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## Tuberculosis in human immunodeficiency virus-infected children starting antiretroviral therapy in Côte d'Ivoire

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### SUMMARY

**SETTING:** In Côte d'Ivoire, more than 2000 human immunodeficiency virus (HIV) infected children aged <15 years were started on antiretroviral therapy (ART) during 2004–2008.

**OBJECTIVES:** To estimate tuberculosis (TB) incidence and determinants among ART enrollees.

**DESIGN:** A nationally representative retrospective cohort study among 2110 children starting ART during 2004–2008 at 29 facilities.

**RESULTS:** At ART initiation, the median age was 5.1 years; 82% had World Health Organization Stage III/IV, median CD4% was 11%, 42% were severely undernourished (weight-for-age *Z*-score [WAZ] <−3), and 150 (7%) were taking anti-tuberculosis treatment. Documentation of TB screening before ART declined from 63% to 46% during 2004–2008. Children taking anti-tuberculosis treatment at ART enrollment had a lower median CD4% (9.0% vs. 11.0%, *P* = 0.037) and a higher prevalence of WAZ <−3 (59% vs. 40%, *P* < 0.001). Among children considered TB-free at ART enrollment, TB incidence was 6.28/100 child-years during days 0–90 of ART, declining to 0.56/100 child-years after 180 days. Children with one unit higher WAZ at ART enrollment had 13% lower TB incidence (adjusted HR 0.87, 95%CI 0.77–1.00, *P* = 0.047).

**CONCLUSIONS:** Ensuring clinician compliance with TB screening before ART and ensuring earlier ART initiation before children suffer from advanced HIV disease and nutritional compromise might reduce TB morbidity during ART.

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## RESUME

En Côte d'Ivoire, plus de 2000 enfants âgés de <15 ans positifs pour le virus de l'immuno-déficience humaine (VIH) ont débuté un traitement antirétroviral (ART) entre 2004 et 2008.

Estimer l'incidence de la tuberculose (TB) et ses déterminants chez ces enfants sous ART.

Une étude rétrospective de cohorte, représentative au niveau national, sur 2110 enfants ayant débuté leur ART entre 2004 et 2008 dans 29 établissements.

Lors de la mise en route du traitement, l'âge médian était de 5,1 ans, 82% étaient au Stade III-IV selon la classification de l'Organisation Mondiale de la Santé, le taux médian de CD4 était de 11%, 42% souffraient de malnutrition grave (score  $Z$  du rapport poids/âge [WAZ]  $<-3$ ) et 7% ( $n=150$ ) recevaient un traitement antituberculeux. Le dépistage de la TB avant la mise en route de l'ART a décliné de 63% à 46% de 2004 à 2008. Les enfants sous traitement anti-tuberculeux lors du démarrage de l'ART avaient un taux médian de CD4 plus bas (9% contre 11%;  $P=0,037$ ) et une prévalence plus élevée de malnutrition grave ( $<-3$ ) (59% contre 40%;  $P<0,001$ ). Parmi les enfants considérés comme exempts de TB lors de l'inclusion, l'incidence de la TB a été de 6,28/100 enfants-années pendant les 90 premiers jours du ART, tombant à 0,56/100 enfants-années au-delà de 180 jours. Les enfants dont le WAZ était plus élevé d'un degré ont eu une incidence de TB inférieure de 13% (aHR 0,87 ; IC95% 0,77–1.00 ;  $P=0,047$ ).

La morbidité de la TB pendant un ART pourrait être réduite à condition que le personnel de santé dépiste systématiquement la TB avant la mise en route du traitement et instaure le ART précocement avant que les enfants ne souffrent d'une infection à VIH avancée et que leur état nutritionnel ne soit compromis.

## RESUMEN

En Côte d'Ivoire, más de 2000 niños de <15 años de edad infectados por el virus de la inmunodeficiencia humana (VIH) iniciaron el tratamiento antirretrovírico (ART) entre el 2004 y el 2008.

Calcular la incidencia de tuberculosis (TB) y los factores determinantes de la aparición de TB en los pacientes inscritos en el programa de ART.

Se llevó a cabo un estudio retrospectivo de cohortes representativo a escala nacional en 2110 niños que comenzaron el ART entre el 2004 y el 2008 en 29 centros.

