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Risk factors for mortality in Malawian children with human immunodeficiency virus and tuberculosis co-infection

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Abstract

SETTING—A large urban pediatric human immunodeficiency virus (HIV) clinic in Lilongwe, Malawi.

OBJECTIVE—To identify demographic and clinical risk factors for mortality in children co-infected with HIV and tuberculosis (TB).

DESIGN—A retrospective cohort study of HIV-infected children (aged <18 years) enrolled between October 2004 and October 2010 with at least one current or historical TB diagnosis. Descriptive statistics and logistic regression analyses were performed to determine factors associated with mortality.

RESULTS—A total of 1561 patients met the inclusion criteria, representing 32% of patients ever enrolled. Median age at TB diagnosis was 3.8 years (interquartile range 1.5–7.4); 60.9% had severe immune suppression and 47.6% of those with available data had some degree of acute malnutrition at TB diagnosis. Of the 1113 patients with known outcomes, 225 (20.2%) died. Children with TB-HIV co-infection not initiated on anti-retroviral therapy (ART) at any time were 8.8 times more likely to die compared to those initiated on ART 0–2 months after initiation of anti-tuberculosis treatment (adjusted OR 8.83, 95%CI 4.42–17.63). Severe immuno-suppression and World Health Organization Stage IV were also associated with mortality.

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CONCLUSIONS—Pediatric TB-HIV co-infection is common and mortality is high in this cohort of Malawian children. Prompt initiation of ART should be emphasized in this high-risk patient population.

Keywords

pediatric; HIV; TB; co-infection; ART

The Human Immunodeficiency Virus (HIV) epidemic in sub-Saharan Africa has led to a large increase in tuberculosis (TB) incidence, as immunocompromised adults and children are at increased risk for reactivation of latent tuberculous and new infections.[1] This has been disproportionately noted in women of child-bearing age, resulting in higher levels of TB exposure and infection in HIV-infected children in these households.[2,3] In addition, children have faster rates of progression from infection to disease, and HIV infection accelerates that process, particularly in young children.[4] Some high-burden African settings have reported a pediatric TB-HIV co-infection burden of 43.4% and above.[5,6] In Malawi, high TB incidence (191 per 100 000 population in 2011) and HIV prevalence (11% in 2009), along with limited TB diagnostic tools and challenges in early infant diagnosis of HIV, make management of co-infected children a challenge, resulting in poor outcomes.[7–10]

The Malawi National TB Control Programme recommends a diagnostic approach focused on exposure history, clinical signs and symptoms, and chest radiography in children.[11] Capacity for tuberculin skin test (TST), mycobacterial culture or pathology services in the country is minimal. Sputum microscopy is widely available, but rarely performed in young children incapable of providing adequate respiratory samples.

In the first and second editions of the Malawi anti-retroviral therapy (ART) guidelines, covering October 2003–April 2008, pulmonary TB (PTB) was a pediatric Stage III diagnosis for which clinicians could defer to the CD4 count to determine ART eligibility.[12,13] These recommendations were consistent with World Health Organization (WHO) recommendations at the time.[14] The third edition of the national guidelines released in April 2008 recommended ART for all HIV-infected children diagnosed with PTB, regardless of CD4, reflecting new advice from the WHO.[15,16]

National guidelines evolved from recommending deferred ART initiation until anti-tuberculosis treatment was completed, then until completion of the 2-month initiation phase of treatment, and finally to recommending ART initiation as early as 2 weeks after starting treatment (October 2010).[12,13,15] Table 1 displays the pediatric anti-tuberculosis treatment and ART regimens during the time period of this study.

In this context of pediatric HIV and TB care in Malawi, we conducted a retrospective review of a large cohort of TB-HIV co-infected children to identify risk factors for mortality. We also sought to describe this cohort receiving routine pediatric HIV care over a period of national guideline changes.

