Incidence of Tuberculosis Among HIV-Positive Individuals Initiating Antiretroviral Treatment at Higher CD4 Counts in the HPTN 071 (PopART) Trial in South Africa

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Introduction: Antiretroviral treatment (ART) guidelines recommend life-long ART for all HIV-positive individuals. This study evaluated tuberculosis (TB) incidence on ART in a cohort of HIV-positive individuals starting ART regardless of CD4 count in a programmatic setting at 3 clinics included in the HPTN 071 (PopART) trial in South Africa.

Methods: A retrospective cohort analysis of HIV-positive individuals aged ≥18 years starting ART, between January 2014 and November 2015, was conducted. Follow-up was continued until 30 May 2016 or censored on the date of (1) incident TB, (2) loss to follow-up from HIV care or death, or (3) elective transfer out; whichever occurred first.

Results: The study included 2423 individuals. Median baseline CD4 count was 328 cells/μL (interquartile range 195–468); TB incidence rate was 4.41/100 person-years (95% confidence interval [CI]: 3.62 to 5.39). The adjusted hazard ratio of incident TB was 0.27 (95% CI: 0.12 to 0.62) when comparing individuals with baseline CD4 >500 and ≤500 cells/μL. Among individuals with baseline CD4 count >500 cells/μL, there were no incident TB cases in the first 3 months of follow-up. Adjusted hazard of incident TB was also higher among men (adjusted hazard ratio 2.16; 95% CI: 1.41 to 3.30).

Conclusions: TB incidence after ART initiation was significantly lower among individuals starting ART at CD4 counts above 500 cells/μL. Scale-up of ART, regardless of CD4 count, has the potential to significantly reduce TB incidence among HIV-positive individuals. However, this needs to be combined with strengthening of other TB prevention strategies that target both HIV-positive and HIV-negative individuals.

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INTRODUCTION

Tuberculosis (TB) remains the leading cause of morbidity and mortality among HIV-positive individuals.[1] Recent antiretroviral treatment (ART) World Health Organization (WHO) guidelines recommend life-long ART for all HIV-positive individuals regardless of CD4 count.[2] This expanded ART access should lead to a reduction of TB and other WHO-defining illnesses and mortality among HIV-positive individuals initiating ART.[3–6]

TB at the time of ART initiation (baseline TB) is significantly higher at lower baseline CD4 counts among HIV-positive individuals.[4] Two South African programmatic studies completed between 2002 and 2008, in patients with low median baseline CD4 counts, reported high baseline TB prevalence, between 20% and 30%,[7,8] and baseline TB prevalence continues to be underestimated because of the difficulties in diagnosing among individuals starting ART in routine settings.[9]

Published TB incidence rates (IRs) in the first 12 months on ART range from 7.3/100 person-years (PY) to 10.9/100PY and are particularly high when pre-ART (baseline) CD4 counts are below 100 cells/μL.[8,10] TB IRs have been reported to be highest during the first 4 months on ART and approximately double in the first year of ART compared with subsequent years.[9] When measuring the association between CD4 count measured after a period of immune reconstitution on ART ("on ART" CD4 counts) and TB incidence, TB incidence is significantly lower among individuals with higher "on ART" CD4 counts.[7,10]

Although randomized controlled trials have shown lower TB incidence among HIV-positive individuals initiating ART at baseline CD4 counts >500 cells/μL compared with CD4 ≤500 cells/μL and CD4 351 to 500 cells/μL,[11,12] there are very few published studies from programmatic settings on the impact of routine ART initiation at CD4 counts >500 cells/μL on TB incidence. This study, embedded in the HPTN 071 (PopART) trial, assessed the association between baseline CD4 count and TB incidence after ART initiation in a cohort of HIV-positive individuals starting ART regardless of CD4 count under programmatic conditions in the Western Cape, South Africa.

STUDY SETTING

The study was conducted at 3 primary health care (PHC) Department Of Health (DOH) clinics that offered ART regardless of CD4 count (arm A) for the "Population Effect of ART to Reduce HIV Incidence," HPTN 071 (PopART) study. Study clinics were in 2 subdistricts in the Cape Metro district (metro 1 and metro 2 clinics) and in 1 subdistrict in the Cape Winelands district (Rural clinic). Antenatal HIV prevalence in the Cape Metro and Cape Winelands districts is 20.3% and 14.3%, respectively, and routine DOH data show that annual TB IRs are 596/100,000 and 880/100,000 population, respectively.[13,14]

