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Tuberculosis prevalence, incidence, and prevention in a South African cohort of children living with HIV

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Summary

Background—We describe tuberculosis (TB) disease among antiretroviral treatment (ART) eligible children living with HIV (CLHIV) in South Africa to highlight TB prevention opportunities.

Methods—In our secondary analysis among 0–12 year-old ART-eligible CLHIV in five Eastern Cape Province health facilities from 2012–2015, prevalent TB occurred 90 days before or after enrollment; incident TB occurred > 90 days after enrollment. Characteristics associated with TB were assessed using logistic and Cox proportional hazards regression with generalized estimating equations.

Results—Of 397 enrolled children, 114 (28.7%) had prevalent TB. Higher income proxy (adjusted odds ratio [aOR] 1.8 [95% confidence interval (CI) 1.3–2.6] for the highest; 1.6 [95% CI 1.6–1.7] for intermediate), CD4+ cell count < 350 cells/μL (aOR 1.6 [95% CI 1.1–2.2]), and malnutrition (aOR 1.6 [95% CI 1.1–2.6]) were associated with prevalent TB. Incident TB was 5.2 per 100 person-years and was associated with delayed ART initiation (hazard ratio [HR] 4.7 [95% CI 2.3–9.4]), malnutrition (HR 1.8 [95% CI 1.1–2.7]), and absence of cotrimoxazole (HR 2.3 [95% CI 1.0–4.9]). Among 362 children with data, 8.6% received TB preventive treatment.

Conclusions—Among these CLHIV, prevalent and incident TB were common. Early ART, cotrimoxazole, and addressing malnutrition may prevent TB in these children.

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Lay summary

Background—We describe tuberculosis (TB) in children living with HIV (CLHIV) eligible for HIV treatment in South Africa to highlight opportunities to prevent TB.

Methods—We analyzed additional data from our original study of CLHIV who were 0–12 years-old and due to start HIV treatment in five health facilities in Eastern Cape Province from 2012–2015 and assessed characteristics associated with existing and new TB.

Results—Of 397 enrolled children, 114 (28.7%) had existing TB. Children with a higher measure of household income had higher odds of existing TB. CD4+ cell count < 350 cells/μL and malnutrition were also associated with existing TB. There were 5.2 new cases of TB for every 100 child-years. New TB was 4.7 times more likely for children with delayed HIV treatment start, 1.8 times more likely for children with malnutrition, and 2.3 times more likely for children who did not get cotrimoxazole. Among 362 children with data, 8.6% received treatment to prevent TB.

Conclusions—Among these CLHIV, existing and new TB were common. Early HIV treatment, cotrimoxazole, and addressing malnutrition may prevent TB in these children.

Keywords

childhood tuberculosis; tuberculosis preventive therapy; antiretroviral therapy; tuberculosis and HIV epidemiology

Introduction

Tuberculosis (TB) is a major cause of morbidity and mortality for adults and children living with HIV (CLHIV). Once infected with TB, persons living with HIV (PLHIV) are more likely to progress to TB disease, and persons living with TB/HIV coinfection are more likely to die of TB disease than persons without HIV[1]. Prior to the novel coronavirus-19 pandemic, TB was the leading cause of global deaths due to infectious disease in PLHIV including adults and children[2]. Of the 1.5 million TB deaths in 2020, 214,000 were in PLHIV[3].

In 2020, 7% of South Africa's reported 328,000 TB cases occurred in children less than 15 years old; however, the World Health Organization (WHO) does not have data on TB prevalence in South African CLHIV[4,5]. In the Western Cape region of South Africa, infants with HIV were 24.2 times more likely to get TB disease compared to infants without HIV[6]. For these reasons, TB and HIV in CLHIV should be appropriately diagnosed, treated, prevented, and reported, in accordance with national guidelines[7] and WHO[8] recommendations.

