Research Square

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Incidence and predictors of tuberculosis disease among people living with HIV who completed tuberculosis preventive treatment: a retrospective cohort study at Baylor- Uganda HIV clinic in Uganda

Pauline Mary Amuge
paulacallista@gmail.com

Joint Clinical Research Centre
Moses Mugerwa
Baylor Foundation Uganda
Spencer Byaruhanga
Joint Clinical Research Centre
Levicatus Mugenyi
Medical Research Council, Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine
Rebecca Nuwematsiko
Makerere University, School of Public Health
Esther Buregyeya
Makerere University, School of Public Health

Research Article

Keywords: Tuberculosis, incidence, preventive treatment, complete, initiate, HIV, new cases, disease, children

Posted Date: August 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10093380/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Even with over 80% tuberculosis preventive treatment (TPT) coverage among people living with HIV (PLHIV), 39% of people with tuberculosis (TB) in Uganda are PLHIV. We explored the TB incidence, and predictors of TB disease after completing TPT.

Methods

We conducted a retrospective cohort study among PLHIV of all ages, comparing TB incidence among PLHIV who completed TPT, with that of PLHIV who did not receive TPT. TB incidence was reported as the number of new TB cases per 1000 person years of follow-up. Poisson regression with robust standard errors was used to assess for the predictors of TB disease after completion of TPT. Time-to-event analysis was done to estimate the median time to TB disease after TPT initiation.

Results

Of the 9505 PLHIV; majority were female (61%), median age was 22 years (IQR 15, 31), 6014 (79.2%) initiated and completed TPT, and 1907 (20.0%) did not initiate TPT. The TB incidence among PLHIV who completed TPT reduced from 4.34 cases/1000 in 2016 to 1.71 TB cases/1000 person years in 2020, and increased slightly in 2021. Among PLHIV who did not receive TPT, TB incidence increased from 3.21 cases/1000 in 2016, to 84.95 cases/1000 person years in 2021. Among PLHIV who completed TPT, unsuppressed viral load (≥ 1000 copies/mL) significantly increased TB risk (aIRR: 6.19; 95% CI: 2.80–13.69, $p < 0.001$). The median time to TB disease after initiating TPT was 2.5 years (IQR: 2.3–2.8 years). The PLHIV on ART for 5–9 years had a significantly lower hazard risk of developing TB (HR = 0.30, 95% CI: 0.11–0.81, $p = 0.018$).

Conclusions

The TB incidence among PLHIV was high, although this was lower and reduced over the years among PLHIV who completed TPT, but increased among PLHIV who did not receive TPT within the six years. Even after completing TPT, HIV viral non-suppression increases the risk of TB disease by six times, with PLHIV developing TB within two and half years after initiating TPT. This emphasizes need for regular TB screening, and research on benefit of repeat TPT doses and longer-term TB prevention options like vaccines.

BACKGROUND

Globally, tuberculosis (TB) remains the leading cause of death from a single infectious agent, especially among people living with HIV (PLHIV) (1). Almost 80% of the TB-HIV co-infection burden is in Sub-Saharan Africa (2), with 11% being children 0–14 years). The risk of mortality due to HIV-TB co-infection is double that due to HIV infection alone(3). Even though antiretroviral therapy (ART) reduces risk of incident TB among PLHIV, HIV positive clients receiving ART are still susceptible to TB disease (4). Among PLHIV, TB preventive treatment (TPT) reduces the incidence of TB by up to 90% (5–7). Antiretroviral therapy (ART) reduces the risk further by 37% (8–10).

In Uganda, the TB case notification rate was 150 cases per 100,000 population, with 62,328 incident TB cases in 2019/2020 (11). Almost 40% of new TB cases are among PLHIV, with TB being the leading cause of mortality among PLHIV (12). The Uganda ministry of health (MOH) launched a TPT scale-up campaign in 2019 with an enhanced catch up phase to ensure that 90% of PLHIV eligible for TPT receive isoniazid (INH) preventive therapy (IPT) for six months (13). Uganda registered a 75% uptake of TPT among PLHIV in 2020, which has progressively increased with recent TPT campaigns (13). Currently, the MOH recommends several shorter TPT regimens in addition to IPT, such as isoniazid and rifapentine for 3months (3HP) or 1month (1HP), and isoniazid and rifampicin for 3months (3RH) (14).

However, the TB-HIV co-infection still oscillates around 30–39% (11), with limited data on the burden and characteristics of PLHIV who develop TB disease after completing TPT.

Tuberculosis (TB) disease, also known as TB, is defined as TB symptoms with confirmed bacteriological or imaging results or clinical decision to treat as TB disease. Tuberculosis disease after TPT initiation may be due to non-completion of TPT, due to several factors such as poor adherence, pill burden (ART plus TPT), stigma (TPT perceived as TB treatment), fear of side effects, misunderstanding about the benefits and duration of TPT(15), poor social support, catastrophic costs related to TB care, and denial or non-disclosure of HIV positive status (16, 17). Incident TB disease after TPT may also be due to TPT interruption, advanced HIV disease, exposure to TB infection, and severe immune suppression(18).

A clear understanding of the factors associated with TB disease even after completion of TPT, may offer clinicians and policy makers guidance on high-risk individuals to prioritise for repeat TPT doses, or long-term TPT option in the era of high TPT and ART uptake.

Therefore, this study aimed at determining the incidence of TB disease, the predictors of TB disease, and median time to TB disease, among PLHIV who completed TPT over a six-year period (Jan 2016 to Dec 2021).

METHODS

Study design and study population

This was a retrospective cohort study conducted among children, adolescents and adults living with HIV, who were receiving HIV care during the period Jan 2016 to Dec 2021. The exposed group were PLHIV receiving ART, who initiated and completed TPT within the six years' study period, 1st January 2016 to 31st December 2021. The unexposed group were PLHIV receiving ART, who did not initiate TPT within the follow-up period.