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METHODS

Patients and setting

This was a retrospective cohort analysis of all HIV-infected pediatric patients (aged <18 years at enrolment) ever diagnosed with TB and enrolled at the Baylor College of Medicine–Abbott Fund Children's Clinical Centre of Excellence (COE), Lilongwe, between October 2004 and October 2010. The COE provides primary HIV care to patients in the Lilongwe area and also acts as a regional and national referral center for complicated pediatric HIV cases, including patients with ART failure and Kaposi's sarcoma. As of October 2010, 4874 HIV-infected pediatric patients had ever been enrolled, with an active caseload of 2461 patients, 1682 (68.3%) of whom were on ART. This represented approximately 8% of all children on ART in Malawi in 2010, making the COE the largest national pediatric ART provider.[17]

All patients enrolled have their demographic, medical and social history, and clinical data stored in an electronic medical record (EMR). The EMR was screened for patients with a TB diagnosis documented in their past medical history, WHO staging and prescription data for anti-tuberculosis treatment. HIV-exposed patients were excluded, as were those who had received only isoniazid preventive therapy (IPT).

The files of patients identified for inclusion were reviewed by two pediatricians (WCB and DO). Study data, including staging, ART regimen, TB history, acute nutritional status (according to national guidelines, which use weight-for-length, mid-upper arm circumference and edema assessments), and CD4 results closest to the time of TB diagnosis, were extracted and entered into an Access® 2007 database (Microsoft Corporation, Redmond, WA, USA) and merged with other demographic and clinical variables retrievable without chart review.[18,19] CD4 results were stratified according to WHO age-based immune classifications, with the lower of the absolute and percentage results used to determine the degree of suppression.[14]

Tuberculosis diagnosis

There was no standardized algorithm for TB diagnosis and it was not always possible to determine how a diagnosis was made. Any patient treated for active TB was therefore included.

Ethics approval

Approval for the study was obtained from the Malawi National Health Sciences Research Committee and the Baylor College of Medicine Institutional Review Board.

Statistics

Stata®, version 11 (StataCorp LP, College Station, TX, USA) was used for analysis. Frequency tables were generated to describe the study population. Categorical variables were described using frequencies and all continuous variables were described using medians and interquartile ranges (IQRs). Nutritional status at the time of TB diagnosis was unavailable for 757 (48.5% of overall cohort) of the historical TB cases prior to enrolment at

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the COE, but as it was deemed to be an important variable for analysis, the missing data were imputed using information from related variables. Univariate logistic regression was performed on a subset of 1113 patients with ascertained mortality outcomes (alive or died) to determine factors associated with mortality; those who transferred out or were lost to follow-up (LTFU) were excluded from logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) for unadjusted associations between mortality and each demographic or clinical factor were generated. The multivariate regression analysis was performed in a backward stepwise fashion, where variables were retained in the model if they were statistically significant at the 0.05 level. The variables included in the logistic regression analysis were age at TB diagnosis, sex, timing of ART and anti-tuberculosis treatment, type of TB, WHO disease stage, acute nutrition status and immune status.

RESULTS

A total of 1561 co-infected patients were identified, representing 32% of all HIV-infected children ever enrolled. As of October 2010, 225 (14.4%) of these patients were known to have died, while 888 (56.9%) were alive and in care (Figure). The median age at TB diagnosis for the 1452 patients with a known diagnosis date was 3.8 years (IQR 1.5–7.4). Of those with CD4 data, 60.9% were severely immune-suppressed. Nearly half (47.6%) of the 804 patients with known nutritional status at TB diagnosis had some degree of acute malnutrition. TB was diagnosed after initiation of ART in 159 patients; for 139 this was in the first 12 months after ART. A comparison of key demographic and clinical variables for patients with known vs. unknown mortality outcomes is shown in Table 2.

Cross-tabulation of ART and immune status showed that 29% of children not on ART and 64% of children on ART had severe immunosuppression near the time of TB diagnosis. Two-by-two cross-tabulation of ART status and outcome showed that TB-HIV co-infected children who had never been started on ART had a more than three-fold higher likelihood of dying compared to those on ART (OR 3.50, 95%CI 2.45– 4.99, $P < 0.001$).

In univariate analysis, age <12 months, male sex, PTB, ART initiation >2 months after anti-tuberculosis treatment, no ART, WHO HIV Stage IV, severe malnutrition, and severe immune suppression were associated with greater mortality ($P < 0.05$; Table 3). In multivariate analysis, male sex, WHO HIV Stage IV, no ART and severe immunosuppression remained associated with increased risk of mortality ($P < 0.05$), after controlling for the other variables in the model. Children with HIV and TB co-infection not initiated on ART at any time were almost nine times more likely to die than those initiated on ART 0–2 months after initiation of anti-tuberculosis treatment (adjusted OR [aOR] 8.83, 95%CI 4.42–17.63, $P < 0.001$). In addition, children with severe immunosuppression were six times more likely to die than children with no immunosuppression (aOR 6.02, 95%CI 2.98–12.17, $P < 0.001$).