A full description of the HPTN 071 (PopART) study design has been previously published.[15] Communities randomly allocated to arm A of the HPTN 071 (PopART) trial received, from January 1, 2014, a combination HIV prevention package including HIV education, HIV testing, screening for TB symptoms, and active linkage to care for individuals diagnosed with HIV, TB, and sexually transmitted infections. Clinics allocated to arm A of the HPTN 071 (PopART) trial provided ART regardless of CD4 count to all HIV-positive individuals aged ≥18 years. Clients initiating ART outside prevailing ART guidelines signed research informed consent before ART initiation. All HIV-positive individuals on ART were otherwise managed according to DOH ART guidelines. Routine assessment before ART initiation included TB symptom and pregnancy screening.[16]

HIV and TB services were integrated at all 3 study clinics. Isoniazid TB prophylaxis (IPT) was recommended for individuals with a positive tuberculin skin test (TST) at ART initiation, to be continued for 36 months. If TST was unavailable or negative, then a 12-month IPT was advised for individuals starting ART.[16] HIV-positive individuals with TB symptoms were investigated according to a standardized diagnostic algorithm that used GeneXpert MTB/RIF (Xpert) for first-line diagnostic investigation, followed by culture if Xpert was negative. HIV-positive individuals, diagnosed with TB at ART initiation and started on TB treatment, were recorded in the routine DOH electronic TB monitoring system (ETR.net) and stabilized on TB treatment for 2 to 8 weeks before ART initiation.[17] The same TB diagnostic algorithm was used for diagnosis of TB in individuals already initiated on ART.[18]

COHORT OVERVIEW, DATA SOURCES, AND DEFINITIONS

A retrospective cohort study design was used. All data were obtained from routine DOH systems including the routine HIV monitoring system, Tier.net,[19] ETR.net, and routine laboratory reports from the National Health Laboratory Services. All HIV-positive individuals aged ≥18 years, recorded in Tier.net as having started ART at the 3 study clinics between January 1, 2014 and November 30, 2015 with a recorded baseline CD4 count, were included in the study sample. Individuals were followed up until May 30, 2016 or until the date of (1) incident TB, (2) loss to follow-up (LTFU) from HIV care or death, or (3) elective transfer out (TFO); whichever occurred first.

Data linkage between Tier.net and ETR.net was conducted using an automated linkage algorithm in Microsoft SQL Server previously validated in other studies, which used the first name, surname, and date of birth as individual identifiers, and linkages were validated manually. CD4 data missing from Tier.net were, where available, extracted directly from the National Health Laboratory Services database and linked to Tier.net data using the DOH unique identifier. Data cleaning and validation included manual checking of automated linkages and cross referencing data of key across data elements within Tier.net and within ETR.net.

The following standardized definitions were used; (1) baseline CD4 as the most recent CD4 count completed within 6 months before starting ART. Baseline CD4 categories were chosen to align with previous guideline ART criteria,[20] (2) baseline TB as recorded in ETR.net as having started on TB treatment in the 6 months before ART initiation, (3) bacteriologically confirmed TB as confirmed with TB on smear microscopy, Xpert, or culture on one of sputum, lymph node tissue, pleural effusion, or cerebrospinal fluid, (4) incident TB as recorded in ETR.net as starting TB treatment after ART initiation; this included individuals on TB treatment at baseline who, after stopping TB treatment while on ART, were subsequently recorded in ETR.net as restarting TB treatment for a new TB episode, (5) LTFU as 3 months late for an antiretroviral pharmacy pickup appointment. LTFU was reported in combination with death because of significant underreporting of death in Tier.net, (6) TFO as electively transferred to another health facility.

Baseline characteristics were described using standard descriptive statistics for continuous and categorical variables. Heterogeneity of baseline characteristics across baseline CD4 count categories was assessed using χ^2 and Kruskal–Wallis tests. Binomial confidence intervals (CIs) were generated for baseline TB prevalence by baseline CD4 count category. Person time was measured from ART initiation or from the estimated date of stopping baseline TB treatment. Recording of the outcome date of baseline TB episodes in ETR.net was of poor quality; therefore, the outcome date for baseline TB cases was assumed to be 6 months after the start of TB treatment in all cases. The date for incident TB was the date an individual started TB treatment recorded in ETR.net. Individuals were permanently censored at the first occurrence of either incident TB, LTFU, TFO, or May 30, 2016.