Al comienzo del ART la mediana de la edad fue 5,1 años; el 82% de los casos se encontraban en la fase III o IV según la clasificación de la Organización Mundial de la Salud; la mediana del recuento de células CD4 fue 11%; el 42% presentaba una desnutrición grave (puntuación  $Z$  del peso según la edad [WAZ]  $<-3$ ); y 150 niños recibían tratamiento antituberculoso (7%). La documentación de una detección sistemática de la TB antes de iniciar el ART disminuyó de 63% a 46% durante el período del estudio. Los niños que recibían tratamiento antituberculoso en el momento de iniciar el ART presentaban una mediana más baja del recuento de células CD4 (9,0% contra 11,0%;  $P=0,037$ ) y una mayor prevalencia de WAZ  $<-3$  (59% contra 40%;  $P<0,001$ ). En los niños que se consideraron sin TB en el momento de iniciar el ART, la incidencia de esta enfermedad fue 6,28 por 100 años-niño en los días 0 a 90 del tratamiento y disminuyó a 0,56 por 100 años-niño después de 180 días. La incidencia de TB en los niños con una unidad más alta en la WAZ al inicio del ART fue un 13% inferior (HR ajustado 0,87; IC95% 0,77 – 1,00;  $P=0,047$ ).

Es posible disminuir la morbilidad por TB durante la administración del ART cuando se logra el cumplimiento de la detección sistemática de la TB antes de iniciar el ART y se inician los medicamentos contra el virus de manera más temprana, antes de que los niños sufran una infección avanzada por el VIH y deterioro nutricional.

## Keywords

pediatric; incident tuberculosis; tuberculosis screening; Ivory Coast

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THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) epidemic in sub-Saharan Africa has fuelled the pre-existing tuberculosis (TB) epidemic.<sup>1</sup> The increased burden of TB among HIV-infected adults has been associated with increased transmission of TB to household members, including children.<sup>2,3</sup> Post mortem studies suggest that TB is a leading cause of mortality in HIV-infected children, accounting for 12–18% of deaths.<sup>4,5</sup> Even if TB is diagnosed and treated, incident TB in children can lead to chronic lung disease, including bronchiectasis,<sup>6</sup> causing lifelong morbidity.

Evaluating the burden and predictors of TB among HIV-infected children starting ART, and clinician compliance with TB screening before ART, can help TB-HIV program managers identify program improvement opportunities.<sup>7</sup> Previous studies in Côte d'Ivoire have focused on small cohorts of children in the capital city, Abidjan,<sup>8,9</sup> limiting the usefulness of findings for national TB-HIV program managers.

We conducted a large, nationally representative retrospective cohort study among 2110 children starting ART in Côte d'Ivoire during 2004–2008 at 29 facilities to assess clinician compliance with TB screening guidelines, the prevalence and determinants of active TB among new pediatric ART enrollees, and incidence and predictors of TB during ART.

## METHODS

### ART eligibility

During 2004–2008, children aged 0–14 years diagnosed with World Health Organization (WHO) Stage IV disease, WHO Stage III disease if <12 months old, or with certain clinical conditions including TB, were eligible for ART regardless of CD4<sup>+</sup> T-cell (CD4) % or count. Children not yet eligible by clinical criteria could be eligible for ART based on age-dependent CD4% or count criteria, as described in the 2006 WHO treatment guidelines.<sup>10</sup> Recommended ART regimens for children with HIV-1 infection include two nucleoside reverse transcriptase inhibitors (NRTI) and either nevirapine (NVP) or efavirenz (EFV). For children with TB co-infection, NVP was replaced with either EFV or a third NRTI, depending on the age of the child. For first-line ART for HIV-2-infected children, two NRTIs and a ritonavir-boosted protease inhibitor were recommended.

### ART monitoring

Côte d'Ivoire guidelines recommend that pediatric ART patients be seen frequently initially (at 2 weeks, monthly for 3 months and quarterly thereafter) until stable, and then at least

every 6 months,<sup>10</sup> to evaluate disease progression or improvement. At each visit, standard Ministry of Health (MOH) recommended medical records are completed. Documentation of whether TB screening was performed and results of any TB diagnostic tests is recommended at all clinic visits. Recommended TB screening practices for children included assessment for 1) poor weight gain, 2) current fever, 3) chronic cough, 4) TB contact history, and 5) night sweats. Recommended TB tests for all child TB suspects included 1) Mantoux skin test, 2) two sputum samples (or gastric aspirates) sent for smear microscopy, 3) one sputum (or gastric aspirate) sent for TB culture, and 4) chest X-ray. If extra-pulmonary TB was suspected, lymph node aspiration, lumbar puncture and abdominal ultra-sound were additional diagnostic tests available at some facilities. In reality, only two laboratories provided TB culture; very few TB suspects would therefore have had sputum samples or gastric aspirates sent for TB culture.