Early and effective antiretroviral treatment (ART) is one of the most important methods for preventing TB in all PLHIV[9]. In 2015 WHO recommended that all CLHIV receive protease inhibitors as part of an effective first line regimen and begin ART at the time of HIV diagnosis to improve outcomes[8]. We reviewed data on TB prevalence, incidence, and prevention at ART eligibility among a longitudinal cohort of South African CLHIV in routine care with recommended first-line ART to highlight characteristics associated with TB and describe opportunities for TB prevention.

Methods:

Study population

From 2012–2014, ART-naïve CLHIV 0–12 years of age receiving routine medical care at five health facilities in Eastern Cape Province were enrolled into a previously described[10] prospective cohort from the time they were identified as ART-eligible based on South African national guidelines[11,12]. Children enrolled in the study received routine medical care at the participating health facilities and CLHIV at two clinics attended referral facilities for TB diagnosis and treatment. Quarterly study visits were co-scheduled with routine HIV care visits and included caregiver interviews to collect data on the child's health and ART adherence. Data from medical charts and records were also abstracted.

During study enrollment and follow-up visits, caregivers were asked about the child's TB history or any new diagnosis of TB. TB diagnosis was also abstracted from the child's medical record at the health facility. Children were followed for up to 24 months with the last study visits in 2015. Enrolled children had routine CD4 cell count (CD4) and HIV RNA viral load (VL) monitoring based on 2010 and 2013 South African guidelines for children on ART[11,12]. ART was started based on recommended first-line regimens from these same guidelines (abacavir [ABC], lamivudine [3TC], lopinavir/ritonavir [LPV/r] for children under three years and ABC, 3TC, efavirenz [EFV] for children three years and older.

Definitions

A child had prevalent TB at study enrollment if there was a recorded TB disease diagnosis date in the medical record 90 days before or after the enrollment date, or if TB was reported in the medical chart or by a caregiver prior to the first follow-up visit which generally occurred 3 months after enrollment. Incident TB was defined as TB disease reported more than 90 days after study enrollment or after the first follow-up visit among children without prevalent TB at enrollment. Use of TB preventive therapy (TPT) prior to enrollment was ascertained from medical charts and defined for children with a recorded isoniazid preventive therapy start date prior to the date of enrollment. TB was categorized as pulmonary or extrapulmonary based on the recorded TB category in the medical record. Moderate malnutrition was defined as weight-for-age standardized Z-score (WAZ) less than or equal to two standard deviations below the mean. We considered the presence of an inside tap, inside toilet, or availability of electricity as a proxy for socioeconomic status or household income; children from households with all three were classified as the highest income proxy category, those with one or two were considered to have an intermediate income and those with none were considered to have the lowest income. Enrollment laboratory values (CD4, VL, and hemoglobin) included those recorded in the medical chart closest to the enrollment date (within one year before or up to 30 days after enrollment). Hemoglobin less than 8 mg/dL was defined as anemia. The definitions for all variables are otherwise included in Table 1.

Analytic methods

In this secondary analysis, characteristics of children with and without prevalent TB, TB treatment or TPT at enrollment were assessed using chi square, Cochran Mantel Haenszel, Wilcoxon rank sum and Kruskal-Wallis tests for categorical and continuous variables. Characteristics of children with and without TB were assessed using logistic regression with generalized estimating equations (GEE) to account for clustering within health facilities. Our multivariable regression model added variables with a p-value of less than 0.10 on bivariable GEE by forward selection (variables with missing values for more than 50% of children were excluded from the multivariable model). P-values of less than 0.05 (excluding missing levels) were considered to be significant. Analyses were conducted in SAS 9.4 (SAS Institute, Cary, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) along with the R survival package[13].

The TB incidence rate was determined using the person-time contributed by children beginning from enrollment until the date of TB diagnosis, or end of study follow-up. We used univariable Cox proportional hazards with GEE and a robust long-rank test to assess enrollment characteristics associated with incident TB disease among CLHIV without prevalent TB at enrollment and with at least one study follow-up visit after enrollment.