Study setting

The study was conducted at Baylor College of Medicine Children's Foundation-Uganda (Baylor-Uganda) center of excellence (COE) HIV clinic, located within Mulago National Referral Hospital Complex, in Kampala Capital City. The Baylor-Uganda HIV clinic provides free comprehensive HIV and TB screening, testing, prevention and treatment services to children, adolescents and adults. The PLHIV without TB disease were offered TPT if eligible (never received TPT, close contacts of TB clients, recently completed TB treatment). During the study period, only daily isoniazid monotherapy for six months (6H) was the available TPT regimen, provided by the ministry of health.

Sample size

The estimated minimum sample was 583 PLHIV (no TPT = 193, received TPT = 390), at 80% power and 5% type I error, assuming; TB incidence of 0.83% TB among PLHIV who received TPT (18), 80% lower TB incidence among clients who received TPT compared to clients who did not receive TPT, in a ratio of 1:3 for the non-exposed (no TPT) to exposed (received TPT) individuals based on a study in Uganda which estimated 75% uptake of TPT(18), with TPT offering up to 90% efficacy (20). The same sample size was found sufficient to determine the factors associated with TB disease and median time to TB disease after TPT initiation. In order to minimize the selection bias and increase power, all eligible participants active in care during the study period were included in the analysis.

Study variables and measurement

The dependent variable was a diagnosis of pulmonary or extra-pulmonary TB disease within the study period, either clinically diagnosed or bacteriologically confirmed based on the clients' medical records. The TB incidence, was reported as number of new TB cases per 1000person years of follow-up. In the survival analysis, the event of interest was a diagnosis of TB disease after initiating TPT. The independent variables included; socio-demographic characteristics such as age and sex, antiretroviral treatment (ART) regimen, duration on ART, history of TB disease prior to TPT initiation, history of TB contact during or after TPT completion, concurrent medication, ART and TPT adherence, WHO HIV clinical stage, baseline CD4 count, HIV viral load at start of TPT or within past one year.

Data Collection

Anonymized data on PLHIV who received and completed TPT and those who did not receive TPT, was abstracted from the electronic medical records (EMR) into an excel sheet. Data collected included, TB screening and other clinical assessments at every clinic visit, HIV-related medical conditions, other medical conditions, laboratory tests and results, counselling services provided, drug prescriptions and dispensed drugs, and conducted community/home visits. Data was checked for completeness.

Data Analysis

The data was analyzed using STATA version 16.0. Complete case analysis was done where there was missing data. Participant variables were descriptively summarised as either frequencies, percentages, mean with standard deviation, or median with interquartile ranges. The TB incidence was reported as the number of TB cases per 1000person years of follow-up, by TPT group (completed TPT vs did not receive TPT) with 95% confidence intervals (CI). A Poisson regression model fitted to the number of TB events per client with person-time set as an off-set variable, to estimate the incidence rate and the 95%CI per group, and comparison was made between the two groups, using incidence rate ratio (IRR) with 95%CI as a measure of association. The analysis was stratified by cohort year of observation, to assess if TB incidence varied across the years of follow-up. A p-value < 0.05 was considered statistically significant. To assess the predictors of TB disease among PLHIV, predictor variables were entered into the Poisson regression model and risk ratio (RR) with 95%CI obtained, adjusting for potential confounders like age, sex, ART duration, WHO staging, and ART regimen. Variables with p-values < 0.2 at bivariable analysis and those considered relevant from literature, were included in the multivariable analysis. A p-value < 0.05 was considered statistically significant. Time-to-event analysis was done to determine the median time to incident TB disease among PLHIV who initiated and completed TPT. Participants were censored on either the date of TB diagnosis, or date of death, or the last date of the follow-up period, whichever occurred first. The TPT initiation date was considered as the start of the risk period. The median time to TB disease was not estimated using Kaplan Meier (KM) curves, because < 50% of the participants did not develop TB disease. Descriptive estimates for median and interquartile range were

obtained, and the log-rank test was used to compare survivor functions. Factors with log-rank test p-value < 0.1 were included in a Cox proportional hazards model to determine factors associated with time to TB disease after initiation of TPT. Any p-values < 0.05 were considered significant.

RESULTS

Among the 9,505 PLHIV in HIV care during the study period, 79.9% (7598/9505) initiated TPT, of whom 6014 (79.2%) completed their full TPT course. A total of 1907 (20%) clients in care, did not initiate TPT. The majority of PLHIV were female (61%), and the median age was 22years. The PLHIV who completed TPT had been on ART for a longer period (3.7years, IQR 0.9–7.2), compared to those who did not receive TPT (0.3 years, IQR 0.3–3.7). Most PLHIV (98.6%) received one course of TPT, and only 1.4% received two or more TPT doses. Baseline characteristics of the study participants are summarized in Table 1.

Incidence of TB disease among PLHIV who completed TPT

The TB incidence varied over the six-year period. The TB incidence among all PLHIV increased from 3.24 TB patients per 1000 person years in 2016, to 56.67 TB patients per 1000 person years in the year 2021. Among PLHIV who completed TPT, TB incidence reduced from 4.34 (95% CI: 1.40-13.46) per 1000 person years in 2016, to 1.71 (95% CI: 0.24–12.15) per 1000 person years in 2021 (*see* Table 2).