Time-to-event analyses were completed using Kaplan–Meier survival estimates. Cox regression was used for crude and adjusted modeling of the association of baseline characteristics with incident TB. Proportional hazard assumptions were tested using Schoenfeld residuals. Baseline variables for inclusion in regression analysis were selected a priori, based on clinical significance. Selection of the baseline variable category used for comparison (hazard ratio [HR] = 1) was based on sample size and clinical significance. All adjusted models included the following baseline characteristics unless otherwise stated: baseline CD4 count, age, sex, pregnancy status, baseline TB, previous ART exposure of more than 3 months, and clinic and year of ART initiation. Likelihood ratios were used to calculate *P* values in regression models for categorical independent variables with more than 2 strata. A subset analysis was conducted excluding individuals with baseline TB. A sensitivity analysis was also conducted in which incident cases of TB were restricted to bacteriologically confirmed cases. Logistic regression was used to compare baseline characteristics of individuals retained in the study sample and those combined LTFU and TFO. All analyses were performed using Stata version 13 (StataCorp LP, College Station, TX).

ETHICS STATEMENT

The HPTN 071 (PopART) study was approved by the Stellenbosch University Health Research Ethics Committee (SU HREC) (Ref. No. N12/11/074) and the London School of Hygiene and Tropical Medicine research ethics committee (Ref no. 6326). All individuals starting ART outside prevailing routine guidelines signed informed consent. Further approvals for this study, including for the use of

TABLE 1. Baseline Characteristics of Study Cohort

	Baseline CD4 Cell Count (Cells/μL)		0–200	201–350	351–500	>500	All	
		N (%)†	631 (26.0)	708 (29.2)	582 (24.0)	502 (20.7)	2423	*P**
Sex	Female	N (%)	355 (56.3)	463 (65.4)	421 (72.3)	404 (80.5)	1643 (67.8)	<0.001
	Male	N (%)	276 (43.7)	245 (34.6)	161 (27.7)	98 (19.5)	780 (32.1)	
Age (yr)		Median (IQR)	33 (29.0–40.0)	31 (25.0–37.0)	31 (26.0–37.0)	30 (25.0–37.0)	31 (26.0–38.0)	<0.001
	18–25	N (%)	79 (12.5)	179 (25.3)	142 (24.4)	134 (26.7)	534 (22.0)	<0.001
	26–35	N	312 (49.6)	311 (43.9)	272 (46.7)	227 (45.2)	1122 (46.3)	
	36–45	N	167 (26.5)	138 (19.5)	109 (18.7)	87 (17.3)	501 (20.7)	
	46–55	N	57 (9.0)	63 (8.9)	46 (7.9)	44 (8.8)	210 (8.7)	
	>55	N	17 (2.7)	17 (2.4)	13 (2.2)	10 (2.0)	57 (2.3)	
Pregnant at ART start	Yes	N	14 (3.9)	39 (8.4)	41 (9.7)	48 (11.9)	142 (8.6%)	<0.001
Baseline TB	Yes	N	162 (25.7)	56 (7.9)	41 (6.7)	26 (5.2)	285 (11.8)	<0.001
Clinic	Rural clinic	N	88 (13.9)	113 (15.9)	126 (21.7)	127 (25.3)	454 (18.7)	<0.001
	Metro clinic 1	N	299 (47.4)	301 (42.5)	231 (39.7)	191 (38.1)	1022 (42.2)	
	Metro clinic 2	N	244 (38.7)	294 (41.5)	225 (38.7)	184 (36.7)	947 (39.1)	
ART exposed‡	Yes	N	27 (4.3)	10 (1.4)	7 (1.2)	5 (1.0)	49 (2.0)	0.005
Year of ART start	2014	N	161 (25.5)	208 (29.4)	160 (27.5)	161 (32.1)	690 (28.5)	0.091
	2015	N	470 (74.2)	500 (70.6)	422 (72.5)	341 (67.9)	1733 (71.5)	

*The *P* value measures heterogeneity across baseline CD4 categories. Chi-square and Kruskal–Wallis tests were used—measure heterogeneity of baseline characteristics.
†For the first row of the table, the % refers to the % across CD4 categories. For all other rows, the % refers to the % within the CD4 category.
‡ART exposed is defined as previous ART exposure of >3 months.

TABLE 2. Incidence of TB and Characteristics of Incident TB Cases by Baseline CD4 Count

Baseline CD4 Categories (Cells/μL)	TB Incidence			Bacteriologically Confirmed TB		Site of TB Disease		Treatment Type	
	PY*	TB Cases	IR (95% CI)	Yes	No	Pulmonary	Extrapulmonary	New TB	Retreatment TB
	N	N	TB Cases/100PY	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
0–200	509	49	9.62 (7.27 to 12.73)	29 (59.2)	20 (40.8)	39 (79.6)	10 (20.4)	31 (63.3)	18 (36.7)
201–350	667	21	3.15 (2.05 to 4.83)	14 (66.7)	7 (33.3)	18 (85.7)	3 (14.3)	15 (71.4)	6 (28.6)
351–500	545	21	3.85 (2.51 to 5.91)	14 (66.7)	7 (33.3)	18 (85.7)	3 (14.3)	17 (80.9)	4 (19.1)
>500	475	6	1.26 (0.57 to 2.81)	5 (83.3)	1 (16.7)	6 (100.0)	0 (0.0)	5 (83.3)	1 (16.7)
Total	2196	97	4.41 (3.62 to 5.39)	62 (63.9)	35 (36.1)	81 (83.5)	16 (16.5)	68 (70.1)	29 (29.9)