Ethical approval

Ethical and procedural reviews were obtained from Columbia University Medical Center Institutional Review Board, University of Cape Town Human Research Ethics Committee, East London Hospital Complex Research Ethics Committee, Walter Sisulu University Health Research Ethics Committee, and the Eastern Cape Department of Health. The protocol was also reviewed by the Centers for Disease Control and Prevention (CDC) and was determined to be research, but CDC investigators did not interact with participants or have access to identifiable data or specimens. Informed consent was not required.

Results

Cohort characteristics

Among 446 CLHIV identified as being eligible for ART, 401 caregivers gave consent, and 397 CLHIV enrolled in the cohort because 4 children had previous ART[10]. Enrolled children had a median age of 1.8 years (interquartile range [IQR] 0.4–7.2 years); 37.3% (n=148) were less than one year of age, and 20.2% (n=80) of children were either single or double orphans. More than half of children were male (52.4%; n=208) or were in the highest income proxy category (n=213; 53.7%). Most children had a CD4 at enrollment ≥ 350 cells/μL (60.5%, n=240/397 or 70.5% among 338 children with data) and a VL ≥ 10^5 copies/mL (62.2%, n=247/397 or 75.5% among 327 children with data). (Table 1).

Prevalent TB

Of 397 enrolled children, 114 (28.7%) had prevalent TB including: 29 (25.4%) infants younger than 1 year old; 39 (34.2%) children 1–4 years old; and 46 (40.4%) children 5–12 years old (Table 1). Children with prevalent TB had lower CD4 compared to children without prevalent TB (odds ratio [OR] 1.7; 95% CI 1.2–2.4) (Table 1). In the multivariable

model, enrollment CD4 less than 350 cells/μL (adjusted OR [aOR] 1.6; 95% CI 1.1–2.2), higher household income proxy (aOR 1.8; 95% CI 1.3–2.6 for the highest income proxy and aOR 1.6; 95% CI 1.6–1.7 for the intermediate income proxy both compared to the lowest income proxy), and moderate malnutrition at enrollment (aOR 1.6; 95% CI 1.1–2.6) were associated with prevalent TB (Table 1).

Incident TB

There were 246 children without enrollment TB who had at least one follow-up visit among the 397 enrolled children. Of the 246 children with follow-up (and no TB at enrollment), 20 (8.1%) had TB during study follow-up resulting in a TB incidence rate of 5.2 cases per 100 person-years. Time from enrollment to ART initiation differed significantly comparing children with and without incident TB: among CLHIV with incident TB, median time to ART was 52 days [interquartile range (IQR) 2–130] versus 9 days [IQR 0–21] in CLHIV without incident TB (p=0.03). CLHIV who initiated ART more than or equal to 60 days after ART eligibility had a nearly five-fold increased risk of incident TB (hazard ratio [HR] of 4.7, 95% CI 2.3–9.4) compared to those who started ART sooner (Table 2). Moderate malnutrition (HR 1.8, 95% CI 1.1–2.7) and lack of cotrimoxazole (HR 2.3, 95% CI 1.0–4.9) at study enrollment were also associated with higher hazards of incident TB (Table 2). Among the 19 children with incident TB who started ART, the median time from ART initiation to TB diagnosis was 253.0 days (IQR 140.5– 422.5).

TB management

Among all 134 CLHIV with prevalent or incident TB, the type of TB was listed for 80 children (59.7%). Of those with known TB type, most (83.8%; n=67) had pulmonary TB, while 10.0% (n=8) had extrapulmonary TB, and 6.3% (n=5) had both pulmonary and extrapulmonary TB. Most TB was diagnosed with a chest radiograph alone (68.6%, n=70), otherwise TB was diagnosed by chest radiograph and sputum (7.8%; n=8), sputum alone (5.9%; n=6), clinical diagnosis alone (4.9%; n=5), or other or unlisted methods (12.7%; n=13). A record of ever receiving TB treatment was documented for 97.8% (n=131) of 134 children with prevalent or incident TB.

