



## **Loss to Follow-up among People Living with HIV on Tuberculosis Preventive Treatment at Four Regional Referral Hospitals, Uganda, 2019–2021**

**Authors:** Edirisa Juniour Nsubuga<sup>1\*</sup>, Stella Martha Migamba<sup>1</sup>, Steven N. Kabwama<sup>1</sup>, Lilian Bulage<sup>1</sup>, Benon Kwesiga<sup>1</sup>, Alex Riolexus Ario<sup>1</sup>

**Affiliations:** <sup>1</sup>Uganda Public Health Fellowship Program, Uganda National Institute of Public Health, Kampala, Uganda

**\*Correspondence:** Email: [nsubugaeddiej@musph.ac.ug](mailto:nsubugaeddiej@musph.ac.ug), Tel: +256704131375

### **Summary**

**Introduction:** Tuberculosis (TB) remains the leading cause of death among people living with HIV (PLHIV). TB prevention among PLHIV can be achieved with TB preventive treatment (TPT) for many years. The six-month course (isoniazid) was the most readily available in Uganda during 2019-2021. While the national TPT completion target is 95%, program data indicated a substantial loss to follow-up (LTFU) of 12% in the period 2019-2021. We determined the factors associated with TPT LTFU among PLHIV in four regional referral hospitals (RRHs) in Uganda from 2019-2021 to inform mitigation measures.

**Methods:** We abstracted program data from the TPT registers on patient LTFU at Masaka, Mbale, Mubende, and Jinja RRHs. Additional data collected included client demographics, duration of HIV antiretroviral therapy (ART), year of TPT initiation, adherence, and point of entry. We conducted bivariate analysis using the chi-square test. Variables with  $p < 0.05$  in bivariate analysis were included in the logistical regression model using a backward stepwise method to establish factors associated with LTFU.

**Results:** Among 24,206 clients who started on TPT in the four RRHs with a median age of 40 years (range, 1-90 years), 15,962 (66%) were female, and 22,260 (92%) had TPT adherence  $>95\%$ . Factors associated with LTFU included being on ART for  $<3$  months (AOR: 3.1, 95% CI: 2.1-4.5) and 20-24 years (AOR: 4.7, 95% CI: 1.9-12) or 25-29 years (AOR: 3.3, 95% CI: 1.3-8.2) compared to 15-19 years.

**Conclusions:** Close follow-up of PLHIV aged 20-29 years and those newly initiated on ART could improve TPT completion.



## Introduction

Tuberculosis (TB) is the leading cause of death among people living with human immunodeficiency virus (PLHIV) infection (1). Of the global TB deaths in 2019, 208,000 (33%) were living with HIV (1). To reduce the TB burden in this population, the World Health Organization (WHO) recommends tuberculosis preventive treatment (TPT) for PLHIV without active TB, including children living with HIV aged  $\geq 12$  months as well as pregnant and breastfeeding mothers (2-6). From 2019–2021, Uganda implemented a six-month course with isoniazid and pyridoxine for TPT (2, 3). Alternative recommended regimens of TPT were a 6-month daily equivalent of a rifamycin-based regimen, 1-month daily rifapentine, and isoniazid regimen as well as a 4-month daily rifampicin regimen (3). TPT can stop the development of TB disease effectively for many years, but reinfection with TB bacilli after completing treatment may reverse this protection (7, 8). Studies on the benefit of repeated TPT are ongoing, and PLHIV who have completed TB treatment may also receive a TPT course (7, 8).

The TPT care cascade includes TB symptom screening to exclude active TB, determining those eligible, enrolling them, and treatment monitoring to ensure completion of TPT (2, 3). Although Uganda rolled out Isoniazid Preventive Therapy (IPT) in June 2014, by July 2019, only 16% of all eligible PLHIV without active TB in Uganda had received TPT. During the period July–October 2019, the Ministry of Health (MoH) in Uganda implemented a 100-day accelerated scale-up of TPT with a target of enrolling 300,000 PLHIV in 100 days and achieving 100% coverage by the end of 2022 in this population (9, 10). Program data in Uganda show that of the 916,345 PLHIV initiated on TPT from January 2019–December 2021, 808,653 (88%) completed, and 107,692 (12%) were lost to follow-up (11). However, contributory factors to this level of loss to follow-up from treatment have not been systematically analyzed. We determined the factors associated with TPT loss to follow-up (LTFU) among PLHIV in four regional referral hospitals (RRHs) in Uganda to inform program improvements in Uganda and beyond.