This table includes all individuals in the study sample including those with baseline TB.
*PY person time was measured from the estimated time of the end of TB treatment in individuals on TB treatment at baseline. In all other participants, person time was measured from the date of ART start.

individual level routine data with a waiver of informed consent, were received from SU HREC (reference number N12/11/074A), the Western Cape Government (Ref no. WC_2015RP51_715), and the City of Cape Town (Ref no 10529) research committees.

RESULTS

A total of 2593 individuals started ART during the study enrollment period. Baseline CD4 counts were missing for 170 individuals (6.6%) who were excluded leaving 2423 (93.4%) individuals in the analysis (Table 1). Median follow-up time was 10.4 months (interquartile range [IQR]: 6.4–15.6). In total, 600 (24.7%) individuals were defined LTFU with a median follow-up of 3.4 (IQR: 0.9–7.2) months among those LTFU. There were 134 (5.5%) individuals with TFO recorded during the follow-up period.

Median baseline CD4 count was 328 cells/μL (IQR: 195–468), median age 31 years (IQR: 26–38), and 1643 (67.8%) individuals were women. The numbers of individuals initiating ART in different baseline CD4 count categories varied from 631 (26.0%) at CD4 0–200 cells/μL to 502 (20.7%) at CD4 >500 cells/μL (Table 1). Baseline TB was recorded in 285 individuals (11.8% 95% CI: 10.5% to 13.1%). Baseline TB prevalence ranged from 25.7% (95% CI: 22.3% to 29.3%) at baseline CD4 counts <200 cells/μL to 5.2% (95% CI: 3.4% to 7.5%) at CD4 >500 cells/μL. A small number of individuals, 49 (2.0%), were recorded as having previous ART exposure of more than 3 months duration at baseline, the majority (33, 67.5%) of whom presented with a baseline CD4 count <200 cells/μL. More individuals attended metro 1 (1022, 42.2%) and metro 2 clinics (947, 39.1%) compared with the rural clinic (454, 18.7%).

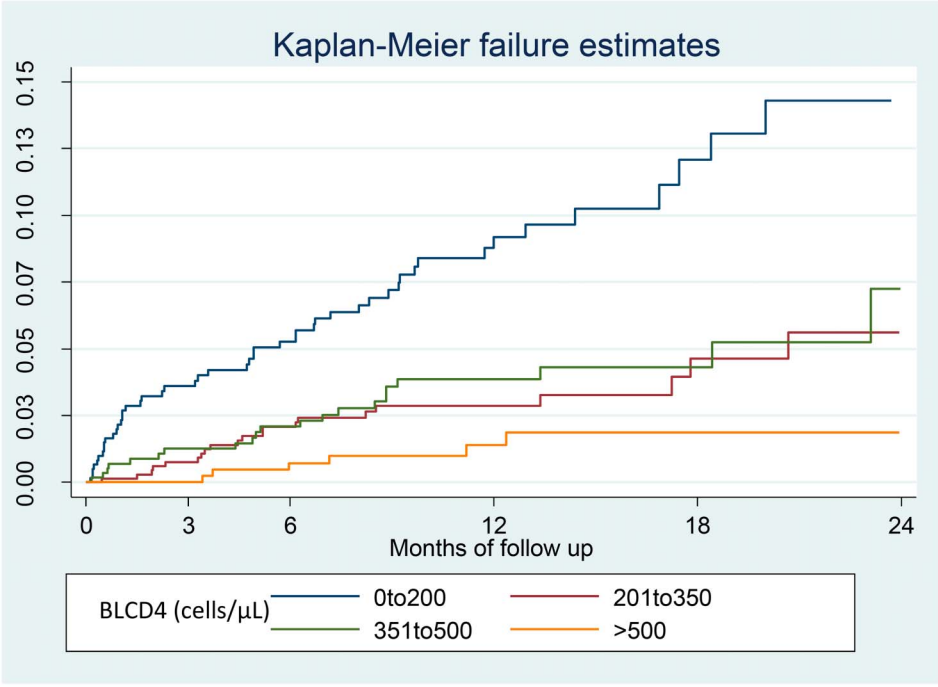

FIGURE 1. Kaplan–Meir failure estimates for incident TB stratified by baseline CD4 cell count categories. BLCD4: Baseline CD4 cell count. Log-rank test for equality of survivor functions: $P < 0.001$.