TPT

TPT data were recorded for 362 of 397 children enrolled. Of these 362 children, 31 (8.6%) received TPT. Overall, TB occurred in 8 (25.8%) of 31 children with TPT. Among the 8 children with TPT who were diagnosed with TB, 7 (87.5%) had both a recorded TPT start date and TB diagnosis date. These 7 children were on TPT for a median of 14.0 days (IQR 6.0–279.0 days; range 3.0 to 529.0 days) before TB was diagnosed. There were 232 children without TB at enrollment who had both follow-up and TPT data. Among these 232 children, incident TB occurred in 1 out of 23 (4.4%) children given TPT and 18 out of 209 (8.6%) children who did not get TPT (p=0.7) (One child with incident TB was missing TPT data). Receipt of TPT did not differ by age (data not shown).

Cohort outcomes

Of 134 children with enrollment or incident TB, TB episode outcome was documented for n=107, or 91.5% of those eligible for outcome data. For children with documentation in the HIV records, 105 (98.1%) completed TB treatment, and 2 children defaulted TB treatment, including one child (8.3%) among the 12 with incident TB and known TB outcome. Among all 397 enrolled children, there were 35 deaths recorded (10.2%) among 342 children with known outcome. Children who died had a median age of 0.4 years (IQR 0.2–2.0 years). Verbal autopsy information was available for 32 deaths (91.4%) with a known cause of death recorded for 18 (56.3%) of these children. Among deaths with known cause, 3 (16.7%) deaths were reported to be related to TB.

Discussion

In this cohort of South African CLHIV eligible for ART from 2012–2014, we conducted a secondary analysis to assess factors associated with the development of TB, a disease with high morbidity and mortality among CLHIV[14]. Nearly one in three children had TB at the time that they were identified as eligible for ART. After entry into the cohort, TB incidence was 5 per 100 child-years. Lower CD4, malnutrition, and presumed higher household resources were associated with prevalent TB while malnutrition, lack of cotrimoxazole, and longer time to initiating ART were associated with incident TB.

The TB prevalence of 28.7% among CLHIV enrolled in this study was higher than has been seen in other sub-Saharan African settings (3.5–20.3%)[15–18] which may reflect the high TB prevalence in South Africa[19]. Our TB incidence of 5.2 cases/100 person-years, however, is similar to other published estimates of TB incidence among CLHIV in low resource settings of 1.3–17.5 per/100 years[15–17,20–23]. We found the median time to ART initiation in children with incident TB was nearly six times longer than in children without incident TB. In addition to better outcomes for PLHIV, early ART is associated with decreased TB risk [9,24,25]. It is possible that delayed ART initiation may have contributed to TB in this cohort. Ideally, CLHIV should start ART as early as possible upon diagnosis.

CLHIV with moderate malnutrition had a higher hazard of incident TB during follow-up in our study. TB at ART initiation was associated with poor growth in a South African study of CLHIV[26]. Poor weight gain is an independent risk factor for TB[22,27]. Although not specifically addressed by these studies, it is possible that focused nutritional supplementation in addition to provision of ART in these children may reduce the risk of developing TB disease.

We found a barely statistically significantly greater hazard of incident TB among children who were not prescribed cotrimoxazole. Crook et al. also found that children randomized to discontinue cotrimoxazole after ART had a higher unadjusted hazard of incident TB noting that cotrimoxazole has shown anti-tuberculous activity and synergy with rifampicin[22]. Another study with increased adjusted hazards for TB in CLHIV without cotrimoxazole did not suggest a proposed mechanism[15].

Current and previous South African HIV treatment guidelines do not recommend TPT for all CLHIV but instead indicate that TPT should be given to known contacts of persons with TB if contacts are children younger than 5 years of age or PLHIV (which includes CLHIV)[11,28]. Of the few children with documented TPT data who later developed TB in our study, isoniazid was started a median of 14 days prior to TB being diagnosed suggesting that at least half of these children had not been on isoniazid long enough for it to have prevented TB and these children likely already had TB when they started TPT. This potential situation underscores the importance of evaluating for (and treating if present) active TB disease in TB contacts prior to starting TPT[29]. The protective effect of TPT in preventing TB has been documented in adult and pediatric studies in which isoniazid was associated with reduced TB and mortality[30,31] excluding one pediatric randomized control trial that did not find reduced TB incidence when isoniazid was given to infants less than 1 year of age[32].