Table 1. Baseline characteristics of the study participants

Table 1
Baseline characteristics of the study participants

	Did Not initiate TPT	Initiated and completed TPT	Total
	N = 1,907	N = 6,014	N = 7,921
Sex	n (%)	n (%)	n (%)
Male	693 (36.3)	2,397 (39.9)	3,090 (39.0)
Female	1,214 (63.7)	3,617 (60.1)	4,831 (61.0)
Age (years)			
<10	453 (23.8)	369 (6.1)	822 (10.4)
10–19	338 (17.7)	2,102 (35.0)	2,440 (30.8)
20–29	514 (27.0)	1,875 (31.2)	2,389 (30.2)
30–39	379 (19.9)	982 (16.3)	1,361 (17.2)
40–49	172 (9.0)	474 (7.9)	646 (8.2)
50+	51 (2.7)	212 (3.5)	263 (3.3)
Median (IQR)	24 (10, 32)	22 (16, 31)	22 (15, 31)
BMI (kg/m^2)			
Normal	680 (35.7)	2,233 (37.1)	2,913 (36.8)
Underweight	824 (43.2)	2,974 (49.5)	3,798 (47.9)
Overweight	242 (12.7%)	791 (13.2%)	1,033 (13.0%)
Missing	161 (8.4)	16 (0.3)	177 (2.2)
Median (IQR)			19.5 (16.6, 22.7)
MUAC (cm)			
<12	173 (9.1)	99 (1.6)	272 (3.4)
>=12	1,552 (81.4)	5,908 (98.2)	7,460 (94.2)
Missing	182 (9.5)	7 (0.1)	189 (2.4)
Median (IQR)	23.1 (15.7, 26.8)	22.3 (17.5, 26.2)	22.5 (17.3, 26.4)
Duration on ART (years)			
<5	1,198 (62.8)	3,585 (59.6)	4,783 (60.4)
5–9	207 (10.9)	1,810 (30.1)	2,017 (25.5)
10+	82 (4.3)	615 (10.2)	697 (8.8)
Missing	420 (22.0)	4 (0.1)	424 (5.4)
Median (IQR)	0.3 (0, 3.7)	3.7 (0.9, 7.2)	3 (0.2, 6.6)
ART backbone			

	Did Not initiate TPT	Initiated and completed TPT	Total
	N = 1,907	N = 6,014	N = 7,921
AZT/3TC	323 (16.9)	2,496 (41.5)	2,819 (35.6)
ABC/3TC	685 (35.9)	1,587 (26.4)	2,272 (28.7)
TDF/3TC	892 (46.8)	1,913 (31.8)	2,805 (35.4)
Other	3 (0.2)	18 (0.3)	21 (0.3)
Missing	4 (0.2)	0 (0.0)	4 (0.1)
ART anchor drug class			
INSTI(DTG-based)	297 (15.6)	405 (6.7)	702 (8.9)
NNRTIs (EFV-based)	741 (38.9)	3,012 (50.1)	3,753 (47.4)
NNRTIs (NVP-based)	172 (9.0)	1,157 (19.2)	1,329 (16.8)
PI-based (ATV/r)	142 (7.4)	394 (6.6)	536 (6.8)
PI-based (LPV/r)	537 (28.2)	1,020 (17.0)	1,557 (19.7)
Tripple NRTIs (ABC/3TC/AZT)	12 (0.6)	19 (0.3)	31 (0.4)
Missing	6 (0.3)	7 (0.1)	13 (0.2)
ART line			
First (1st)	1,224 (64.2)	4,592 (76.4)	5,816 (73.4)
Second (2nd)	678 (35.6)	1,412 (23.5)	2,090 (26.4)
Third (3rd)	1 (0.1)	10 (0.2)	11 (0.1)
Missing	4 (0.2)	0 (0.0)	4 (0.1)
WHO HIV stage			
I	590 (30.9)	1,364 (22.7)	1,954 (24.7)
II	268 (14.1)	1,731 (28.8)	1,999 (25.2)
III	264 (13.8)	2,042 (34.0)	2,306 (29.1)
IV	377 (19.8)	854 (14.2)	1,231 (15.5)
Deferred	106 (5.6)	19 (0.3)	125 (1.6)
Missing	302 (15.8)	4 (0.1)	306 (3.9)
Viral load			
0-<50	423 (22.2)	4,037 (67.1)	4,460 (56.3)
50-<500	125 (6.6)	796 (13.2)	921 (11.6)
500-<1000	23 (1.2)	121 (2.0)	144 (1.8)
>=1000	304 (15.9)	997 (16.6)	1,301 (16.4)
Missing	1,032 (54.1)	63 (1.0)	1,095 (13.8)

	Did Not initiate TPT	Initiated and completed TPT	Total
	N = 1,907	N = 6,014	N = 7,921
CD4 count			
Median (IQR)	541 (265, 926)	596 (308, 1018)	581.5 (297, 993.5)

Among the PLHIV who did not receive TPT, the TB incidence increased from 3.21 (95% CI: 2.65–3.90) per 1000 person years in 2016, to 84.95 (95% CI: 61.27-117.76) per 1000 person years in 2021 **(see** Table 2**).** By 2021, the non-TPT group experienced a much higher TB incidence (84.95 per 1,000 person-years), while no (00) TB cases were recorded among those who completed TPT, with an adjusted IRR of 0.09 (95% CI 0.02–0.38, p = 0.001).

Factors associated with TB disease among PLHIV who received TPT

Among the 6014 PLHIV who completed TPT, 33 (0.5%) PLHIV developed TB disease, compared to 162 (8.5%) out of the 1907 PLHIV who did not receive TPT (**see** Table 3**).** Among PLHIV who completed TPT, individuals on ABC/3TC had a significantly higher TB risk (aIRR = 5.29; 95% CI: 1.40–20.05, p = 0.014), compared to those on AZT/3TC. Those that completed TPT and were on EFV-based ART had significantly lower TB risk (aIRR: 0.20; 95% CI: 0.05–0.74, P = 0.016) compared to those on DTG. Similar protective associations were observed for NVP (aIRR: 0.14; 95% CI: 0.02–0.97, P = 0.047) and LPV/r-based ART regimens (aIRR: 0.08; 95% CI: 0.02–0.44, P = 0.004).