There were 97 incident TB cases during 2196 PY of follow-up [IR: 4.41/100 PY (95% CI: 3.62 to 5.39) (Table 2)]. Eleven (11.3%) of these incident cases occurred in individuals with baseline TB. Kaplan–Meier estimates showed lower rates of incident TB in individuals with baseline CD4 counts >500 cells/μL when compared with those with CD4 <500 cells/μL and across all CD4 categories ($P < 0.001$) (Fig. 1). TB IRs in different baseline CD4 count categories ranged from 9.62/100 PY (95% CI: 7.27 to 12.73) at CD4 0–200 cells/μL to 1.26/100 PY (95% CI: 0.57 to 2.81) at CD4 >500 cells/μL (Table 2). There was a nonsignificant trend toward a decrease in TB incidence at longer follow-up duration; IRs were 5.96/100PY (95% CI: 4.24 to 8.38) from 0 to 3 months, 4.73/100PY (95% CI: 3.14 to 7.12) from 4 to 6 months, 4.73/100PY (95% CI: 3.14 to 7.12) from 4 to 6 months, and 3.04/100PY (95% CI: 1.79 to 5.13) from 13 to 24 months. When analyzing TB incidence by baseline CD4 category and follow-up duration, there were, notably, no recorded incident TB cases during the first 3 months of follow-up among individuals with baseline CD4 counts >500 cells/μL. Subset analysis excluding individuals with baseline TB showed similar TB IRs and with IRs ranging from 6.6/100PY (95% CI: 4.69 to 9.29) from 0 to 3 months to 2.97/100PY (95% CI: 1.72 to 5.12) from 13 to 24 months.

Of 97 incident TB cases, 81 (83.5%) cases were pulmonary and 16 (16.5%) extrapulmonary. (Table 2). Sixty-eight (70.1%) cases were recorded as new (not previously treated) and 29 (39.9%) as having been previously treated but were not on TB treatment at initiation of ART.

Sixty-two (63.9%) incident TB cases were bacteriologically confirmed, most commonly on sputum using Xpert (54, 86.0%). Of the 35 (36.1%) incident TB cases not bacteriologically confirmed, diagnosis was based on x-ray for 21 (60.0%). There were no significant differences across baseline CD4 count categories in the proportions of TB cases that were pulmonary or extrapulmonary, new or retreatment cases, or bacteriologically confirmed.

TABLE 3. Cox Regression Modeling of Baseline Characteristics and Incident TB

	Unadjusted Analyses		Adjusted Analyses	
	HR (95% CI)	*P*	AHR (95% CI)	*P*
Baseline CD4* (Cells/μL)				
>500	0.13 (0.06 to 0.32)	<0.001	0.15 (0.06 to 0.36)	<0.001
350–500	0.41 (0.24 to 0.68)		0.45 (0.27 to 0.77)	
200–350	0.33 (0.20 to 0.56)		0.36 (0.21 to 0.60)	
0–200	1.00		1.00	
Gender				
Male	2.58 (1.73 to 3.85)	<0.001	2.16 (1.41 to 3.30)	<0.001
Female	1.00		1.00	
Clinic				
Metro 1	1.00	0.212	1.00	0.047
Metro 2	1.26 (0.77 to 2.05)		1.54 (0.89 to 2.66)	
Rural 1	1.63 (0.95 to 2.79)		2.17 (1.19 to 3.97)	
Age category, yrs				
15–25	0.84 (0.47 to 1.49)	0.465	1.18 (0.66 to 2.13)	0.951
26–35	1.00			
36–45	1.38 (0.84 to 2.27)		1.28 (0.68 to 1.87)	
46–55	1.34 (0.69 to 2.61)		1.22 (0.62 to 2.38)	
>55	1.52 (0.47 to 4.89)		1.34 (0.41 to 4.38)	
Pregnant at baseline†				
Yes	0.51 (0.16 to 1.62)	0.207	0.79 (0.23 to 2.46)	0.727
Baseline TB‡				
Yes	1.50 (0.80 to 2.82)	0.155	0.83 (0.41 to 1.53)	0.487
Previous ART exposure of >3 mo				
Yes	3.94 (1.82 to 8.52)	0.001	3.28 (1.49 to 7.2)	0.003
Year ART start				
2014	0.97 (0.62 to 1.53)	0.906	0.75 (0.45 to 1.26)	0.272
2015	1.00		1.00	

All individuals were included in this analysis regardless of baseline TB status. Follow-up time is therefore not equal; time on ART as follow-up for individuals on TB treatment at ART initiation was delayed until the estimated end of TB treatment (6 months after TB treatment initiation).