TB indicators may have had missing values because of the 1) limitations of data collected in a programmatic setting, 2) separate institutions for TB and HIV care for two HIV facilities, and 3) fact that the initial data collection was not focused on TB indicators as this was a secondary analysis. Data on TB indicators should be included in HIV program records as recommend by WHO guidelines for TB HIV program integration[33]. Finally, there is the possibility that TB was misclassified because TB diagnosis was not standardized and may not have captured all children with TB. Additionally, among children for whom TB was diagnosed, there were 5 children for whom TB was diagnosed on the basis of clinical features alone, and another 13 children for whom TB diagnostic methods were not specified leading to additional diagnostic uncertainty in the TB diagnosis. TB microbiological diagnosis in these CLHIV could be increased since only 14% had sputum collected and radiographic evaluation alone may miss children with TB[34]. Newer molecular TB diagnostics can improve the diagnostic yield particularly compared to microscopy[35].

Among the CLHIV in this longitudinal South African cohort representative of CLHIV in these facilities, we found that nearly a third of children had reported TB at the time of enrollment into ART treatment and 5% developed incident TB. Additional studies to evaluate TPT use in routine programmatic settings are needed to document the impact of TPT in South African CLHIV. Ensuring that CLHIV have a timely HIV diagnosis, initiating CLHIV on ART as soon as possible after HIV diagnosis, ensuring that children are started on cotrimoxazole, and preventing malnutrition may contribute to lowering the incidence of this deadly infectious disease.

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Table 1:

Characteristics of children living with HIV with and without enrollment (prevalent) tuberculosis (TB) with odds ratio for prevalent TB at enrollment [antiretroviral therapy (ART) eligibility]; N=397

Characteristic at enrollment (antiretroviral therapy eligibility)	Total N	Total percent	No enrollment (prevalent) TB[a] N= 283 n (%)	Enrollment (prevalent) TB[a] N=114 n (%)	P-value (chi square or Cochran Mantel Haenszel)	Univariate OR[b] (95% CI[c])	P-value	Multivariable aOR[d] (95% CI[c])	P-value
Age category									
< 1 year	148	37.3%	119 (42.0)	29 (25.4)	0.01	0.4 (0.2–1.0)	0.05		
1-<5 years	120	30.2%	81 (28.6)	39 (34.2)		0.8 (0.4–1.5)	0.53		
5–12 years	129	32.5%	83 (29.3)	46 (40.4)		Reference			
Sex									
Female	189	47.6%	137 (48.4)	52 (45.6)	0.61	0.9 (0.6–1.4)	0.64		
Male	208	52.4%	146 (51.6)	62 (54.4)		Reference			
Orphan and vulnerable child status									
Both parents alive	308	77.6%	222 (78.4)	86 (75.4)	0.29	0.8 (0.5–1.2)	0.28		
At least one parent died	80	20.2%	53 (18.7)	27 (23.7)		Reference			
Missing	9	2.3%	8 (2.8)	1 (0.9)		0.2 (0.1–0.5)	<0.01		
Income proxy category									
Lowest	35	8.8%	27 (9.5)	8 (7.0)	0.72	Reference		Reference	
Intermediate	149	37.5%	105 (37.1)	44 (38.6)		1.5 (1.3–1.8)	<0.01	1.6 (1.6–1.7)	<0.01
Highest	213	53.7%	151 (53.4)	62 (54.4)		1.8 (1.4–2.4)	<0.01	1.8 (1.3–2.6)	<0.01
CD4 cell count									
<350 cells/μL	98	24.7%	63 (22.3)	35 (30.7)	0.19	1.7 (1.2–2.4)	0.01	1.6 (1.1–2.2)	0.01
>=350 cells/μL	240	60.5%	178 (62.9)	62 (54.4)		Reference		Reference	
Missing	59	14.9%	42 (14.8)	17 (14.9)		1.3 (0.8–2.1)	0.26	1.3 (0.9–2.0)	0.15
HIV RNA viral load									
>= 10^5 copies/mL	247	62.2%	171 (60.4)	76 (66.7)	0.46	1.3 (0.8–2.1)	0.30		
< 10^5 copies/mL	80	20.2%	61 (21.6)	19 (16.7)		Reference			
Missing	70	17.6%	51 (18)	19 (16.7)		1.2 (0.9–1.6)	0.14		