## Methods

### Study design and data source

We conducted a secondary analysis of routinely collected program surveillance data in the national TPT registers to determine the magnitude of LTFU and associated factors among PLHIV attending Masaka, Mbale, Mubende, and Jinja RRHs in Uganda. These facilities contributed 63,908 (3.5%) of the cumulative number of PLHIV clients ever enrolled in ART care across the country as of December 31, 2021 (11).

### Study population

Our study population included all PLHIV in Uganda who received HIV/ART services from the highlighted four health facilities from January 1, 2019–31 December 2021.

### Data abstraction

We abstracted data on the factors associated with TPT LTFU among PLHIV from the TPT registers of Mbale, Jinja, Mubende, and Masaka RRHs. No personal identification information was collected from the TPT registers.

### Study variables

**Outcome variable:** This was the outcome at the end of six months after TPT initiation, which was indicated by either completion or loss to follow-up. Other outcomes (still on TPT, died, referred to another health facility, and deliberately stopped by health workers) were also collected. However, they were not included in determining factors associated with LTFU after TPT initiation.

**Exposure variables:** These included the patient's age, sex, regional referral hospital, year of TPT initiation (either 2019, 2020, or 2021), ART status at TPT initiation (being on ART for <3 months), being on ART for  $\geq 3$  months, and not indicated), point of entry (either HIV/ART clinic or OPD), TPT regimen (either isoniazid/INH or Q-TIB/cotrimoxazole plus isoniazid plus vitamin B 6), and average adherence levels (either good ( $>95\%$ ), fair ( $\geq 85-95\%$ ), or poor ( $<85\%$ )).

### Data analysis

We used STATA Version 14.0 for the analysis of TPT outcomes, levels, and factors associated with loss to follow-up. At the bivariate level, we used the chi-square test ( $\text{Chi}^2$ ) to



determine factors associated with loss to follow-up, while at the multivariate analysis level, we used logistic regression to generate adjusted odds ratios (AORs) with 95% confidence intervals (CIs). Variables with  $p < 0.05$  in bivariate analysis were included in the model. At the multivariate analysis level,  $p < 0.05$  showed statistically significant associations between the outcome and the independent variables. AORs were used instead of prevalence ratios because the prevalence of loss to follow-up was less than 10% (12). We tested the model using the Hosmer–Lemeshow goodness of fit test.

### **Ethical considerations**

The Office of the Associate Director for Science, U.S. CDC/Uganda, and the U.S. CDC human subjects review determined that this activity was not human subjects research. Its primary intent was public health response and tuberculosis control. This activity was reviewed by the U.S. CDC and was conducted consistent with applicable federal law and CDC policy. All experimental protocols were approved by the US CDC human subjects review board and the Uganda Ministry of Health and were performed in accordance with the Declaration of Helsinki. We used routinely collected aggregate surveillance data that did not have any personal identifiers. No personal identification information was collected from any of the records sources.

### **Results**

#### **Demographic and clinical characteristics**

A total of 24,206 records of PLHIV were abstracted. Of these 10,047 (42%) PLHIV were from Masaka RRH, 15,962 (66%) were female, and 20,740 (86%) had been on ART for more than three months. A total of 4,986 (21%) were aged more than 50 years, 24,204 (99.99%) were enrolled in the ART clinic, and 23,677 (98%) were on isoniazid and pyridoxine. TPT outcomes included 23,592 (97%) completed, of which 22,260 (92%) had good adherence. Other outcomes included 76 (0.3%) who died, 31 (0.1%) who were stopped, 96 (0.4%) who were transferred to other facilities, 141 (0.6%) still on TPT, 36 (0.2%) not evaluated, and 234 (1.0%) lost to follow-up (Table 1).