Baseline characteristics for inclusion in multivariate modeling were chosen based on clinical significance. For baseline characteristics with more than 2 categories, likelihood ratios were used—estimate *P* values for hazard of incident TB.

*Baseline CD4 count was the most recent CD4 count completed in the 6 months before ART initiation.

†All individuals initiating ART are screened for pregnancy at baseline.

‡Baseline TB was defined as having started TB treatment within the 6 months before ART initiation.

Multivariate Cox regression showed a lower hazard of incident TB (adjusted HR [aHR] 0.27; 95% CI: 0.12 to 0.62) among individuals with baseline CD4 count >500 cells/μL when compared with CD4 ≤500 cells/μL. When stratifying by all baseline CD4 count categories, aHR for incident TB were as follows: aHR 0.15 (95% CI: 0.06 to 0.36) at CD4 >500 cells/μL; aHR 0.45 (95% CI: 0.27 to 0.77) at CD4 351–500 cells/μL; and aHR 0.36 (95% CI: 0.21 to 0.60) at CD4 201–350 cells/μL compared with CD4 0–200 cells/μL (Table 3). The aHR of incident TB was higher among men (aHR 2.16; 95% CI: 1.41 to 3.30), individuals with previous ART exposure more than 3 months (aHR 3.28; 95% CI: 1.49 to 7.2), and individuals attending the rural clinic (aHR 2.17; 95% CI: 1.19 to 3.97).

A subset analysis that excluded the 285 individuals with baseline TB showed similar results (Table 4). Hazard of TB remained lower at higher baseline CD4 counts; aHR = 0.13 (95% CI: 0.05 to 0.33) at CD4 >500 cells/μL; aHR = 0.42 (95% CI: 0.24 to 0.74) at CD4 351–500 cells/μL; and aHR 0.35 (95% CI: 0.20 to 0.60) at CD4 201–350 cells/μL compared with CD4 0–200 cells/μL. Hazard of incident TB remained higher in men (aHR 2.31; 95% CI: 1.48 to 3.60), individuals with previous ART exposure more than 3 months (aHR 2.71; 95% CI: 1.08 to 6.81), and among individuals attending the rural clinic (aHR 2.16; 95% CI: 1.13 to 4.13) on subset analysis.

Sensitivity analysis using bacteriologically confirmed incident TB as the primary outcome showed similar results with a lower hazard of bacteriologically confirmed incident TB in individuals starting ART at baseline CD4 counts >500 cells/μL compared with CD4 ≤500 cells/μL (aHR 0.35; 95% CI: 0.14 to 0.89). Sensitivity analyses also confirmed reduced hazard of bacteriologically confirmed incident TB at higher baseline CD4 counts when comparing across all baseline CD4 count categories; aHR: 0.21 (95% CI: 0.08 to 0.57) at CD4 >500 cells/μL; aHR: 0.51 (95% CI: 0.26 to 0.98) at 350–500 cells/μL; aHR: 0.41 (95% CI: 0.22 to 0.79) at 201–350 cells/μL compared with CD4 <200 cells/μL.

Logistic regression analysis of the association of baseline characteristics with an end point that combined LTFU and TFO showed that adjusted odds ratios (aORs) of LTFU and TFO at different baseline CD4 categories were 1.23 (95% CI: 0.95 to 1.61), 0.74 (95% CI: 0.56 to 0.96), and 1.05 (95% CI: 0.82 to 1.33) among individuals with baseline CD4 counts >500, 351–500, and 201–350 cells/μL, respectively when compared with those with baseline CD4 counts ≤200 cells/μL. Other baseline characteristics associated with combined LTFU and TFO included age 18 to 25 (aOR = 1.36;

TABLE 4. Subset Cox Regression Modeling of Baseline Characteristics and Incident TB Excluding Individuals With Baseline TB

	Crude Hazard Ratio (95% CI)	*P*	aHR (95% CI)	*P*
Baseline CD4 (Cells/μL)				
>500	0.11 (0.04 to 0.28)	<0.001	0.13 (0.05 to 0.33)	<0.001
351–500	0.37 (0.22 to 0.64)		0.42 (0.24 to 0.74)	
201–350	0.32 (0.19 to 0.55)		0.35 (0.20 to 0.60)	
0–200	1.0		1.0	
Sex				
Male	2.75 (1.8 to 4.19)	<0.001	2.31 (1.48 to 3.60)	<0.001
Female	1.0		1.0	
Clinic				
Metro 1	1.0	0.286	1.0	0.059
Metro 2	1.35 (0.8 to 2.26)		1.73 (0.98 to 3.07)	
Rural 1	1.58 (0.88 to 2.84)		2.16 (1.13 to 4.13)	
Age category, yrs				
15–25	0.91 (0.5 to 1.63)	0.416	1.28 (0.7 to 2.32)	0.762
26–35	1		1	
36–45	1.55 (0.92 to 2.61)		1.30 (0.77 to 2.21)	
46–55	1.27 (0.61 to 2.63)		1.17 (0.56 to 2.44)	
>55	0.65 (0.09 to 4.71)		0.57 (0.08 to 4.16)	
Pregnant at baseline*				
Yes	0.53 (0.17 to 1.69)	0.285	0.85 (0.26 to 2.77)	0.785
Previous ART exposure of >3 months				
Yes	3.46 (1.4 to 8.55)	0.007	2.71 (1.08 to 6.81)	0.785
Year ART start				
2014	0.93 (0.57 to 1.52)	0.780	1.36 (0.79 to 2.36)	0.271
2015	1.0		1.0	