Table 3
Predictors of TB disease among PLHIV who completed TPT compared to those who did not receive TPT

Variable	Did not Initiate TPT					Initiated and Completed TPT				
	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	p-value	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	P value
Sex										
Female	1138 (93.7)	76 (6.3)				3599 (99.5)	18 (0.5)			
Male	607 (87.6)	86 (12.4)	1.98 (1.48, 2.66)	1.30 (0.90, 1.86)	0.156	2382 (99.4)	15 (0.6)	1.26 (0.64, 2.49)	0.97 (0.48, 1.99)	0.94
Age Group										
< 10 years	377 (83.2)	76 (16.8)				367 (99.5)	2 (0.5)			
10 to 19 years	310 (91.7)	28 (8.3)	0.49 (0.33, 0.74)	0.80 (0.45, 1.41)	0.431	2091 (99.5)	11 (0.5)	0.97 (0.22, 4.34)	1.57 (0.22, 11.02)	0.652
20–29 years	485 (94.4)	29 (5.6)	0.34 (0.22, 0.51)	1.66 (0.68, 4.03)	0.264	1862 (99.3)	13 (0.7)	1.28 (0.29, 5.65)	2.60 (0.34, 19.73)	0.357
30–39 years	364 (96.0)	15 (4.0)	0.24 (0.14, 0.40)	1.75 (0.61, 4.99)	0.294	979 (99.7)	3 (0.3)	0.56 (0.10, 3.36)	1.38 (0.11, 16.85)	0.802
40–49 years	164 (95.4)	8 (4.6)	0.28 (0.14, 0.56)	1.86 (0.63, 5.52)	0.264	471 (99.4)	3 (0.6)	1.17 (0.20, 6.95)	3.90 (0.36, 41.75)	0.261
50 + years	45 (88.2)	6 (11.8)	0.70 (0.32, 1.53)	2.85 (0.72, 11.26)	0.136	211 (99.5)	1 (0.5)	0.87 (0.08, 9.54)	2.92 (0.21, 41.30)	0.428
BMI Category										
Normal	652 (95.9)	28 (4.1)				2220 (99.4)	13 (0.6)			
Underweight	706 (85.7)	118 (14.3)	3.48 (2.33, 5.19)	1.84 (1.08, 3.13)	**0.025**	2957 (99.4)	17 (0.6)	0.98 (0.48, 2.02)	1.25 (0.44, 3.60)	0.678
Overweight	237 (97.9)	5 (2.1)	0.50 (0.20, 1.29)	0.46 (0.15, 1.37)	0.163	788 (99.6)	3 (0.4)	0.65 (0.19, 2.28)	0.87 (0.25, 3.00)	0.829
MUAC Category										
< 12	125 (72.3)	48 (27.8)				98 (99.0)	1 (1.0)			

NE: Not estimable due to the absence of participants in the TB case group

Variable	Did not Initiate TPT					Initiated and Completed TPT				
	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	p-value	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	P value
Sex										
≥ 12	1452 (93.6)	100 (6.4)	0.23 (0.17, 0.32)	0.44 (0.26, 0.73)	**0.002**	5876 (99.5)	32 (0.5)	0.54 (0.07, 3.89)	0.57 (0.07, 4.87)	0.604
ART Duration (years)										
< 5	1121 (93.6)	77 (6.4)				3563 (99.4)	22 (0.6)			
5–9 years	196 (94.7)	11 (5.3)	0.83 (0.45, 1.53)	0.57 (0.26, 1.23)	0.15	1803 (99.6)	7 (0.4)	0.63 (0.27, 1.47)	0.67 (0.25, 1.83)	0.437
10 + years	79 (96.3)	3 (3.7)	0.57 (0.18, 1.77)	0.35 (0.10, 1.19)	0.092	611 (99.3)	4 (0.7)	1.06 (0.37, 3.07)	0.93 (0.22, 3.85)	0.914
Regimen Backbone										
AZT/3TC	309 (95.67)	14 (4.33)				2,491 (99.8)	5 (0.2)			
ABC/3TC	576 (84.09)	109 (15.91)	3.67 (2.14, 6.30)	1.30 (0.68, 2.49)	0.428	1,569 (98.9)	18 (1.1)	5.66 (2.11, 15.22)	5.29 (1.40, 20.05)	**0.014**
TDF/3TC	853 (95.63)	39 (4.37)	1.01 (0.56, 1.83)	0.67 (0.28, 1.57)	0.353	1,903 (99.4)	10 (0.5)	2.61 (0.89, 7.62)	1.55 (0.30, 7.89)	0.599
Other	3 (100.00)	0 (0.00)	NE	NE	< 0.001	18 (100.00)	0 (0.0)	NE	NE	< 0.001
Regimen Anchor Base										
INSTI (DTG-based)	277 (93.3)	20 (6.7)				400 (98.8)	5 (1.2)			
NNRTIs (EFV-based)	694 (93.7)	47 (6.3)	0.94 (0.57, 1.56)	1.04 (0.58, 1.85)	0.905	2,998 (99.5)	14 (0.5)	0.38 (0.14, 1.04)	0.20 (0.05, 0.74)	**0.016**
NNRTIs (NVP-based)	166 (96.5)	6 (3.5)	0.52 (0.21, 1.27)	0.79 (0.31, 2.03)	0.618	1,154 (99.7)	3 (0.3)	0.21 (0.05, 0.88)	0.14 (0.02, 0.97)	**0.047**
PI-based (ATV/r)	134 (94.4)	8 (5.6)	0.84 (0.38, 1.85)	1.31 (0.51, 3.37)	0.574	387 (98.2)	7 (1.8)	1.44 (0.46, 4.50)	0.43 (0.11, 1.67)	0.222

