculosis (10%), recurrent severe bacterial infections (11%), and Kaposi's sarcoma (9%) were the most common diagnoses. Sixteen per cent had lost both parents, 28% had a living father but had lost their mother. Of those with a living father, 70% did not list their father as the primary caregiver, but rather another member of the extended family. Twenty-four per cent had active TB, 25% had a history of TB, and 47% had neither a history of nor active TB. Thirteen per cent of the children had received single-dose nevirapine as a prevention of mother to child transmission (PMTCT) regimen. Only 19% of the children were receiving co-trimoxazole preventive therapy.

Treatment outcomes and correlates of mortality

The median duration of follow-up on ART overall was 196 days, based on the representative subcohort (25th percentile = 105 days; 75th percentile = 310 days). In contrast, among children who died or defaulted, the median duration of follow-up on ART was only 35 days (25th percentile = 15 days; 75th percentile = 87 days).

The mean age of children who had died (4.46 years) or defaulted (4.30 years) was younger than that of survivors (6.14 years). The average weight of the population was 14.9 kg, with an average of 11.9 kg in the deceased, 16.2 kg in the living, and 11.2 kg in the defaulters. Weight loss at presentation was apparent in 94% of the deceased population and in 67% of the defaulters, compared with 69% in survivors. Median CD4 counts were 332 [inter quartile range (IQR) 174–590] cells/μl in survivors; 411 (IQR 59–1026) cells/μl in the deceased and 411 (IQR 234–800) in the defaulters. CD4 percentages were not available. Of the stage IV children, 54% were deceased and among the stage III children, 41% were deceased.

In the multivariable Cox model, both age <18 months and being WHO stage IV remained significantly associated with mortality and loss to follow-up. Children <18 months old were 2.15 times more likely to die as children aged at least 18 months (95% CI 1.00–4.61). Children presenting with stage IV illness were 2.0 times as likely to die as those with stage I–III illness (95% CI 1.07–3.76) (Table 2). Using dead *vs*. alive as the outcome excluding the defaulters (Table 3), results show similar trends to the dead/defaulter *vs*. alive analysis (Table 2). Kaplan–Meier estimates show significantly higher rate of death in the <18 months age category (Figure 1).

Discussion

Children receiving ART in Malawi experience high mortality compared with children in rich countries (Resino *et al.* 2006; Judd *et al.* 2007). Their mortality appears to be greater than that of adults in similar settings (Etard *et al*. 2006; Zachariah *et al*. 2006). Young age (<18 months) and late WHO stage presentation were most strongly associated with mortality in our study. Gender, being orphaned from the mother, or area of residence did not appear to play a predictive role regarding mortality.

In adults on ART, most deaths occur within the first 3 months of treatment (Zachariah *et al*. 2006; Libamba *et al*. 2007). Children have been thought to follow similar trends (Bolton-Moore *et al*. 2007; Boyd & Cooper 2007; Callens *et al*. 2009). Most deaths occurred within the first 100 days on treatment, particularly among the youngest patients. However, given that the population was largely identified through hospital admissions, it may be expected to have a relatively high mortality rate early on.

Age <18 months is associated with mortality when the defaulter population remains grouped with the deceased, which is consistent with other studies (Violari *et al*. 2008). This trend remained the same when defaulters were removed from the analysis, though precision was lost. Rapid disease progression has been documented in perinatally infected infants (Eley *et al*. 2006) and delays in diagnosis are inevitable in this age group in settings where diagnosis is dependent on antibody testing. This type of testing is well known to be unreliable in infants, because it can reflect maternal antibodies. HIV DNA testing can accurately determine an infant's status and could allow earlier initiation of anti-retroviral therapy in this age group. However, earlier testing must be combined with Prevention of Mother to Child Transmission programmes in order to ensure that all exposed infants are reached. We acknowledge that children who initiated ART at older ages may have an additional survival advantage as they have already managed to survive to the older age.

The association of WHO stage IV with mortality on multivariate modelling is similar to other studies (Zachariah *et al*. 2006; Bong *et al*. 2007). Moreover, our cohort had an unexpectedly high death rate among stage I patients, which may have influenced the findings. However, our sample included very few stage I and stage II children and was insufficient to determine gradations in mortality risk according to stage.