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DISCUSSION

This study presents data from a large pediatric TB-HIV co-infected cohort using retrospective data from routine patient care. This is operational research reflecting conditions in the field, thereby facilitating the evaluation of national health policies.

The most striking findings were the high overall mortality (20% of patients with known outcomes) and the significant difference in mortality between TB-HIV co-infected patients who never started ART compared to those who did. We have previously reported a mortality of 4.8% in our overall cohort of infected children who started ART.[20] Those co-infected patients who never received ART fell predominantly into one of two groups: patients deemed ineligible for ART due to pre-2008 guidelines, which permitted using CD4 counts to determine eligibility for WHO Stage III PTB patients, and those who needed ART but never started due to clinical instability or lack of social/care giver readiness. We were not able to determine with certainty which patients in our cohort fell into each category, but a subset analysis of those with available CD4 data showed that 29.8% of patients who did not start ART had severe immune suppression. At least these patients, and possibly others, were ART-eligible and likely not started on treatment due to lack of clinical stability or social readiness.

For the former group, ART eligibility guidelines have since evolved to include all TB patients, as numerous studies have shown that ART improves TB outcomes and mortality in HIV-infected children, regardless of immune status.[21–24] For the latter group, who were identified as needing ART but were never initiated on it, increased emphasis on timely ART initiation after TB diagnosis is needed, with consideration of reduced requirements for pre-ART care giver education, especially if the child is unwell. New national ART guideline revisions in 2011 allowing for more timely, and even simultaneous, initiation of ART and anti-tuberculosis treatment will help, as increasing evidence links earlier ART initiation to reduced mortality in TB-HIV co-infected adults and children.[25–27] While other risk factors for mortality in TB-HIV co-infected adults have been well established, and include severe immunodeficiency, advanced age, and malnutrition, similar risk factors in children have not been well established.[28,29] A unique and important consideration when comparing our outcomes with those of other studies is our chosen starting point of enrolment into HIV care, and not the TB clinic. We do not know how many co-infected children in our area were diagnosed with TB and were either never tested for HIV or never enrolled into HIV care, and how many of those children died. If we had been able to include such patients, we would likely have seen an even greater difference in mortality between those who were and were not enrolled in HIV care and received ART.

Our cohort included 139 patients diagnosed with TB in the 12 months after ART initiation. We lacked sufficient data to determine exactly how many of these cases met definitions for immune reconstitution inflammatory syndrome (IRIS). Regional studies have reported incidences of TB IRIS of 7.4–15.4% in children starting ART.[30,31] Other patients in our cohort likely had active TB that was missed before initiating ART. A Ugandan pediatric study demonstrated a 70% reduction in new TB cases diagnosed after ART initiation with implementation of standardized pre-ART TST screening.[32] The lack of TB screening tools

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such as TST, gastric lavage and sputum induction is a major barrier to improved recognition of TB in Malawi.

Our analysis was suggestive of an increased risk of mortality in TB-HIV co-infected infants (although not conclusive in multivariate analysis, with an adjusted OR of 1.69, 95%CI 0.89–3.22), and adds to the literature that demonstrates an increased risk of severe disease and mortality in TB-HIV co-infected infants.[33,34] This vulnerability likely results from several factors, including poorly controlled HIV replication in infants not on ART, greater likelihood of TB exposure due to close contact with source mothers and immune immaturity, which is known to lead to rapid progression from TB infection to disease and higher mortality, even in non-HIV-infected children.[5] Regardless of the cause, this is a high-risk sub-group that warrants more frequent and higher-level follow-up and emphasis on timely ART initiation.

Male sex was associated with a statistically significantly increased risk of mortality in multivariate analysis. There were no differences in care provision at the COE based on sex, and we cannot explain these results. However, we doubt that sex would truly have a bearing on mortality outcomes in the context of pediatric TB-HIV co-infection.