NE: Not estimable due to the absence of participants in the TB case group

Variable	Did not Initiate TPT					Initiated and Completed TPT				
	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	p-value	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	P value
Sex										
PI-based (LPV/r)	463 (86.2)	74 (13.8)	2.05 (1.27, 3.29)	0.68 (0.35, 1.35)	0.273	1,016 (99.6)	4 (0.4)	0.32 (0.09, 1.18)	0.08 (0.02, 0.44)	**0.004**
Triple NRTIs (ABC/3TC)	5 (41.7)	7 (58.3)	8.66 (4.57, 16.41)	1.74 (0.64, 4.73)	0.279	19 (100.00)	0 (0.00)	NE	NE	**< 0.001**
WHO Stage										
I	575 (97.5)	15 (2.5)				1,360 (99.7)	4 (0.3)			
II	253 (94.4)	15 (5.6)	2.20 (1.09, 4.44)	1.66 (0.77, 3.54)	0.193	1,719 (99.3)	12 (0.7)	2.36 (0.76, 7.31)	2.66 (0.71, 9.96)	0.146
III	232 (87.9)	32 (12.1)	4.77 (2.63, 8.65)	2.76 (1.40, 5.45)	**0.004**	2,031 (99.5)	11 (0.5)	1.84 (0.59, 5.76)	2.19 (0.60, 8.02)	0.235
IV	305 (80.9)	72 (19.1)	7.51 (4.37, 12.91)	2.24 (1.13, 4.46)	**0.022**	848 (99.3)	6 (0.7)	2.40 (0.68, 8.47)	2.16 (0.44, 10.59)	0.344
Deferred	93 (87.7)	13 (12.3)	4.82 (2.36, 9.85)	1.74 (0.67, 4.50)	0.254	19 (100.0)	0 (0.0)	NE	NE	< 0.001
Viral Load										
0-<50	414 (97.9)	9 (2.1)				4,026 (99.7)	11 (0.3)			
50-<500	115 (92.0)	10 (8.0)	3.76 (1.56, 9.05)	2.30 (0.85, 6.22)	0.101	791 (99.4)	5 (0.6)	2.31 (0.80, 6.62)	1.81 (0.65, 5.08)	0.257
500-<1000	21 (91.3)	2 (8.7)	4.09 (0.94, 17.85)	2.72 (0.68, 10.87)	0.156	121 (100.0)	0 (0.0)	NE	NE	**< 0.001**
≥ 1000	268 (88.2)	36 (11.8)	5.57 (2.72, 11.38)	2.64 (1.27, 5.47)	**0.009**	980 (98.3)	17 (1.7)	6.26 (2.94, 13.32)	6.19 (2.80, 13.69)	**< 0.001**
CD4 Count										
< 200	229 (81.8)	51 (18.2)				916 (99.1)	8 (0.9)			
200–<350	202 (92.2)	17 (7.8)	0.43 (0.25, 0.71)	0.58 (0.34, 0.96)	**0.036**	729 (99.2)	6 (0.8)	0.94 (0.33, 2.71)	1.32 (0.43, 4.06)	0.633

NE: Not estimable due to the absence of participants in the TB case group

Variable	Did not Initiate TPT					Initiated and Completed TPT				
	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	p-value	None TB n(%)	TB Case n(%)	c RR (95% CI)	a RR (95% CI)	P value
Sex										
350–<500	174 (94.1)	11 (5.9)	0.33 (0.17, 0.61)	0.49 (0.27, 0.90)	**0.021**	755 (99.5)	4 (0.5)	0.61 (0.18, 2.01)	0.85 (0.24, 2.99)	0.801
500+	768 (95.3)	38 (4.7)	0.26 (0.17, 0.39)	0.34 (0.23, 0.50)	**< 0.001**	3333 (99.6)	15 (0.4)	0.52 (0.22, 1.22)	0.87 (0.30, 2.47)	0.787
NE: Not estimable due to the absence of participants in the TB case group										

HIV viral non-suppression emerged as a significant risk factor for TB in both groups. PLHIV with unsuppressed viral load (≥ 1000 copies/mL) had significantly higher TB risk, among those who completed TPT (aIRR: 6.19; 95% CI: 2.80–13.69, $p < 0.001$).

Table 2
Comparison of annual TB Incidence among PLHIV who did not initiate TPT and those who completed TPT

	Participants N (%)	Person time (1000pers on years)	Crude Incidence Rate per 1000 Person Years (95% CI)	Crude incidence rate ratio (IRR) (95% CI)	Adjusted IRR (95% CI)	p-value
Cohort Year 2016						
Overall	**5980**	32758	3.24 (2.68–3.91)			
No TPT	5837 (97.6)	32067	3.21 (2.65–3.90)	1	1	
TPT	143 (2.4)	691	4.34 (1.40-13.46)	1.35 (0.43–4.26)	2.08 (0.65–6.69)	0.22
Cohort Year 2017						
Overall	6374	28928	4.53 (3.82–5.37)			
No TPT	6203 (97.3)	28242	4.39 (3.68–5.24)	1	1	
TPT	171 (2.7)	686	10.21 (4.87–21.41)	2.33 (1.09–4.98)	2.54 (1.14–5.66)	**0.022**
Cohort Year 2018						
Overall	6613	23426	6.06 (5.14–7.15)			
No TPT	5928 (89.6)	21341	6.28 (5.30–7.44)	1	1	
TPT	685 (10.4)	2086	3.84 (1.92–7.67)	0.61 (0.30–1.25)	0.90 (0.44–1.86)	0.785
Cohort Year 2019						
Overall	5535	13093	7.33 (6.00-8.96)			
No TPT	1290 (23.3)	2527	32.45 (26.13–40.29)	1	1	
TPT	4245 (76.7)	10566	1.33 (0.78–2.24)	0.04 (0.02–0.07)	0.08 (0.05–0.15)	**< 0.001**
Cohort Year 2020						
Overall	1067	1698	25.92 (19.29–34.82)			
No TPT	652 (61.1)	1113	38.62 (28.64–52.07)	1	1	
TPT	415 (38.9)	584	1.71 (0.24–12.15)	0.04 (0.01–0.32)	0.10 (0.01–0.73)	**0.023**
Cohort Year 2021						
Overall	852	635	56.67 (40.87–78.56)			
No TPT	497 (58.3)	424	84.95 (61.27-117.76)	1	1	