**Table 1: Characteristics of people living with HIV who were initiated on tuberculosis preventive treatment, Uganda, 2019–2021**

<b>Characteristic</b>	<b>Frequency (n=24,206)</b>	<b>Percent</b>
<b>Regional Referral Hospital</b>		
Masaka	10,047	42
Mbale	5,653	23
Mubende	4,902	20
Jinja	3,604	15
<b>Sex</b>		
Female	15,962	66
<b>Year of TPT initiation</b>		
2019	17,671	73
2020	3,755	16
2021	2,780	12
<b>ART Status at TPT Initiation</b>		
Being on ART for $\geq 3$ months	20,740	86
Being on ART for $< 3$ months	1,531	6
Not indicated	1,935	8
<b>Age group</b>		
	Median (40 years)	Range (1, 90)
1–4	76	0.3
5–9	292	1
10–14	523	2
15–19	657	3
20–24	1,127	5
25–29	2,306	10
30–34	3,510	15
35–39	4,086	17
40–44	3,617	15
45–49	3,026	13
$\geq 50$	4,986	21
<b>Point of entry</b>		
HIV/ART Clinic	24,204	99.99



#### TPT Regimen

INH	23,677	98
Q-TIB (CTX+ INH+ Vit B6)	529	2

#### Outcome at end of 6 months

Completed	23,592	97
Loss to follow-up	234	1
Still on TPT	141	0.6
Died	76	0.3
Transferred to another facility	96	0.4
Not evaluated	36	0.2
Stopped by health workers	31	0.1

#### Reason for stopping TPT \*

Side effects	14	45
Developed active TB	7	23
Treatment Interaction	2	7
Others	8	26

#### Average adherence levels

Good (>95%)	22,260	92
Fair ( $\geq 85$ –95%)	255	1
Poor (<85)	5	0.02
Not indicated	1,686	7

\* Deliberately stopped by health workers (31)

#### Factors associated with loss to follow-up after TPT initiation among PLHIV in Uganda, 2019–2021

In the bivariate analysis, sex ( $p=0.009$ ), age group ( $p<0.001$ ), TPT regimen ( $p=0.019$ ), regional referral hospitals ( $p<0.001$ ), average adherence levels ( $p<0.001$ ), and ART status at TPT initiation ( $p<0.001$ ) were significantly different between those who completed the six-month course of TPT and those who were lost to follow-up (Table 2).



**Table 2: Bivariate analysis of factors associated with loss to follow-up after tuberculosis preventive treatment initiation among people living with HIV, Uganda, 2019–2021**

Characteristics	TPT Status at the end of treatment				Chi <sup>2</sup>	p-value
	Completed n=22,723		LTFU <sup>†</sup> n=232			
		%	%			
<b>Sex</b>					6.9	0.009 *
Female	15,090	99	173	1		
Male	7,633	99	59	1		
<b>Age group</b>					241	<0.001 *
15–19	645	99	5	1		
20–24	1,034	96	48	4		
25–29	2,182	97	65	3		
30–34	3,428	99	18	1		
35–39	4,011	99	20	1		
40–44	3,540	99	28	1		
45–49	2,977	99	20	1		
≥50	4,906	99	28	1		
<b>TPT Regimen</b>					5.5	0.019 *
INH	22,199	99	232	1		
Q-TIB (CTX+ INH+ Vit B6)	524	100	0	0		
<b>Regional Referral Hospital</b>					766	<0.001 *
Masaka	9,639	100	0	0		
Mbale	5,265	99	51	1		
Mubende	4,559	100	0	0		
Jinja	3,260	95	181	5		
<b>Average adherence levels ‡</b>					2.6	<0.001 *
Good (>95%)	21,293	99.8	34	0.2		
Fair (≥85–95%)	249	99	2	1		
Poor (<85)	5	100	0	0		
<b>Year of TPT initiation</b>					3.5	0.172
2019	16,638	99	176	1		
2020	3,541	99	39	1		
2021	2,544	99	17	1		
<b>ART Status at TPT Initiation</b>					196	<0.001 *
Being on ART for ≥3 months	19,587	99	126	1		
Being on ART for <3 months	1,371	97	41	3		
Not indicated	1,765	96	65	4		



†Loss to follow-up, \* Significant association at  $p < 0.05$ , ‡ Among 21,547 that completed and 36 who were lost to follow-up

After adjusting for all statistically significant variables in the bivariate analysis (Table 2), new patients on HIV/ART care during the quarter (AOR: 3.1, 95% CI: 2.1–4.5), ages 20–24 years (AOR: 4.7, 95% CI: 1.9–12) and 25–29 years (AOR: 3.3, 95% CI: 1.3–8.2) were more likely to be lost from TPT (Table 3).