Individuals (285) with baseline TB were excluded. In this analysis, follow-up time equals time on ART. Baseline characteristics for inclusion in multivariate modeling were chosen based on clinical significance. For baseline characteristics with more than 2 categories, likelihood ratios were used—estimate *P* values for hazard of incident TB. Baseline CD4 count was the most recent CD4 count completed in the 6 months before ART initiation.

*All individuals initiating ART are screened for pregnancy at baseline. Baseline TB was defined as having started TB treatment within the 6 months before ART initiation.

95% CI: 1.09 to 1.70) and age 46 to 55 (aOR 0.65; 95% CI: 0.46 to 0.93) compared with age 26 to 35, being treated at metro 2 (aOR: 1.31; 95% CI: 1.05 to 1.66) compared with metro 1 and baseline TB treatment (aOR: 1.44; 95% CI: 1.09 to 1.91). Male sex was not associated with increased LTFU and TFO (aOR 1.11; 95% CI: 0.90 to 1.36) when compared with female sex.

DISCUSSION

Life-long ART is now recommended for all HIV-positive individuals regardless of CD4 count.[2] In addition to improving individual level clinical outcomes and potentially reducing community HIV transmission, earlier ART initiation has the potential to reduce population level TB incidence.[3,5] The impact of starting ART at baseline CD4 counts >500 cells/μL on subsequent TB incidence has been demonstrated in randomized controlled trials; however, there are very limited data from programmatic settings. This study has demonstrated significantly lower TB incidence for individuals starting ART at CD4 counts >500 cells/μL (1.26/100 PY (95% CI: 0.57 to 2.81) compared with those starting at lower CD4 counts. This rate is, however, higher than previously reported TB case notification rates for the HIV-negative population, aged 15–60 years, in the Cape Town area (0.48/100PY).[21] A direct comparison cannot be made because these were different studies with different methodologies, and interpretation of this comparison is limited by the relatively small sample size of our study and should be the subject of further evaluation.

In contrast to previous studies among HIV-positive individuals,[7,8,10] the hazard of incident TB on ART in this study was higher among men, reasons for which are not clear from these data. This may, however, be due to lower ART adherence among men, with associated greater immunosuppression, as reported in other studies.[22] There is a reported trend toward recurrent episodes of ART nonadherence among individuals on ART, and it is therefore possible that individuals with previous ART exposure were more likely to be nonadherent to ART, which may account for the higher TB incidence in this group.[23] The higher TB incidence at the rural clinic is likely to, in part, reflect higher background annual TB incidence.[17] Previous studies have shown a strong trend toward decreasing TB incidence with increasing duration of follow-up after ART initiation.[8,10] By contrast, in this study, there was a trend toward decreased TB incidence at longer durations of ART; however, it was not statistically significant. This may be in part due to limited sample size; however, there were no recorded incident TB cases during the first 3 months on ART among individuals with baseline CD4 counts starting >500 cells/μL, which would have reduced overall cohort incidence during early ART.

Unmasking of TB is known to contribute to TB incidence during the first 3 months on ART.[24,25] The absence of incident TB cases during this period of ART in HIV-positive individuals who have not spent time pre-ART at CD4 counts lower than 500 cells/μL in this high-TB burden setting is promising and should be the subject of future research.

Effective management of HIV and TB at PHC clinics is critical in reducing associated morbidity and mortality in high-burden settings.[26,27] Integration of HIV and TB services in PHC clinics is increasingly recommended,[26,27] but has not always been shown to lead to improved clinical outcomes. The best way to integrate services may be highly context specific,[28,29] and there remains the need for high quality data evaluating best practices for HIV and TB integration.[2] Differentiated models of care, which provide intensified care for high-risk individuals in PHC clinics, may be a successful strategy for improving integrated HIV and TB care.[30,31] To this end, studies such as this one, which have identified key baseline risk factors for TB incidence on ART, could be used to develop risk matrices for incorporation into differentiated models of care for improving clinical outcomes in HIV and TB co-infected individuals.