	Participants N (%)	Person time (1000pers on years)	Crude Incidence Rate per 1000 Person Years (95% CI)	Crude incidence rate ratio (IRR) (95% CI)	Adjusted IRR (95% CI)	p-value
Cohort Year 2016						
TPT	355 (41.7)	212	7.83 (1.96–31.32)	0.09 (0.02–0.38)		

The overall median survival time to TB disease after completing TPT PLHIV was 2.5 years (IQR: 2.3–2.8 years). The Kaplan-Meier curve survival below *(*Fig. 1a*)* illustrates the cumulative probability of PLHIV developing TB disease over a six-year period, after initiating TPT. The six-year survival rate of PLHIV who initiated TPT in this study was 99.3%. Age was a strong determinant of survival after completing TPT (**see** Table 4). Despite a relatively uniform median survival time across age categories (ranging from 2.4 to 2.6 years), individuals aged 40–49 years showed a significantly increased risk of TB disease (HR = 12.56, 95% CI: 1.30–121.15, p = 0.029), which was supported by a statistically significant log-rank p-value (< 0.001).

Duration on ART was a significant determinant of TB risk. Those on ART for 5–9 years had a significantly lower hazard risk of developing TB (HR = 0.30, 95% CI: 0.11–0.81, p = 0.018). A similar protective, though not statistically significant effect was observed among individuals on ART for over 10 years (HR = 0.39, p = 0.072). The significant log-rank test (p < 0.001) shows a protective effect of longer ART exposure.

Table 4
Factors associated with the difference in survival time to TB disease after initiating TPT among PLHIV

Variable	Median Time (Years)	IQR (p25-p75) years	HR (95% CI)	p-value	Log-rank p-value
Sex					**0.023**
Female	2.5	2.3–2.8	1	1	
Male	2.5	2.3–2.8	1.23 (0.58–2.58)	0.59	
Age Group (years)					**< 0.001**
< 10	2.4	1.4–2.8	1	1	
10–19	2.6	2.4–2.9	2.61 (0.49–13.86)	0.259	
20–29	2.5	2.3–2.8	5.69 (0.83–39.02)	0.077	
30–39	2.4	2.2–2.7	3.91 (0.41–37.34)	0.236	
40–49	2.4	2.1–2.7	12.56 (1.30–121.15)	0.029	
50+	2.5	2.2–2.8	8.86 (0.55–143.71)	0.125	
BMI Category					**< 0.001**
Normal	2.5	2.3–2.8	1	1	
Underweight	2.6	2.3–2.9	1.07 (0.37–3.08)	0.907	
Overweight	2.4	2.0–2.7	0.37 (0.05–2.95)	0.351	
Duration on ART (years)					**< 0.001**
< 5	2.5	1.9–2.9	Reference		
05–09	2.5	2.3–2.8	0.30 (0.11–0.81)	0.018	
10+	2.5	2.3–2.8	0.39 (0.14–1.09)	0.072	
Backbone Regimen					**< 0.001**
AZT/3TC	2.6	2.4–2.9	1	1	
ABC/3TC	2.5	2.3–2.8	2.24 (0.73–6.82)	0.157	
TDF/3TC	2.4	2.3–2.8	0.27 (0.06–1.15)	0.077	
TDF/FTC	2.5	2.3–2.8	0.89 (0.20–4.04)	0.879	
Other	2.5	2.3–2.8	NA	NA	
Anchor Regimen					**< 0.001**
INSTI (DTG-based)	2.4	1.5–2.7	1	1	
NNRTIs (EFV-based)	2.6	2.4–2.9	0.86 (0.28–2.61)	0.784	
NNRTIs (NVP-based)	2.7	2.4–3.1	0.47 (0.05–4.91)	0.529	

Variable	Median Time (Years)	IQR (p25-p75) years	HR (95% CI)	p-value	Log-rank p-value
Sex					**0.023**
PI-based (ATV/r)	2.4	2.3–2.7	1.21 (0.24–5.94)	0.818	
PI-based (LPV/r)	2.5	2.3–2.8	0.46 (0.11–1.88)	0.283	
WHO Stage					**< 0.001**
I	2.4	1.7–2.8	1	1	
II	2.5	2.3–2.8	2.73 (0.84–8.84)	0.095	
III	2.5	2.3–2.8	1.64 (0.47–5.76)	0.437	
IV	2.5	2.3–2.8	1.73 (0.44–6.88)	0.436	
TPT Courses					0.668
1	2.5	2.3–2.8	1	1	
2+	2.3	1.9–2.8	38.45 (17.61–83.97)	< 0.001	

DISCUSSION

This study showed that the annual TB incidence among PLHIV who completed TB reduced over the six-year period. The overall TB incidence in this study was very high compared to the TB incidence (0.189 per 1000 person years) that was reported among PLHIV in a Ugandan study by Kazibwe et al (48). This study showed increasing TB incidence among PLHIV who did not receive TPT (from 3.2 in 2016 to 84.95 TB cases per 1000person years in 2021), while the TB incidence among those who completed TPT reduced over the study period (from 4.34 in 2016 to 1.71 TB cases per 1000person years in 2020), with an increase in 2021. This trend is similar to what was reported in a similar comparison of PLHIV who received TPT and those who did not receive TPT in Ethiopia (21); although the TB incidence in our study was higher than reported in the Ethiopian retrospective cohort (2.1 per 1000person years) (21).