### Study design and population

This was a nationally representative retrospective cohort study. By 1 January 2008, about 3000 children had initiated ART at 64 health facilities.<sup>11</sup> To improve study feasibility, only facilities with >10 pediatric ART enrollees by 1 January 2008 were considered eligible. Of 30 eligible facilities, 29 agreed to participate. According to MOH records, these 29 facilities had enrolled 2820 (94%) of all 3000 children enrolled nationally during 1998–2008. Because the medical records of ART enrollees before 2004 had considerable missing data, the protocol excluded 427/2820 enrollees (15%) who started treatment before 2004. A further 195 (7%) records could not be found, and 88 (3%) had been transferred with the child to another facility. All remaining 2110 records were included in the study. Data were collected from the MOH-recommended ART medical records by trained data abstractors from November 2009 to March 2010.

### Treatment outcomes

Children taking anti-tuberculosis treatment at ART initiation were considered prevalent TB cases. Children starting anti-tuberculosis treatment (for pulmonary or extra-pulmonary TB) during ART were considered incident TB cases.

### Exposure variables

All variables on MOH-recommended ART records were assessed as possible risk factors for TB (Table 1). Weight was recoded as weight-for-age Z-score (WAZ score), using Centers for Disease Control and Prevention (CDC) growth curves for children aged 5–14 years, and WHO curves for children aged 0–<5 years.

### Analysis

Data were analyzed using Stata 11 (StataCorp, 2009, Stata Statistical Software, Release 11, College Station, TX, USA). Missing data are reported for each covariate of interest and were assumed to be missing at random (MAR). If <30% of observations were missing data for a baseline covariate of interest, multiple imputation with chained equations was used to impute the missing data.<sup>12</sup> The ICE (imputation by chained equations)<sup>13</sup> procedure in Stata was used to create 20 imputed data sets for the key outcome of interest: TB incidence. The

imputation model included the event indicator, all study variables and the Nelson-Aalen estimate of cumulative hazard.<sup>14</sup> In all analyses involving imputed data, estimates were combined across data sets according to Rubin's rules.<sup>12</sup> Using imputed data, associations between baseline covariates and prevalent TB were assessed using bivariate logistic regression, with random effects specified for each facility.

As ART medical records did not routinely document the date of anti-tuberculosis treatment cessation, time at risk for incident TB among prevalent TB cases could not be estimated. As in other studies, in time-to-event analysis, patients with prevalent TB were excluded from the cohort at risk.<sup>15</sup> Patients who were included in the cohort at risk, but were not diagnosed as having incident TB during follow-up, were censored at the most recent visit, date of death if death occurred, or date of transfer if transferred.

Cox proportional hazards regression models were used to estimate non-adjusted and adjusted hazard ratios (HR and aHR), with random effects specified for ART facility. The proportional hazards assumption was assessed using visual methods and the Grambsch and Therneau test.<sup>16</sup> Kaplan-Meier curves were used to examine the cumulative probability of remaining undiagnosed with TB over time stratified by baseline variables.

## Ethics

This study was approved by the Ivorian Ethics Review Committee and the Institutional Review Boards of the United States CDC and the Harvard School of Public Health.

## RESULTS

### Patient characteristics at ART initiation

Among 2110 children starting ART during 2004–2008, the median age was 5.1 years, and 150 (7%) were receiving anti-tuberculosis treatment (prevalent TB cases). The median age of the prevalent TB cases was older than that of children considered TB-free (6.7 vs. 5.0 years,  $P < 0.001$ ) (Table 1). The majority of the children (99%) were HIV-1-infected; only 15 (0.7%) were HIV-2-infected, and five (0.2%) were dually HIV-1 and -2 seroreactive. HIV type was not associated with prevalent TB ( $P = 0.553$ ).