The HPTN 071 (PopART) trial has provided a unique opportunity to evaluate, under programmatic conditions, a cohort of HIV-positive individuals routinely starting ART at baseline CD4 counts >500 cells/μL, before ART regardless of CD4 count being recommended by WHO and South African guidelines. The primary outcome of this study, TB incidence, is a topic of great public health importance, and the analysis of an objective primary end point was strengthened by sensitivity analyses of microbiologically confirmed TB. Data included in this analysis were representative of the planned study cohort with only 170 (6.6%) of eligible individuals excluded because of missing baseline CD4 count. The prospective health systems support provided by HPTN 071 (PopART) to the study clinics was likely to have improved the accuracy with which TB was diagnosed and reported in ETR.net.

There were, however, limitations that require consideration. ETR.net captures only individuals starting TB treatment. Individuals diagnosed with TB but not started on TB treatment were, therefore, excluded along with individuals starting TB treatment who were erroneously not recorded in ETR.net. Similarly, the majority of the estimated 4%–5% of individuals diagnosed with drug-resistant TB at the time of TB treatment start[32] were not captured in ETR.net, but into a separate database [Electronic Drug-Resistant TB register (EDR.net)] and were therefore excluded in this analysis. The authors were, therefore, not able to report the contribution of MDR to incident TB cases. The omission of MDR TB cases in this study may have reduced the overall reported TB incidence, but given that CD4 count has not been shown to be associated with the risk of MDR TB versus drug susceptible TB,[33] there is no evidence that the missing MDR data differentially affected TB incidence across different baseline CD4 categories in this study. Despite these missing data, baseline TB prevalence stratified by baseline CD4 count category in this study was similar to that reported for corresponding baseline CD4 count categories by another South African study, from a comparable area in the Cape Metro, in which data were limited to individuals with baseline CD4 counts ≤ 500 cells/μL.[4]

Furthermore, there was marked heterogeneity of baseline characteristics across baseline CD4 categories, and although we adjusted for some of these characteristics in

the Cox regression analysis, we cannot rule out that there may be residual confounding. There were also high rates of LTFU (24.7%) and TFO (5.5%), which are likely to have reduced the overall reported TB incidence. When analyzing LTFU and TFO across baseline CD4 categories, although there was reduced LTFU and TFO among individuals with baseline CD4 counts of 351–500 cells/μL. However, LTFU and TFO amongst individuals with baseline CD4 counts of >500 cells/μL, and 201–350 cells/μL was not different from LTFU and TFO among individuals with baseline CD4 counts ≤200 cells/μL, and it is therefore not evident that LTFU and TFO differentially affected TB incidence across baseline CD4 categories. LTFU and TFO were similar with respect to other baseline characteristics associated with TB incidence. Non-availability of viral load data after ART initiation is a further limitation of this study. Increased viral load after ART initiation is associated with increased incidence of TB on ART,[8] and inclusion of these data would have assisted in interpreting the association of key baseline characteristics with TB incidence, such as the increased hazard of TB in men who are also associated with decreased ART adherence and increased risk of increased viral load on ART.[22]

IPT has been shown to decrease the risk of TB among individuals starting ART.[11] The nonreporting of IPT provision in this study due to missing data in ETR.net and Tier.net is a limitation. It was not apparent whether IPT uptake in this study differed across baseline CD4 categories and the non-availability of IPT data may therefore have biased the primary outcomes. Anecdotally, the use of IPT was low and inconsistent in PHC clinics in the Western Cape at the time of this study. IPT has been shown to be effective in reducing TB incidence in HIV-positive individuals testing TST positive.[11,34,35] The need for TST testing and concerns about isoniazid resistance are thought to have contributed to low uptake of IPT.[36,37] The need for TST testing before IPT is debated, and recent changes to ART guidelines, with more individuals starting ART at higher CD4 counts, when TST testing is more sensitive,[35] should be a critical consideration in this debate going forward.

CONCLUSIONS

The HPTN 071 (PopART) trial has provided a unique opportunity to evaluate TB incidence in the setting of universal offer of ART through programmatic clinic data. This study showed a significantly lower TB prevalence and on ART incidence among HIV-positive individuals initiating ART at CD4 counts >500 cells/μL, suggesting that the scale-up of ART regardless of CD4 count has the potential to significantly reduce TB burden among HIV-positive individuals. At the same time, scale-up of other TB prevention strategies that target both HIV-positive and HIV-negative individuals is urgently required to contribute substantially to TB elimination in high-HIV prevalence settings.

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