Transfer-out and LTFU patients (respectively 21.4% and 7.3% of the cohort) were excluded from mortality analyses, and this may have biased the estimates of mortality risk. During the time of this study, the COE had the policy of actively transferring stable patients out to ART centers closer to their homes, so the majority of those patients were likely still alive and on ART. However, it is customary to assume that a fairly high proportion of LTFU patients have died, meaning our true mortality was possibly higher than reported.[35]

This retrospective study had several limitations. There were gaps in our data, particularly in identifying the exact dates of TB diagnosis before clinic enrolment and nutritional status for historical TB diagnoses, requiring data imputation for logistic regression analysis. We also had to assume that all patients were vertically infected, including adolescents (13.7% of our cohort), and established that this was reasonable given observed local pediatric transmission patterns. If some patients were horizontally infected and had a historical TB diagnosis, there is a chance they did not have true TB-HIV co-infection. These missing data and limitations were partially offset by our rigorous data collection process and the breadth of clinical information included, coupled with the relatively large sample size. Furthermore, due to inherent challenges in diagnosing TB in children, particularly in Malawi, there were likely cases of other lung disease misdiagnosed as TB, and also cases where anti-tuberculosis treatment was used without strong diagnostic evidence in critically ill patients who showed no improvement on ART.

CONCLUSIONS

Pediatric TB-HIV co-infection is common, and mortality was high in this cohort. Better TB diagnostic tools for children, along with national guidelines and clinic protocols that prioritize prompt initiation of ART and close follow-up of co-infected patients, with special attention to infants and those with advanced clinical stage and severe immunosuppression,

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should lead to improved outcomes. Future research can evaluate the impact of a new national pre-ART IPT program and of universal ART for all children aged <5 years if implemented.

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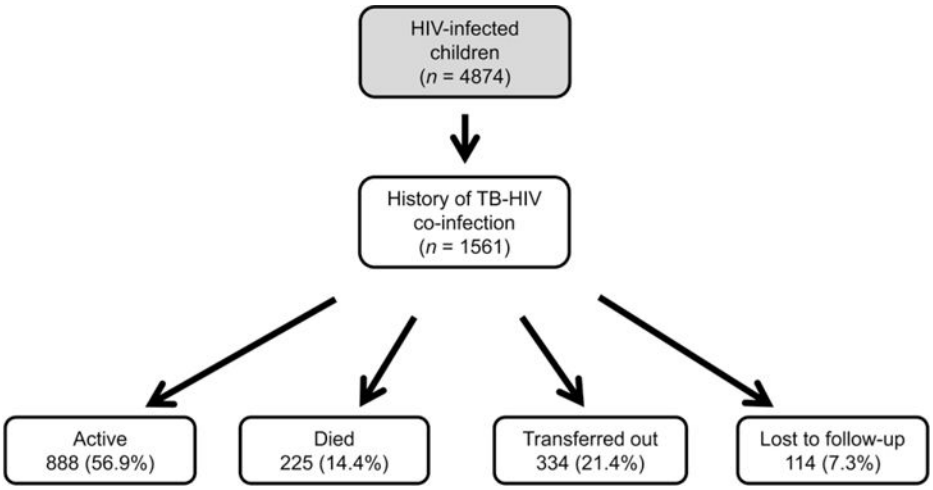

Figure.

Study enrolment and outcomes in Malawian TB-HIV co-infected children, October 2004–October 2010. TB = tuberculosis; HIV = human immunodeficiency virus.

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Table 1

Malawi pediatric anti-tuberculosis and ART regimens, 2006–2010

	Regimen
Anti-tuberculosis treatment	
Type of TB case	
New (first case)	2RHZE/4RH (Regimen 1) *
Relapse, return after default, treatment failure, recurrent †	2SRHZE/1RHZE/5RHE (Regimen 2) *
Meningitis	2SRHZ/7RH *
Suspected or confirmed multidrug-resistant or extensively drug-resistant TB	Handled on a case-by-case basis with NTP
ART	
Standard first-line ‡	d4T/3TC/NVP
Standard second-line ‡	ABC/ddI/LPV-r

* R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; S = streptomycin. Numbers represent duration of therapy in months.

† In practice, many recurrent cases are treated with Regimen 1 if they are thought to represent re-infection after successful treatment of a previous episode.