Markers of advanced HIV disease were common among ART enrollees; 29% had WHO Stage IV, 42% had severe under-nutrition (WAZ  $< -3$ ), and median CD4% was 11%. Compared with children considered TB-free at ART initiation, children with prevalent TB were more likely to have WHO Stage IV disease (72% vs. 25%,  $P < 0.001$ ), to have severe under-nutrition (59% vs. 40%,  $P < 0.001$ ), and to have a lower median CD4% (9.0% vs. 11.0%,  $P = 0.037$ ).

Compared with children assessed as TB-free, prevalent TB cases were more likely to start ART at tertiary care facilities (51% vs. 32%,  $P = 0.011$ ) and at facilities lacking nutritional support programs (83% vs. 65%,  $P = 0.007$ ).

## TB screening

Overall, 1012 (48%) children had documentation of TB screening before ART initiation; 723 (34%) were screened for chronic cough, 565 (27%) for fever, 391 (19%) for TB contact, 366 (17%) for weight loss, and 228 (11%) for night sweats. Only 10% of children had documentation of screening for all five symptoms. The proportion of medical records with documentation of any TB screening before the start of ART declined from 63% to 46% during 2004–2008. The proportions of patients screened for at least one TB symptom before ART varied widely by clinic, from 0% to 93%. At 25/29 clinics, <80% of ART enrollees had some documentation of screening for TB (Figure 1).

## TB incidence

Among the 1960 children assessed as TB-free at the start of ART, 56 (3%) were documented to start TB treatment during 4190 child-years (cy) of follow-up, at a rate of 1.34 cases/100 cy (95% confidence interval [CI] 1.03–1.74). Of 56 TB cases, 8 were extra-pulmonary TB (0.19 cases/100 cy, 95% CI 0.09–0.37) and 48 were pulmonary TB (1.14 cases/100 cy, 95% CI 0.86–1.52). The overall TB incidence rate was highest in days 0–90 of ART, at 6.28/100 cy (95% CI 4.31–9.16). This rate declined to 2.52/100 cy (95% CI 1.36–4.69) during days 91–180 of ART, and 0.56/100 cy (95% CI 0.36–0.89) thereafter.

## Incident TB risk factors

A 1-year increase in age was borderline associated with increased TB incidence (aHR 1.08, 95% CI 0.99–1.15,  $P=0.067$ ) (Table 2). Each one-unit increase in WAZ was associated with a 13% reduction in TB incidence (aHR 0.87, 95% CI 0.77–1.00,  $P=0.047$ ) (Figure 2). Maternal and paternal orphan status and severe anemia were not associated with TB incidence risk.

## DISCUSSION

This is the largest and first nationally representative evaluation of TB incidence among children starting ART in Côte d'Ivoire,<sup>8,9</sup> and has several important findings.

### TB burden

TB prevalence at enrollment on ART (7%) is higher than that reported from previous studies in Western Kenya (3.6%),<sup>17</sup> Côte d'Ivoire (2–4%),<sup>8,9</sup> and Zambia (5.7%),<sup>18</sup> but is lower than that reported from Johannesburg, South Africa (29%).<sup>19</sup> There could be many reasons for the variation in TB prevalence at ART initiation, including variations in TB screening and diagnostic algorithms,<sup>20</sup> variations in the degree of immune suppression,<sup>7</sup> and variations in background TB incidence in the general population.<sup>19</sup> Earlier ART enrollment for HIV-infected children could reduce the burden of TB among ART enrollees.<sup>7,17</sup> To facilitate earlier ART enrollment, expansion of early infant diagnostic and referral services would be needed.<sup>11</sup>

Our reported TB incidence (1.34/100 cy), equivalent to about 1340 per 100 000 population, is considerably higher than the national average of 399/100000.<sup>21</sup> Our TB incidence rate is similar to previous Ivorian reports (1.3–2.1/100 cy),<sup>8,9</sup> but lower than reported South African

incidence rates among children starting ART (6.4/100 cy).<sup>22</sup> Higher background TB incidence in South Africa (971 vs. 399/100 000),<sup>21</sup> or better TB screening and diagnostic capability in South Africa, might explain the different rates.<sup>7</sup>