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Characteristic at enrollment (antiretroviral therapy eligibility)	Total N	Total percent	No enrollment (prevalent) TB[a] N= 283 n (%)	Enrollment (prevalent) TB[a] N=114 n (%)	P-value (chi square or Cochran Mantel Haenszel)	Univariate OR[b] (95% CI[c])	P-value	Multivariable aOR[d] (95% CI[c])	P-value
Any prior TB[a] disease									
No	347	87.4%	246 (86.9)	101 (88.6)	0.65	1.2 (0.8–1.8)	0.31		
Yes	50	12.6%	37 (13.1)	13 (11.4)		Reference			
Moderate malnutrition (weight for age z score < 2 sd[e] below the mean)									
No	184	46.3%	139 (49.1)	45 (39.5)	0.01	0.6 (0.4–0.9)	0.02	Reference	
Yes	161	40.6%	102 (36.0)	59 (51.8)		Reference		1.6 (1.1–2.6)	0.03
Missing	52	13.1%	42 (14.8)	10 (8.8)		0.5 (0.4–0.7)	<0.01	0.9 (0.8–1.0)	0.11
Anemia (hemoglobin < 8 mg/dL)									
No	157	39.5%	119 (42)	38 (33.3)	<0.01	Reference			
Yes	19	4.8%	7 (2.5)	12 (10.5)		4.9 (3.2–7.3)	<0.01		
Missing	221	55.7%	157 (55.5)	64 (56.1)		1.4 (1.0–1.8)	0.03		
Cotrimoxazole ever given									
No	332	83.6%	233 (82.3)	99 (86.8)	0.39	0.9 (0.7–1.2)	0.57		
Yes	46	11.6%	34 (12.0)	12 (10.5)		Reference			
Missing	19	4.8%	16 (5.7)	3 (2.6)		0.5 (0.1–2.5)	0.42		
Isoniazid preventive therapy ever given									
No	331	83.4%	236 (83.4)	95 (83.3)	0.58	1.4 (0.8–2.5)	0.25		
Yes	31	7.8%	24 (8.5)	7 (6.1)		Reference			
Missing	35	8.8%	23 (8.1)	12 (10.5)		1.8 (0.6–5.9)	0.31		

[a] TB=tuberculosis

[b] OR=odds ratio

[c] CI=confidence interval

[d] aOR=adjusted odds ratio

[e] sd= standard deviations

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Table 2:

Characteristics of children with and without incident tuberculosis (TB) and hazard ratio for incident TB among children with no tuberculosis and a follow-up visit; N=246