This study revealed that the incidence of TB disease significantly reduced by up to 96% among the PLHIV who completed TPT in 2019 to 2020, compared to those who did not receive TPT. The risk reduction observed among those who completed TPT was higher than the 55% risk reduction reported by Gavin Churchyard in South Africa among male HIV-infected miners who received TPT (57). The higher risk reduction for TB disease among PLHIV who received TPT may be due to the additional benefit of ART, which was reported to have reduced risk of TB disease among PLHIV in Ethiopia by 93.7% (57). This further emphasizes the need for ART adherence among PLHIV, even when they are taking TPT.

This study showed that older PLHIV aged 40 years and above are more than eight times at risk of TB disease. This is contrary to a study in India where age was not associated with TB disease among PLHIV (22). Advanced HIV disease (WHO stage III and IV HIV disease) were significantly associated with TB disease, similar to the Ugandan study by Kazibwe, where PLHIV with WHO HIV stage III were four times at higher risk of developing TB disease compared with those of WHO stage II (18). The WHO stage III and IV are advanced HIV disease, and indicators of a defective immune system, increasing the risk of TB disease. Similar to the Thailand study by Gompol (61), PLHIV who did not receive

TPT and had HIV viral non-suppression (viral load ≥ 1000copies/ml) were more than two times at increased the risk of TB disease. As reported by Samandari et al (62), higher CD4 count > 500cells/ul, was strongly protective from TB disease among PLHIV who did not receive TPT. The higher CD4 count is an indicator of a functional immune system, mounting an effective immune response against TB infection. Having low BMI (< 18.5-<25kg/m^2) increased the risk of TB disease by 84% among PLHIV who did not receive TPT. Good ART adherence improves immune recovery, achieves viral suppression which are associated with increase in BMI, and reduced TB risk (23, 24). This highlights the need for proper nutrition among PLHIV to reduce risk of TB disease. In a study among PLHIV in Ethiopia (50), BMI was not associated with TB disease, but the odds of developing TB were almost five times among PLHIV who did not receive cotrimoxazole prophylaxis (50). Due the change in the HIV treatment guidelines during the study period in Uganda, which limited cotrimoxazole prophylaxis to specific high-risk groups (newly enrolled in HIV care, pregnant and breastfeeding mothers, children < 15years of age, on ART <1year, having a detectable HIV viral load), cotrimoxazole prophylaxis was not included in the multi-variable regression model. Although not found in other studies, PLHIV who received ABC/3TC as ART backbone were five times more at risk of developing TB disease. This may be due to the adherence to guidelines were ART changes or simplification were recommended for PLHIV diagnosed with TB.

The estimated median time to developing TB disease after completing TPT in this study was 2.5years, which was longer than the 18months (1.5years) reported by Kazibwe et al in a cohort of adult PLHIV in Uganda (48), 19months in an Ethiopian cohort on PLHIV (57), and 2.5months in a Kenyan cohort of PLHIV (59). The longer time to TB after receiving TPT may be due to the additional benefit of ART, and compliance to TB treatment guidelines that recommended repeat TPT for PLHIV who completed TB treatment. The short time to TB disease after TPT in the other PLHIV cohorts may be due to breakthrough TB (60), or missed TB diagnosis before initiating TPT. Breakthrough TB was less likely in our study most likely due to the routine TB screening at each clinic visit. Similar to the adult PLHIV in TASO HIV treatment centres, advanced HIV WHO clinical stage was significantly associated with higher risk of developing TB within the median time (48). None of these studies mentions recommended time after which to repeat a course of TPT among PLHIV, especially those identified as being at higher risk of developing TB even after receiving TPT.

Strengths

This study enrolled participants of all ages, compared to most studies which enrolled only adults. Using the census approach, minimized the risk of sampling bias. The cohort study design was appropriate to study an outcome that requires a long follow-up period, and enabled the evaluation of risk within the limited time, compared to cross-sectional studies. This study compared TB incidence among PLHIV who received TPT with those who did not receive TPT, to clearly evaluate the benefit of TPT in reducing risk of TB disease among PLHIV.

Limitations

Although the cohort study design was appropriate to determine the primary outcome, the retrospective approach is prone to missing data and the non-random selection of study participants was a source of selection bias. The study site was a center of excellence (COE) for HIV care, which may also contribute to the limited external validity of the results, because the quality of HIV-TB care provided at a COE, may be different from that provided at other public and private health facilities. The study period also included periods when there was limited supply of TPT drugs, and periods on adequate supply.

CONCLUSIONS

The TB incidence among PLHIV who received and completed TPT was lower compared to the TB incidence among PLHIV who did not receive TPT. This emphasizes the benefit of TPT in reducing risk of TB disease among PLHIV. Even after completing TPT, viral non-suppression increases the risk of TB disease by six times. Among PLHIV who do not receive TPT, the risk of TB disease significantly increases with being underweight, having advanced HIV disease, unsuppressed viral load, and low CD4 count. On the other hand, having normal BMI, HIV viral suppression, and high CD4 count > 200cells/ul, reduces the risk of TB among PLHIV who receive TPT. The short time to TB disease after initiating TPT underscores the need for regular TB screening even after receiving TPT. Health workers are encouraged to continue providing ART and TPT adherence support, to support achievement and maintenance of viral suppression, which reduces the risk of TB disease. All PLHIV with low CD4 count and un-suppressed viral load should be screened for TB disease, and offered TPT. There is still need for evidence on the need and timing for repeat TPT doses. There is also need for longer-term TPT interventions to mitigate TB risk among PLHIV even after receiving TPT.