‡ For patients on anti-tuberculosis treatment and first-line ART, there is no recommended switch from NVP to EFV. For patients needing simultaneous anti-tuberculosis treatment and second-line ART, double-dose LPV-r is usually recommended, as individual ritonavir is not available in the country for superboosting.

ART = antiretroviral therapy; TB = tuberculosis; NTP = National TB Control Programme; d4T = stavudine; 3TC = lamivudine; NVP = nevirapine; ABC = abacavir; ddI = didanosine; LPV-r = lopinavir/ritonavir; EFV = efavirenz.

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Table 2

Description of a Malawian pediatric TB-HIV co-infected cohort

	Known outcomes		Unknown outcomes		
Characteristic	**Alive *n* (%)**	**Died *n* (%)**	**Lost to follow-up *n* (%)**	**Transferred out *n* (%)**	**Total**
Age at TB diagnosis					
≤12 months	92 (10.4)	57 (25.3)	13 (11.4)	39 (11.7)	201 (12.9)
1–3 years	245 (27.6)	64 (28.4)	35 (30.7)	101 (30.2)	445 (28.5)
>3–5 years	128 (14.4)	18 (8.0)	26 (22.8)	49 (14.7)	221 (14.1)
>5–10 years	235 (26.4)	33 (14.8)	23 (20.2)	80 (24.0)	371 (23.8)
>10–18 years	133 (15.0)	28 (12.4)	8 (7.0)	45 (13.4)	214 (13.7)
Unknown	55 (6.2)	25 (11.1)	9 (7.9)	20 (6.0)	109 (7.0)
Sex					
Male	440 (49.6)	134 (59.6)	65 (57.0)	176 (52.7)	815 (52.2)
Female	448 (50.4)	91 (40.4)	49 (43.0)	158 (47.3)	746 (47.8)
Type of TB					
PTB *	828 (93.2)	197 (87.6)	110 (96.5)	301 (90.1)	1436 (92.0)
Lymph node TB	32 (3.6)	15 (6.7)	3 (2.6)	17 (5.1)	67 (4.3)
Abdominal TB	8 (0.9)	5 (2.2)	0	8 (2.4)	21 (1.3)
Miliary TB	6 (0.7)	3 (1.3)	0	4 (1.2)	13 (0.8)
TB meningitis	6 (0.7)	1 (0.4)	0	0	7 (0.4)
Unknown	8 (0.9)	4 (1.8)	1 (0.9)	4 (1.2)	17 (1.1)
Maximum WHO Stage †					
I	5 (0.6)	0	1 (0.9)	3 (0.9)	9 (0.6)
II	18 (2.0)	0	4 (3.5)	6 (1.8)	28 (1.8)
III	680 (76.6)	99 (44.0)	90 (79.0)	250 (74.9)	1119 (71.7)
IV	185 (20.8)	126 (56.0)	19 (16.6)	75 (22.4)	405 (25.9)
Immune suppression ‡					
None	213 (24.0)	14 (6.3)	14 (12.2)	50 (15.0)	291 (18.6)
Mild	85 (9.6)	10 (4.4)	10 (8.8)	28 (8.4)	133 (8.5)
Advanced	97 (10.9)	10 (4.4)	10 (8.8)	28 (8.4)	145 (9.3)
Severe	479 (53.9)	150 (66.7)	49 (43.0)	208 (62.2)	886 (56.8)

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Characteristic	Known outcomes		Unknown outcomes		
	Alive *n* (%)	Died *n* (%)	Lost to follow-up *n* (%)	Transferred out *n* (%)	Total
Unknown (no CD4 count)	14 (1.6)	41 (18.2)	31 (27.2)	20 (6.0)	106 (6.8)
Acute nutrition status[§]					
Normal	476 (53.6)	91 (40.4)	59 (51.8)	189 (56.6)	815 (52.2)
Mild malnutrition	70 (7.8)	15 (6.7)	6 (5.2)	13 (3.9)	104 (6.7)
Moderate malnutrition	183 (20.7)	30 (13.3)	15 (13.2)	64 (19.2)	292 (18.7)
Severe malnutrition	159 (17.9)	89 (39.6)	34 (29.8)	68 (20.3)	350 (22.4)
Sequence of anti-tuberculosis treatment and ART					
ART 0–2 months after start of anti-tuberculosis treatment	137 (15.4)	44 (19.5)	11 (9.7)	51 (15.3)	243 (15.6)
ART 2–6 months after start of anti-tuberculosis treatment	173 (19.5)	31 (13.8)	15 (13.2)	52 (15.6)	271 (17.4)
ART >6 months after start of anti-tuberculosis treatment	335 (37.7)	48 (21.4)	12 (10.5)	86 (25.7)	481 (30.8)
ART before start of anti-tuberculosis treatment	132 (14.9)	27 (12.0)	3 (2.6)	36 (10.8)	198 (12.7)
No ART	111 (12.5)	75 (33.3)	73 (64.0)	109 (32.6)	368 (23.5)
Total	888 (100)	225 (100)	114 (100)	334 (100)	1561 (100)