Other studies have shown that weight or body mass index (BMI) is a good clinical predictor of response to ART (Nyandiko *et al.* 2006; Zachariah *et al.* 2006). Likewise, total lymphocyte count, low CD4 count, and low CD4 percentage predict mortality (HIV Paediatric Prognostic Markers Collaborative Study 2005; Bong *et al*. 2007; Kiboneka *et al*. 2008). While our data suggest that weight loss and low CD4 count are more commonly associated with death on bivariable analysis, these variables were not included in multivariate modelling, as >5% of values were missing from the patient records. Therefore, we are unable to know if these variables independently predicted mortality in our study.

As community follow-up was not performed to confirm the status of the defaulters, we conducted two analyses to determine how vital status influenced the results. Our findings suggest that defaulters display characteristics more similar to dead children, particularly with respect to duration on ART. Further, the marked similarity in the analysis when evaluating the defaulters as assumed dead *vs*. excluded also suggests that defaulters are deceased. With a greater sample size, we expect that the analysis would retain significance with regard to age <18 months and WHO staging, given the high comparability of the dead and defaulter populations and similar effect size. Several other studies also suggest defaulters are more likely to be deceased in this setting (Hosseinipour *et al*. 2004; Brahmbhatt *et al*. 2006), Yu et al. 2007.

As a proxy for the orphan status of the child, we evaluated maternal vital status in our cohort and did not find this to be associated with mortality. However, other studies have suggested maternal health status may play a strong role in early death for children (Chearskul *et al*. 2002; Brahmbhatt *et al.* 2006; Marinda *et al.* 2007; Chilongozi *et al.* 2008). As our population included only children who presented for ART care, we likely missed the population where maternal health and vital status may have had the greatest impact. Further study of the health status of the parents may be critical to understanding the high mortality rate in the <18 month age group.

In this study, we were limited by the information contained on the clinic visit forms, which were initially created for record keeping purposes at the Paediatric HIV Clinic at KCH. Consequently, information could be recorded inconsistently and with varying skill and experience of the clinicians. Staging itself may be somewhat unreliable in this setting. Diagnoses such as the AIDS defining illness are often based upon clinical presentation and rarely confirmed with sophisticated laboratory or radiographic data. Therefore it is also possible that some of the children may have been staged incorrectly based on an erroneous diagnosis. Although we limited the variables included in the Cox proportional hazards analyses to those with at least 95% complete data, we could not account for measurement error introduced by varying clinician performance.

The findings of this study suggest that earlier diagnosis in infants is critical, as late presentation and advanced disease play a significant role in mortality. To improve outcomes among HIV-positive children, clearly the <18 months age group must be specifically targeted and identified with early identification techniques such as PCR DNA testing. The Malawi HIV program has recognized this and is currently piloting an Early Infant Diagnosis program.

In poor settings these more expensive techniques may not be ideal. More novel techniques such as p24 testing may be more feasible and also warrant further exploration (Cachafeiro *et al*. 2008). High mortality rates in the youngest children underscore the growing importance of integrated prevention of mother to child transmission programs that emphasize optimal regimens to maximize maternal health, prevent HIV transmission, and accurately diagnose infant HIV infection as early as possible.