LIST OF ABBREVIATIONS

3TC Lamivudine

ABC Abacavir

ART Anti-retroviral therapy

aIRR Adjusted incidence rate ratio

ATV/r Atazanavir

AZT Zidovudine

BMI Body mass index

DTG Dolutegravir

HIV Human Immune-deficiency Virus

3HP Three months course of Isoniazid and Rifapentine

3RH Three months course of Isoniazid and Rifampicin

INH Isoniazid (isonicotinylhydrazide)

IPT Isoniazid Preventive Therapy

IRR Incidence rate ratio

LPV/r Lopinavir boosted with ritonavir

MOH Ministry of Health

PLHIV People Living with HIV

RR Risk ratio

TB Tuberculosis

TPT Tuberculosis Preventive Treatment

WHO World Health Organization

Declarations

Ethical Considerations

This study was conducted in compliance to the Declaration of Helsinki, and ethical approval was obtained from the Makerere University School of Public health Research and ethics committee (MakSPH REC-186). A waiver of written informed consent was obtained, because no human subjects were involved in this secondary data analysis. Administrative clearance was obtained from Baylor Uganda before start of the data collection. The data did not include client identifying information such as names, address, or phone numbers to maintain client confidentiality. The database was password protected, only accessible to the authorized study team.

Consent to publication

Not Applicable

Availability of data and materials

The anonymised data that support the findings of this study are available within this manuscript. All data are stored under controlled access at Baylor Foundation Uganda. The original data generated in this research and any secondary data that supports this the results and analyses are available from the corresponding author Pauline Mary Amuge (PMA) paulacallista@gmail.com and the institutional representative regulatoryaffairs@baylor-uganda.org , upon reasonable request and submission of a research protocol approved by an accredited research and ethics committee. This is to ensure that the data is shared within the Uganda data protection and privacy regulations, and provisions of the protocol approved by the Makerere University School of Public Health Research and Ethics Committee.

Competing interests

All the authors declare that they have no known competing financial interests or personal relationships that may have influenced the research reported in this manuscript.

Funding

This research was partly funded by the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) grant programme at the International AIDS Society (IAS), through the CIPHER Research grant awarded to PMA.

Authors' contributions

PMA conceptualized the research idea and wrote the main manuscript text.

PMA and MM collected the data.

PMA, SB and LM analyzed the data.

MM, LM, RN, EB reviewed and made significant contribution to the final manuscript.

All authors reviewed the manuscript.

Acknowledgement

Baylor Foundation Uganda: Henry Balwa, Rachel Namuddu Kikabi, Patricia Nahirya-Ntege, Alex Tekakwo, David Mpagi, Adeodata R. Kekitiinwa, Dithan Kiragga.

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Figures

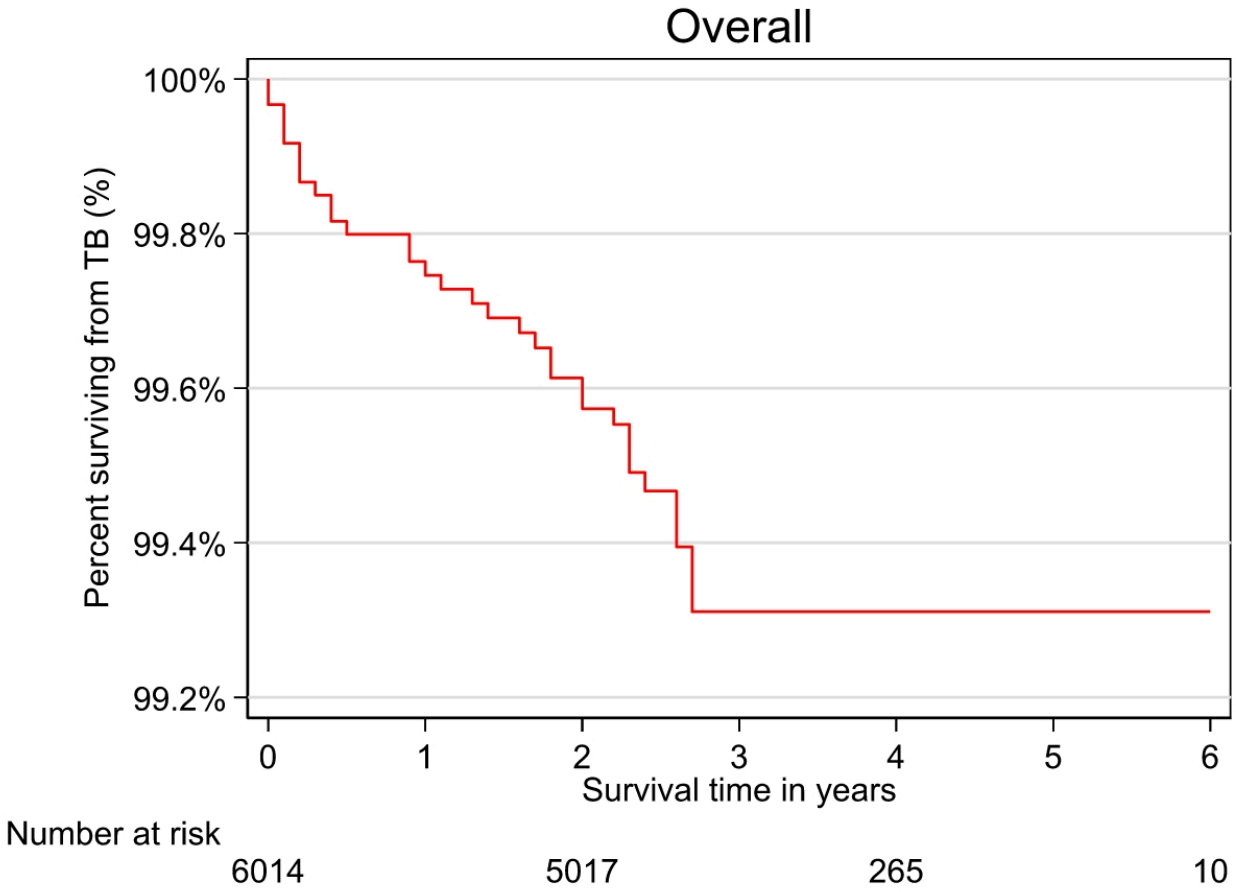


Figure 1

(a) Survival curve showing the probability of PLHIV developing TB disease after initiating TPT