Characteristic at antiretroviral therapy eligibility	Total N	Total percent	No incident TB[a] N=226 n (%)	Incident TB[a] N=20 n (%)	Hazard ratio (95% CI[b])	P-value
Age category						
< 1 year	95	38.6%	88 (38.9%)	7 (35.0%)	Reference	
1-<5 years	73	29.7%	64 (28.3%)	9 (45.0%)	1.6 (0.9–2.7)	0.11
5–12 years	78	31.7%	74 (32.7%)	4 (20.0%)	0.6 (0.3–1.2)	0.16
Sex						
Female	122	49.6%	112 (49.6%)	10 (50.0%)	Reference	
Male	124	50.4%	114 (50.4%)	10 (50.0%)	1.0 (0.2–4.3)	0.99
Orphan and vulnerable child status						
Both parents alive	188	76.4%	171 (75.7%)	17 (85.0%)	Reference	
At least one parent died	50	20.3%	47 (20.8%)	3 (15.0%)	0.6 (0.2–2.0)	0.41
Missing	8	3.3%	8 (3.5%)	0	**	**
Income proxy category						
Lowest	21	8.5%	19 (8.4%)	2 (10.0%)	Reference	
Intermediate	93	37.8%	83 (36.7%)	10 (50.0%)	1.4 (0.4–5.5)	0.63
Highest	132	53.7%	124 (54.9%)	8 (40.0%)	0.7 (0.1–5.8)	0.77
CD4 count						
<350 cells/ μL	55	22.4%	55 (24.3%)	0	Reference	
>=350 cells/ μL	162	65.9%	144 (63.7%)	18 (90.0%)	**	**
Missing	29	11.8%	27 (11.9%)	2 (10.0%)	**	**
HIV RNA viral load						
>= 10^5 copies/mL	152	61.8%	138 (61.1%)	14 (70.0%)	Reference	
< 10^5 copies/mL	58	23.6%	54 (23.9%)	4 (20.0%)	0.8 (0.3–1.9)	0.55
Missing	36	14.6%	34 (15.0%)	2 (10.0%)	0.6 (0.1–2.3)	0.46
Any prior TB[a] disease						

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Characteristic at antiretroviral therapy eligibility	Total N	Total percent	No incident TB[a] N=226 n (%)	Incident TB[a] N=20 n (%)	Hazard ratio (95% CI[b])	P-value
No	218	88.6%	199 (88.1%)	19 (95.0%)	Reference	
Yes	28	11.4%	27 (11.9%)	1 (5.0%)	0.3 (0.1–1.6)	0.17
Moderate malnutrition (weight for age z score < 2 sd[c] below the mean)						
No	131	53.3%	123 (54.5%)	8 (40.0%)	Reference	
Yes	92	37.4%	82 (36.3%)	10 (50.0%)	1.8 (1.1–2.7)	0.01
Missing	23	9.3%	21 (9.3%)	2 (10.0%)	1.8 (0.5–7.2)	0.40
Anemia (hemoglobin < 8 mg/dL)						
No	107	43.5%	98 (43.4%)	9 (45.0%)	Reference	
Yes	7	2.8%	7 (3.1%)	0	**	**
Missing	132	53.7%	121 (53.5%)	11 (55.0%)	1.2 (0.5–2.8)	0.67
Cotrimoxazole ever given						
No	26	10.6%	22 (9.7%)	4 (20.0%)	2.3 (1.0–4.9)	0.04
Yes	210	85.4%	194 (85.8%)	16 (80.0%)	Reference	
Missing	10	4.1%	10 (4.4%)	0	**	**
Isoniazid preventive therapy ever given						
No	209	85.0%	191 (84.5%)	18 (90.0%)	2.2 (0.5–8.8)	0.27
Yes	23	9.3%	22 (9.7%)	1 (5.0%)	Reference	
Missing	14	5.7%	13 (5.8%)	1 (5.0%)	2.7 (1.3–5.7)	0.01
Initial ART regimen						
NRTI[d] + NNRTI[e]	88	35.8%	84 (37.2%)	4 (20.0%)	Reference	
NRTI[d]+PI[f]	150	61.0%	135 (59.7%)	15 (75.0%)	3.3 (1.0–10.4)	0.05
No regimen	8	3.3%	7 (3.1%)	1 (5.0%)	9.5 (4.0–22.7)	<0.01
Time to ART after eligibility						
< 60 days	206	83.7%	195 (86.3%)	11 (55.0%)	Reference	
≥ 60 days	35	14.2%	27 (11.9%)	8 (40.0%)	4.7 (2.3–9.4)	< 0.01
Missing	5	2.0%	4 (1.8%)	1 (5.0%)	14.1 (1.9–107.8)	0.01

[a] TB=tuberculosis

[b] CI=confidence interval

[c] sd= standard deviations

[d] NRTI= Nucleoside reverse transcriptase inhibitor

[e] NNRTI=Non-nucleoside reverse transcriptase inhibitor

[f] PI=protease inhibitor

** = indicates hazard ratio models that did not converge, indicating that the estimate was unstable and thus could not be calculated