**Table 3: Multivariate analysis of factors associated with loss to follow-up after tuberculosis preventive treatment initiation among people living with HIV, Uganda, 2019–2021**

Characteristics	TPT Status at the end				AOR (95% CI)	p-value
	Completed		LTFU†			
	n	%	n	%		
<b>Sex</b>						
Female	15,090	99	173	1	1.0	
Male	7,633	99	59	1	0.9 (0.6–1.2)	0.381
<b>Age group</b>						
15–19	645	99	5	1	1.0	
20–24	1,034	96	48	4	4.7 (1.9–12)	0.001*
25–29	2,182	97	65	3	3.3 (1.3–8.2)	0.012*
30–34	3,428	99	18	1	0.6 (0.2–1.6)	0.317
35–39	4,011	99	20	1	0.6 (0.2–1.7)	0.337
40–44	3,540	99	28	1	1.0 (0.4–2.7)	0.921
45–49	2,977	99	20	1	0.9 (0.3–2.5)	0.882
≥50	4,906	99	28	1	0.9 (0.3–2.3)	0.780
<b>ART Status at TPT</b>						
<b>Initiation</b>						
Being on ART for ≥3 months	19,587	99	126	1	1.0	
Being on ART for <3 months	1,371	97	41	3	3.1 (2.1–4.5)	<0.001*

†Loss to follow-up, \* Significant association at  $p < 0.05$





## **Discussion**

In this study, we analyzed outcomes of TPT among PLHIV in regional referral hospitals and factors associated with LTFU, which contributes the most among the unsuccessful outcomes. This study showed that having been newly started on ART (being on ART for less than 3 months) during the quarter, ages of 20–24 years and 25–29 years were associated with increased odds of LTFU after initiation on TPT among PLHIV.

Our findings are similar to findings from other settings in the Democratic Republic of Congo, Zimbabwe, Tanzania, Ethiopia, Malawi, and Botswana that showed that patients who were already on ART at the time of TPT initiation had increased TPT completion rates compared to the new ones on ART or those not yet enrolled on ART (13-18). This occurrence could be attributed to stigma (19-21), poor adherence (22), and a lack of understanding of the role of TB prevention in the absence of symptoms (23). It is also plausible that the pill burden among PLHIV newly starting ART and TPT at the same time presents a larger challenge than in ART-experienced patients (14). However, a study in Nigeria suggested otherwise, which may be attributed to the very low number of PLHIV who were newly on ART compared to the number of those who were already on ART included in that study (24).

We found patients in the 20–24 years and 25–29-year age groups with increased odds of loss to follow-up after initiation on TPT, similar to findings from other studies in Zimbabwe, Malawi, Italy, and the United States. (14, 25-27). We could attribute this to the high stigma among younger PLHIV aged 20–29 years compared to the older population, as reported elsewhere (28). Older PLHIV have developed coping mechanisms and hence have low levels of negative self-image (29-32). On the other hand, this could be attributed to migration or movement of the young population in search of employment opportunities as previously reported (33), hence the higher likelihood of loss to follow-up among them.



### **Study limitations**

The secondary data that we used were limited by the number of possible variables we could use in determining factors associated with LTFU after TPT initiation. Nonetheless, the data we used provided a good reflection of the factors associated with LTFU after TPT initiation in Masaka, Mbale, Mubende, and Jinja RRHs in Uganda during the study period. Since we only collected data on regional referral hospitals, our results might have been less representative if the loss of follow-up in lower-level health facilities differed along with associated factors.

### **Conclusions and recommendations**

Although our study had limited coverage, the findings concur with what has been established in other settings. Patients newly initiated on ART and those in the 20–29 age group are more likely to be lost from TPT before completion. MoH could prioritize these patient categories for close follow-up to improve TPT outcomes and reduce the burden of TB among PLHIV. Given that some patients may be lost due to migration while on longer TPT regimens, MOH could expedite the scale-up of shorter WHO-recommended regimens as one of the mitigation measures.

### **Conflict of interest**

The authors declare that they had no conflict of interest.

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