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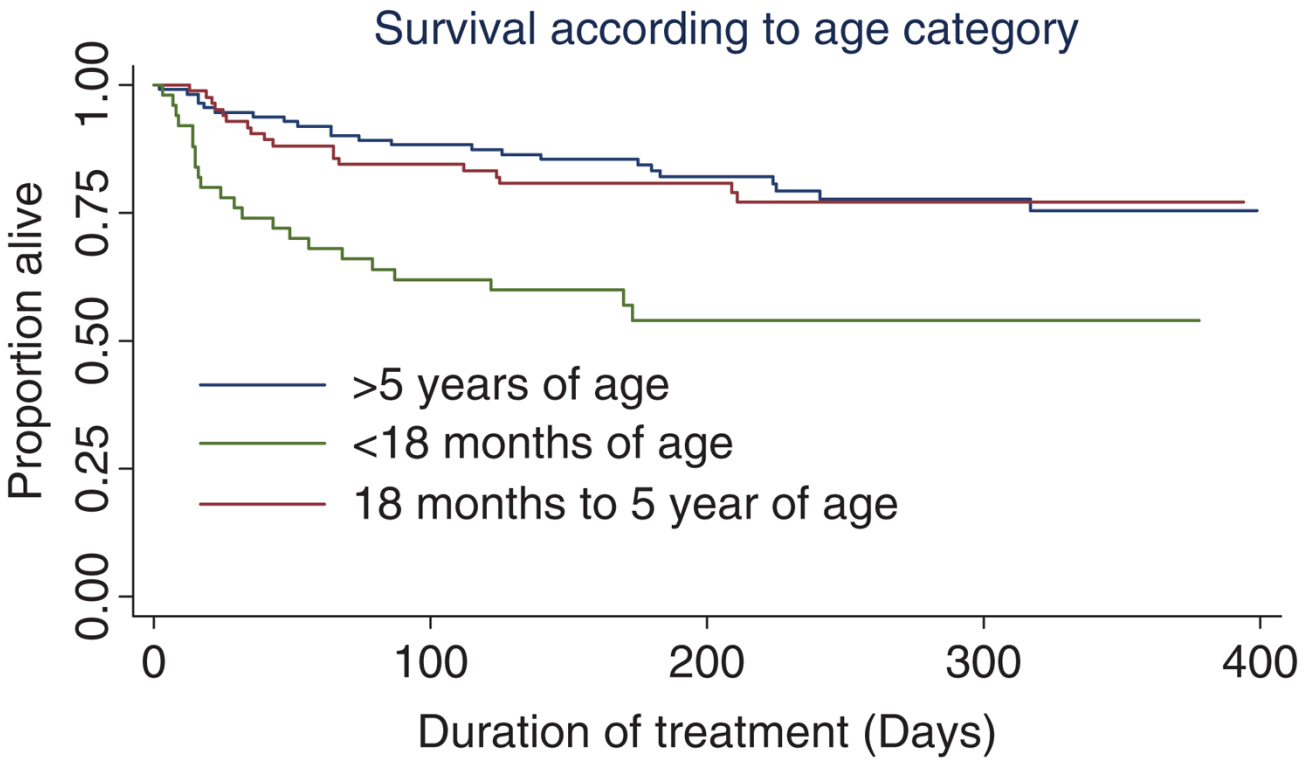

Figure 1.
Survival estimates according to age ($P = 0.0003$).

Table 1

Characteristics at initial visit of children started on anti-retroviral therapy at Kumuzu Central Hospital in Lilongwe, Malawi

Characteristics	Total (*n* = 258)	Dead/default (*n* = 73)	Alive (*n* = 185)
	n (%)	*n* (%)	*n* (%)
Gender			
Male	119 (48.80)	27 (39.10)	92 (52.60)
Female	125 (51.20)	42 (60.90)	83 (47.40)
Age			
<18 months	55 (21.40)	27 (37.00)	28 (15.20)
18 months–5 years	87 (33.90)	21 (28.80)	66 (35.90)
>5 years–18 years	115 (44.70)	25 (34.20)	90 (48.90)
From Lilongwe			
Yes	186 (74.10)	55 (77.50)	131 (72.80)
No	65 (25.90)	16 (22.50)	49 (27.20)
Mother alive			
Yes	164 (64.60)	53 (73.60)	111 (61.00)
No	90 (35.40)	19 (26.40)	71 (39.00)
Ill at presentation			
Yes	142 (55.70)	50 (68.50)	92 (50.50)
No	113 (44.30)	23 (31.50)	90 (49.50)
Weight loss			
Yes	170 (72.30)	52 (81.30)	118 (69.00)
No	65 (27.70)	12 (18.80)	53 (31.00)
Fever			
Yes	67 (28.80)	16 (25.40)	51 (30.00)
No	166 (71.20)	47 (74.60)	119 (70.00)
Diarrhoea			
Yes	56 (24.10)	18 (28.60)	38 (22.50)
No	176 (75.90)	45 (71.40)	131 (77.50)
Developmental delay			
Yes	51 (22.60)	19 (31.10)	32 (19.40)
No	175 (77.40)	42 (68.90)	133 (80.60)
Shingles			
Yes	37 (16.20)	6 (9.70)	31 (18.60)
No	192 (83.80)	56 (90.30)	136 (81.40)
Oral candidiasis			
Yes	139 (59.90)	41 (66.10)	98 (57.60)
No	93 (40.10)	21 (33.90)	72 (42.40)
Lymphadenopathy			
Yes	138 (63.60)	35 (61.40)	103 (64.40)
No	79 (36.40)	22 (38.60)	57 (35.60)
Skin abnormalities			