As in other studies,<sup>17,23,24</sup> TB incidence in our cohort was highest in days 0–90 of ART, and declined thereafter. Several mechanisms might explain the high early TB incidence rates.<sup>24</sup> Some early incident TB may be new active TB disease.<sup>24</sup> However, the majority of TB cases detected and treated in early ART are probably due to 1) ‘unmasking’ of subclinical disease present at ART initiation, or 2) worsening of symptomatic disease that went unscreened or undiagnosed before the start of ART.<sup>24</sup> Active disease may be subclinical at ART initiation because TB symptoms are dependent on both bacillary burden and immune response. The immune reconstitution associated with early ART can unmask new TB signs and symptoms, which in turn will initiate TB diagnostic or trial treatment protocols.<sup>24</sup> Among symptomatic children who went undiagnosed through failure to screen or diagnose pediatric TB,<sup>7</sup> ART could worsen TB symptoms, prompting more intensive TB diagnostics or a clinical trial of anti-tuberculosis treatment.<sup>24</sup> As in other retrospective cohort studies,<sup>22</sup> our reported TB prevalence and incidence rates may be underestimates due to failure to screen for and/or diagnose TB disease, or overestimates due to incorrect trials of anti-tuberculosis treatment in children with clinical TB diagnoses.

### **TB screening**

TB screening practices were suboptimal, appeared to worsen over time, and varied widely by clinic. Operational research assessing TB screening practices among pediatric ART enrollees is limited; one Thai study reported documentation of TB screening before pediatric ART for 60–90% of patients.<sup>25</sup> Poor documentation of, and declining clinician compliance with, TB screening are worrying, because undiagnosed TB at the start of ART is an important cause of morbidity and mortality.<sup>26</sup> Targeting the 25 clinics where <80% of pediatric ART enrollees were screened for at least one TB symptom with intensified training and supervision could reduce TB-associated morbidity and mortality among children starting ART.<sup>20</sup>

### **TB risk factors**

Markers of advanced HIV disease (advanced WHO stage, under-nutrition and low CD4%) were predictive of prevalent TB,<sup>8,17</sup> and higher WAZ at enrollment was protective against incident TB. Earlier initiation of ART, before advanced HIV disease, could reduce the TB burden among HIV-infected children.<sup>17</sup>

The association between lower WAZ and incident TB has been reported previously.<sup>17,23</sup> Possible explanations include the following: 1) active TB at ART enrollment, a possible cause of low WAZ, went undiagnosed due to insensitive diagnostic tests or failure to screen for TB;<sup>27</sup> 2) clinicians made presumptive diagnoses of TB after ART initiation because WAZ gain was suboptimal;<sup>17</sup> or 3) under-weight TB-free children at ART initiation are more at risk of developing active TB during follow-up due to malnutrition-induced impairment of cell-mediated immunity.<sup>28</sup>

To address failure to diagnose active TB at start of ART, it is essential to monitor and ensure TB screening before ART initiation. In addition, the rollout of the GeneXpert® MTB/RIF assay (Xpert, Cepheid, Sunnyvale, CA, USA), whose sensitivity in diagnosing culture-positive TB in HIV-infected children is twice that of smear microscopy (76% vs. 38%), should be accelerated.<sup>27</sup> To address the possibility that malnutrition is a root cause of the development of active TB during ART, there may be a role for expanding existing nutrition programs.<sup>28</sup> In our study, lack of a nutrition program at the clinic was associated with prevalent TB at ART initiation ( $P=0.007$ ), and was marginally associated with TB incidence in crude ( $P=0.075$ ), but not adjusted ( $P=0.323$ ), analysis. Further evaluation of pediatric HIV food supplementation programs are needed to assess their benefit and cost-effectiveness.<sup>28</sup>

As in other studies,<sup>17</sup> increased age was associated with prevalent TB and incident TB during follow-up. This may be due to more advanced immune suppression in older children at ART enrollment, or difficulties in diagnosing TB in younger children.<sup>17</sup>

### Limitations

This report has several limitations. First, due to the lack of data on the timing of anti-tuberculosis treatment cessation among prevalent TB cases, prevalent TB cases were excluded from the cohort at risk to estimate TB incidence. However, in a sensitivity analysis (data not shown), estimates of TB incidence with all patients included in the cohort at risk ( $n=2110$ ) did not differ from our reported TB incidence rate ( $n=1960$ ). Second, as described earlier, reported TB prevalence and incidence rates may be underestimates or overestimates of true TB burden due to difficulties in diagnosing pediatric TB. Third, missing data on covariates probably introduced non-differential measurement error. Fourth, some incident TB may have been prevalent cases, for whom the results of diagnostic tests only returned after ART initiation. Finally, lack of information on which children screened positive for TB, and, among TB suspects, which children were tested for and diagnosed with TB, limits our ability to assess clinician compliance with TB diagnosis guidelines.