[*] Patients with concurrent PTB and lymph node TB were classified as PTB.

[†] Patients with a distant history of TB could be WHO Clinical Stage I or II, depending on other history and examination findings.

[‡] Based on CD4 result closest in time to anti-tuberculosis treatment, classification per WHO guidelines.

[§] Includes imputed data for 757 patients with missing historical nutritional data at the time of TB diagnosis.

TB = tuberculosis; HIV = human immunodeficiency virus; PTB = pulmonary TB; WHO = World Health Organization; ART = antiretroviral therapy.

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Table 3

Factors associated with mortality in Malawian TB-HIV co-infected children

	Univariate regression		Multivariate regression	
Variable	**OR (95%CI)**	***P* value**	**aOR (95%CI)***	***P* value**
Age at TB diagnosis				
<12 months	2.94 (1.74– 4.97)	<0.001†	1.69 (0.89–3.22)	0.112
1–3 years	1.24 (0.76–2.03)	0.39	1.03 (0.57–1.86)	0.920
>3–5 years	0.67 (0.35–1.27)	0.22	0.78 (0.36–1.68)	0.521
>5–10 years	0.67 (0.39–1.15)	0.15	0.70 (0.37–1.31)	0.259
>10–18 years	Reference		Reference	
Sequence of anti-tuberculosis treatment and ART				
ART 0–2 months after start of anti-tuberculosis treatment	Reference		Reference	
ART 2–6 months after start of anti-tuberculosis treatment	0.45 (0.33–0.93)	0.025†	0.88 (0.49–1.59)	0.673
ART >6 months after start of anti-tuberculosis treatment	0.45 (0.28–0.70)	0.001†	0.72 (0.39–1.33)	0.292
ART before start of anti-tuberculosis treatment	0.64 (0.37–1.09)	0.099	1.23 (0.65–2.31)	0.524
No ART	2.10 (1.34–3.29)	0.001†	8.83 (4.42–17.63)	<0.001†
Sex				
Male	1.50 (1.11–2.02)	0.008†	1.70 (1.15–2.52)	0.008†
Female	Reference		Reference	
Type of TB				
Pulmonary TB	1.94 (1.17–3.22)	0.013†	1.56 (0.83–2.93)	0.169
Other TB	Reference		Reference	
Maximum WHO Stage				
Stage III	Reference		Reference	
Stage IV	4.67 (3.43–6.37)	<0.001†	4.48 (2.91–6.90)	<0.001†
Acute nutrition status				
Normal	Reference		Reference	
Mild malnutrition	1.12 (0.61–2.04)	0.710	1.51 (0.74–3.11)	0.259
Moderate malnutrition	0.86 (0.55–1.34)	0.500	1.00 (0.58–1.71)	0.988
Severe malnutrition	2.93 (2.08– 4.13)	<0.001†	1.06 (0.63–1.80)	0.822
Immune suppression				
None	Reference		Reference	
Mild	1.78 (0.77– 4.19)	0.179	1.86 (0.74– 4.73)	0.189
Advanced	1.57 (0.67–3.66)	0.297	1.84 (0.70– 4.82)	0.217
Severe	4.76 (2.69–8.43)	<0.001†	6.02 (2.98–12.17)	<0.001†

*Adjusted for all other covariates in the model.

†Statistically significant.

TB = tuberculosis; HIV = human immunodeficiency virus; OR = odds ratio; CI = confidence interval; aOR = a djusted OR; ART = antiretroviral therapy; WHO = World Health Organization.