Characteristics	Total (*n* = 258)	Dead/default (*n* = 73)	Alive (*n* = 185)
	n (%)	*n* (%)	*n* (%)
Yes	154 (68.40)	45 (73.80)	109 (66.50)
No	71 (31.60)	16 (26.20)	55 (33.50)
Tuberculosis			
Current TB	63 (24.90)	12 (16.90)	51 (28.00)
Previous TB	65 (25.70)	16 (22.50)	49 (26.90)
Suspected TB	3 (1.20)	2 (2.80)	1 (0.50)
No TB	122 (48.20)	41 (57.70)	81 (44.50)
Co-trimoxazole prophylaxis			
Yes	50 (19.40)	21 (28.80)	29 (15.70)
No	208 (80.60)	52 (71.20)	156 (84.30)
WHO stage			
Stage 1	7 (2.80)	5 (6.80)	2 (1.10)
Stage 2	12 (4.70)	2 (2.70)	10 (5.50)
Stage 3	142 (55.90)	27 (37.00)	115 (63.50)
Stage 4	93 (36.60)	39 (53.40)	54 (29.80)

TB, tuberculosis; WHO, World Health Organization.

Table 2

Unadjusted and adjusted hazard ratios for outcome of death/default by baseline characteristics

	Unadjusted		Adjusted	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Gender				
Male	0.60	(0.36, 1.01)	0.67	(0.36, 1.24)
Female	1.00	–	1.00	–
Age				
<18 months	3.44	(1.88, 6.30)	2.15	(1.00, 4.61)
18 months–5 years	1.18	(0.64, 2.16)	0.86	(0.41, 1.77)
>5 years–18 years	1.00	–	1.00	–
From Lilongwe				
Yes	1.31	(0.73, 2.35)	1.61	(0.82, 3.19)
No	1.00	–	1.00	–
Mother alive				
Yes	1.78	(1.03, 3.07)	1.92	(0.94, 3.92)
No	1.00	–	1.00	–
Ill at presentation				
Yes	1.90	(1.12, 3.23)	1.03	(0.56, 1.89)
No	1.00	–	1.00	–
Tuberculosis				
Active TB	0.54	(0.28, 1.02)	0.63	(0.30, 1.30)
No active TB	1.00	–	1.00	–
Co-trimoxazole prophylaxis				
Yes	1.99	(1.13, 3.48)	1.47	(0.77, 2.78)
No	1.00	–	1.00	–
WHO stage				
Stage 1, 2 or 3	1.00	–	1.00	–
Stage 4	2.36	(1.44, 3.88)	2.00	(1.07, 3.76)

HR, hazard ratios; CI, confidence intervals; TB, tuberculosis; WHO, World Health Organization.

Table 3

Unadjusted and adjusted hazard ratios for outcome of death by baseline characteristics (sensitivity analysis)

	Unadjusted		Adjusted	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Gender				
Male	0.73	(0.38, 1.40)	0.78	(0.37, 1.65)
Female	1.00	–	1.00	–
Age				
<18 months	3.40	(1.58, 7.34)	2.79	(1.01, 7.73)
18 months–5 years	1.20	(0.54, 2.64)	1.07	(0.40, 2.85)
>5 years–18 years	1.00	–	1.00	–
From Lilongwe				
Yes	2.09	(0.86, 5.08)	2.09	(0.87, 5.01)
No	1.00	–	1.00	–
Mother alive				
Yes	1.67	(0.82, 3.40)	1.52	(0.60, 3.86)
No	1.00	–	1.00	–
Ill at presentation				
Yes	2.74	(1.31, 5.74)	1.70	(0.69, 4.20)
No	1.00	–	1.00	–
Tuberculosis				
Active TB	0.57	(0.24, 1.31)	0.61	(0.25, 1.49)
No active TB	1.00	–	1.00	–
Co-trimoxazole prophylaxis				
Yes	1.56	(0.74, 3.30)	1.08	(0.45, 2.60)
No	1.00	–	1.00	–
WHO stage				
Stage 1, 2 or 3	1.00	–	1.00	–
Stage 4	2.38	(1.25, 4.52)	1.68	(0.74, 3.78)

HR, hazard ratios; CI, confidence intervals; TB, tuberculosis; WHO, World Health Organization.

Note: Children who defaulted are included with the subcohort and are censored at the time of loss to follow-up.