### CONCLUSIONS

Among our cohort of pediatric ART enrollees, advanced HIV disease was common and was associated with both prevalent TB and incident TB. Earlier ART initiation could reduce the TB burden. In particular, initiation of ART at higher WAZ could reduce TB burden during ART. In addition, improved pre-ART clinician compliance with TB screening, and improved TB diagnostics (i.e., Xpert), could reduce TB incidence during ART.

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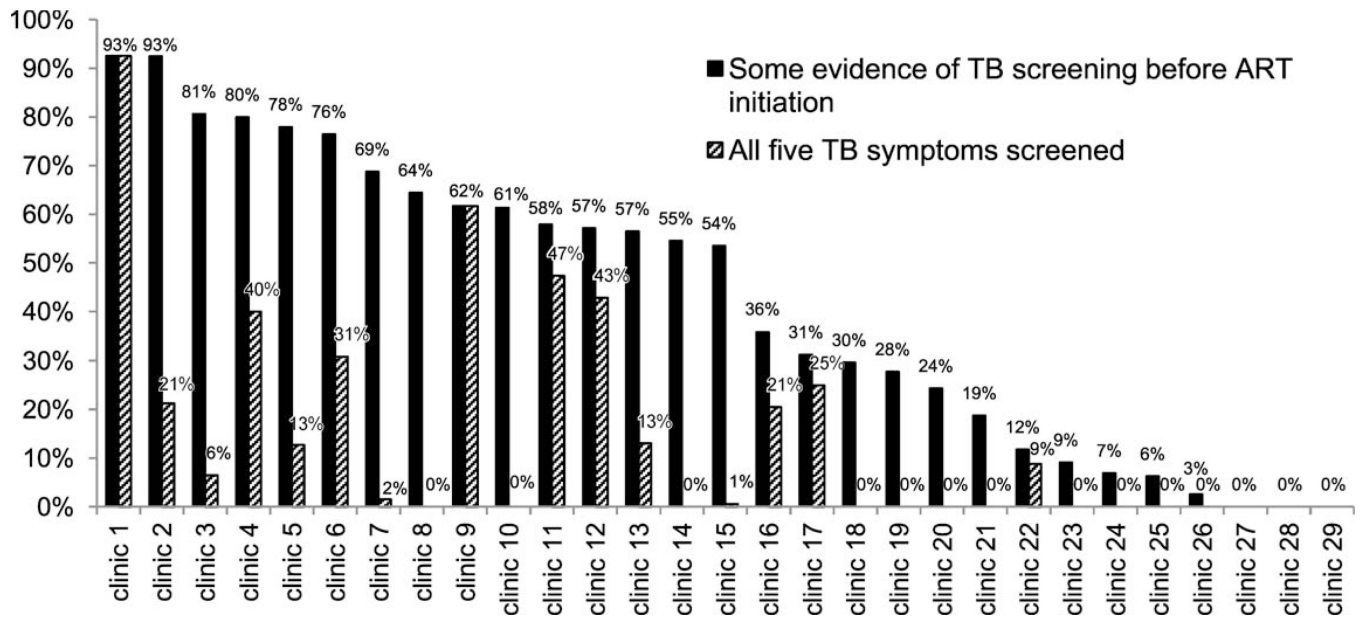
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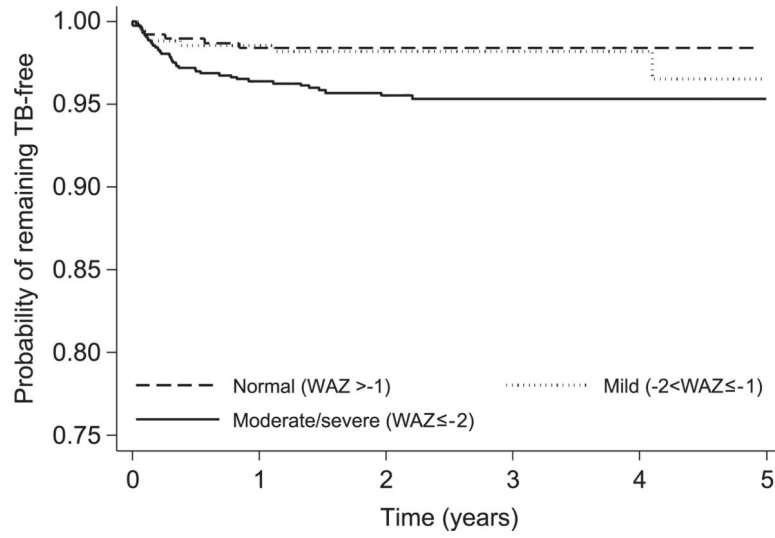


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**Figure 1.** Clinic-level differences in the proportion of pediatric ART medical records with documentation of TB screening before ART initiation. \*Some evidence of TB screening before ART initiation was defined as documentation of screening for at least one of the following: 1) poor weight gain, 2) current cough, 3) chronic fever, 4) TB contact, and 5) night sweats. Patients taking treatment at ART initiation were considered to have been screened for TB. TB = tuberculosis; ART = antiretroviral therapy.



**Figure 2.** Cumulative probability of remaining tuberculosis-free by WAZ. TB = tuberculosis; WAZ = weight-for-age Z-score.

Patient- and site-level characteristics at ART initiation by tuberculosis treatment status, Côte d'Ivoire, 2004–2008

Table 1

	All patients at enrollment (n = 2110)		Receiving anti-tuberculosis treatment* (n = 150)		Not receiving anti-tuberculosis treatment* (n = 1960)		P value <sup>†</sup>
	Original <sup>‡</sup>		Imputed <sup>*</sup>				
	n	%	n	%	n	%	
Age at enrollment, years, median [IQR]	2110	5.1 [2.2–8.8]	5.1 [2.2–8.8]	6.7 [3.2–10.7]	5.0 [2.1–3.2]	<0.001	
Sex							
Male	1146	54	54	54	54	0.952	
Females	964	46	46	46	46		
Maternal vital status							
Mother alive	1128	67	67	64	68	0.510	
Mother dead	549	33	33	36	32		
Missing	433	21					
Paternal vital status							
Father alive	1155	77	77	77	77	0.964	
Father dead	348	23	23	23	23		
Missing	607	29					
Type of HIV							
HIV-1	2044	99	99	99	99	0.553	
HIV-2 or dual HIV-1 & 2	20	1	1	1	1		
Missing	46	2					
WHO Stage							
I/II	329	19	19	4	20	<0.001	
III	939	53	53	24	55		
IV	510	29	29	72	25		
Missing	332	16					
Weight-for-age Z-score							
-1 (normal)	372	19	20	13	21	<0.001	
-2 — < -1 (mild)	357	19	18	15	19		

	All patients at enrollment ( <i>n</i> = 2110)				Receiving anti-tuberculosis treatment* ( <i>n</i> = 150)		Not receiving anti-tuberculosis treatment* ( <i>n</i> = 1960)		<i>P</i> value <sup>†</sup>
	Original <sup>‡</sup>		Imputed <sup>*</sup>		%	%	%	%	
	<i>n</i>	%	<i>n</i>	%					
-3 — < -2 (moderate)	383	20	20	20	14	20	20		
< -3 (severe)	798	42	42	42	59	40	40		
Missing	200	9							
CD4 cell count %, median [IQR]	1835	10.8 [5.4–15.0]	11.0 [6.0–15.0]		9.0 [4.0–13.0]	11.0 [6.0–15.0]		0.037	
Missing	275	13							
CD4 cell count, cells/ $\mu$ l, median [IQR]	1894	333 [116–618]	337 [122–621]		261 [78–547]	342 [126–624]		0.089	
Missing	216	10							
Hemoglobin, g/dl, median [IQR]	1759	9.3 [8.3–10.3]	9.3 [8.3–10.4]		9.5 [8.5–10.6]	9.3 [8.3–10.3]		0.246	
Missing	351	17							
ART site size									
100 ART children ever	1210	57	57		69	56	56	0.072	
< 100 ART children ever	900	43	43		31	44	44		
ART site type									
Primary	1181	56	56		43	57	57	0.011	
Secondary	231	11	11		6	11	11		
Tertiary	698	33	33		51	32	32		
Any stock-out of ARVs (first- or second-line) in last year at ART site									
Yes	955	45	45		45	45	45	0.804	
No	1155	55	55		55	55	55		
Nutritional support at ART site?									
Yes	713	34	34		17	35	35	0.007	
No	1397	66	66		83	65	65		

\* Analyses utilized imputed data sets.

<sup>†</sup> Random effects bivariate logistic regression.

<sup>‡</sup> Original data before imputation.

ART = antiretroviral therapy; IQR = interquartile range; HIV = human immunodeficiency virus; WHO = World Health Organization; ARV = antiretroviral.

**Table 2** Patient- and site-level characteristics associated with TB incidence during ART among children starting ART, Côte d'Ivoire, 2004–2008

	Original <i>n</i>	Crude			Adjusted			
		Rate (per 100 cy)	HR	(95%CI)	<i>P</i> value	aHR	(95%CI)	<i>P</i> value
Age at enrollment, per year increase	1960	—	1.10	(1.03–1.18)	0.003	1.08	(0.99–1.15)	0.067
Sex								
Male	1065	1.03	1.00	—	—	1.00	—	—
Females	895	1.72	1.64	(0.96–2.78)	0.068	1.61	(0.94–2.76)	0.081
Maternal vital status								
Mother alive	1048	1.06	1.00	—	—	1.00	—	—
Mother dead	502	1.87	1.87	(1.05–3.34)	0.033	1.45	(0.77–2.72)	0.250
Paternal vital status								
Father alive	1067	1.31	1.00	—	—	1.00	—	—
Father dead	324	1.40	1.13	(0.58–2.23)	0.714	0.73	(0.35–1.52)	0.584
Year of ART start, per increase in calendar year	1960	—	0.98	(0.79–1.21)	0.841	0.88	(0.69–1.13)	0.313
WHO Stage								
I/II	324	0.70	1.00	—	—	1.00	—	—
III	904	1.28	1.95	(0.65–5.83)	0.232	1.82	(0.58–5.66)	0.299
IV	410	2.09	3.04	(0.98–9.41)	0.054	2.00	(0.58–6.93)	0.271
Undernutrition								
Per WAZ unit increase in severity	1911	—	0.81	(0.73–0.91)	0.001	0.87	(0.77–1.00)	0.047
CD4 cell count, %								
>20	149	0.71	1.00	—	—	1.00	—	—
10–20	825	1.15	1.78	(0.42–7.49)	0.434	1.75	(0.41–7.40)	0.446
<10	722	1.71	2.60	(0.61–11.0)	0.194	1.86	(0.42–8.23)	0.413
Hemoglobin, g/dl								
8	1327	1.21	1.00	—	—	1.00	—	—
<8	300	2.01	1.56	(0.78–3.13)	0.210	1.24	(0.58–2.66)	0.572
Site size								
>100 ART patients aged <15 years ever	1106	1.16	1.00	—	—	1.00	—	—
100 ART patients aged <15 years ever	854	1.75	1.22	(0.71–2.067)	0.471	1.26	(0.49–3.24)	0.996

	Original <i>n</i>	Crude			Adjusted		
		Rate (per 100 cy)	HR	(95%CI)	aHR	(95%CI)	P value
Site type							
Primary	1117	1.51	1.00	—	1.00	—	—
Secondary	222	0.66	0.43	(0.13–1.40)	0.32	(0.08–1.29)	0.109
Tertiary	621	1.34	0.84	(0.47–1.50)	0.82	(0.26–2.62)	0.742
Any stock-out of ARVs (first- or second-line) in last year							
No	1073	0.91	1.00	—	1.00	—	—
Yes	887	2.18	2.00	(1.17–3.43)	1.47	(0.60–3.59)	0.398
Nutritional support at site?							
Yes	687	0.86	1.00	—	1.00	—	—
No	1273	1.66	1.73	(0.95–3.18)	1.42	(0.55–3.68)	0.467
TB care provided onsite?							
Yes	625	1.63	1.00	—	1.00	—	—
No	1335	1.27	0.89	(0.51–1.57)	1.09	(0.45–2.67)	0.844

TB = tuberculosis; ART = antiretroviral therapy; cy = child-years; HR = hazard ratio; CI = confidence interval; aHR = adjusted hazard ratio; WHO = World Health Organization; WAZ = weight-for-age Z-score; ARV = antiretroviral.