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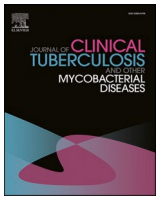

Loss to follow-up among people living with HIV on tuberculosis preventive treatment at four regional referral hospitals, Uganda, 2019–2021

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ABSTRACT

Introduction: Tuberculosis (TB) remains the leading cause of death among people living with HIV (PLHIV). TB preventive treatment (TPT) can prevent active TB infection in PLHIV for several years after it is completed. During 2019–2021, the six-month course of TPT (using isoniazid) was the most readily available in Uganda; however, program data indicated a TPT program loss to follow-up (LTFU) rate of 12 % during this period. We evaluated factors associated with TPT LTFU among PLHIV in four regional referral hospitals (RRHs) in Uganda from 2019 to 2021.

Methods: We abstracted program data from TPT registers on patient LTFU at Masaka, Mbale, Mubende, and Jinja RRHs. Additional data collected included client demographics, duration on HIV antiretroviral therapy (ART), year of TPT initiation, adherence, and point of entry. LTFU was defined as the failure to finish six consecutive months of isoniazid without stopping for more than two months at a time. We conducted bivariate analysis using the chi-square test for independence. Variables with $p < 0.05$ in bivariate analysis were included in a logistic regression model to establish independent factors associated with LTFU.

Results: Overall, 24,206 clients were started on TPT in the four RRHs. Their median age was 40 years (range, 1–90 years), and 15,962 (66 %) were female. A total of 22,260 (92 %) had TPT adherence >95 %. Independent 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: PLHIV just starting ART and young adults had higher odds of being LTFU from TPT during 2019–2021 in the four RRHs. Close follow-up of PLHIV aged 20–29 years and those newly initiated on ART could improve TPT completion.

1. Background

Tuberculosis (TB) is the leading cause of death among people living with human immunodeficiency virus (PLHIV) infection [1]. PLHIV have an increased risk of TB due to depletion of TB-specific T helper cells [2,3], increasing their risk 5–10 % per year of progressing from TB infection to TB disease [4,5]. PLHIV are more likely to advance from TB infection to TB disease and have accelerated disease progression, and both factors can contribute to outbreaks of TB in PLHIV [4]. Additionally, HIV increases the risk of recurrent TB disease in individuals with a history of TB disease [5]. Of the 1.6 million global TB deaths in 2021, 187,000 (12 %) were among PLHIV, with over 95 % of TB mortality among PLHIV occurring in low- and middle-income countries [1].

To reduce the TB burden in PLHIV, the World Health Organization (WHO) recommends tuberculosis preventive treatment (TPT) for PLHIV without active TB, including children living with HIV aged ≥12 months

Abbreviations: AOR(s), adjusted odds ratio(s); ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; MoH, Ministry of Health; PLHIV, people living with HIV; TB, tuberculosis; TPT, tuberculosis preventive treatment.

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and pregnant and breastfeeding mothers [6,7]. TPT can effectively stop the development of TB disease for many years, but reinfection with TB bacilli after completing treatment may reverse this protection [8,9]. The WHO recommends seven TPT regimens, six of which are daily and one is taken weekly. The daily regimens are a 6-month course of isoniazid (IPT), a 6-month course of rifamycin, a 4-month course of rifampicin (4R), a 3-month course of rifampicin and isoniazid (3HR), and a 1-month course of rifapentine and isoniazid (1HP) [7,8]. The latest regimen to be approved by the WHO is the 3-month weekly course of rifapentine and isoniazid (3HP) [7,8]. Studies on the benefit of repeated TPT are ongoing, and PLHIV who have completed TB treatment may also receive a TPT course [8,9]. Globally, different challenges of TPT implementation among PLHIV have been identified in resource-limited settings [10], including but not limited to logistical and supply problems [11], drug interactions and TPT side effects [12], substandard monitoring and evaluation activities [13], inadequate health care infrastructure [14], poor TB screening practices [15], limited understanding of TPT by prescribers [16] and patients [17,18], limited access to health care [19], HIV stigma [20], and socioeconomic issues that undermine household security [21].

The scale-up of TPT in Uganda has been slower than desired, with only 16 % of all eligible PLHIV without active TB in Uganda having received TPT five years after it was rolled out in the form of isoniazid preventive therapy (IPT) in June 2014 [22]. During 2019–2021, Uganda implemented the daily 6-month course of TPT using isoniazid, which was the most readily available TPT regimen at the time [6,7]. Preventing loss to follow-up among people enrolled on TPT is key to the success of such programs. For all the WHO recommended TPT regimens, the desired TPT completion rate is 100 %. However, 95 % TPT completion is the acceptable target of the Uganda Ministry of Health (MoH), implying that the tolerable TPT LTFU is 5 % [23]. Program data in Uganda showed that of the 916,345 PLHIV initiated on TPT from January 2019–December 2021, 107,692 (12 %) were lost to follow-up, which was far more than the tolerable LTFU of 5 % [24]. A few studies have been conducted in Uganda on the factors associated with TPT incompletion [23]. However, factors associated with follow-up from treatment have not been systematically analyzed. We determined the factors associated with TPT lost to follow-up (LTFU) among PLHIV in four regional referral hospitals (RRHs) in Uganda to inform program improvements.

2. Methods

2.1. Study design and data source

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 [6,7]. We conducted a secondary analysis of routinely collected program surveillance data in the TPT health facility registers to determine the magnitude of LTFU and associated factors among PLHIV attending Masaka, Mbale, Mubende, and Jinja RRHs in Uganda. These facilities were randomly selected.

2.2. Study population

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

2.3. 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.

2.4. 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 due to side effects, developed active TB, and Treatment Interaction) were also collected. However, they were not included in determining factors associated with LTFU after TPT initiation. LTFU was defined as the failure to finish six consecutive months of isoniazid without stopping for more than two months at a time [8].

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 ≥3 months, and not indicated), point of entry (either HIV/ART clinic or OPD), and TPT regimen (either isoniazid/INH or Q-TIB/cotrimoxazole plus isoniazid plus vitamin B6). We also collected data on adherence to the TPT regimen calculated as the number of self-reported days that the client swallowed TPT drugs divided by the number of days of TPT given multiplied by 100, which, for purposes of this study, was defined as 'good' if higher than 95 % of adherence, 'fair' if ≥85–95 %, and poor if <85 %.

2.5. 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 to determine factors associated with LTFU. We used logistic regression to generate adjusted odds ratios (AORs) with 95 % confidence intervals (CIs) for multivariable analysis. Variables with $p < 0.05$ in bivariate analysis were included in the model. AORs were used because the prevalence of LTFU was less than 10 % [25]. We tested the model using the Hosmer–Lemeshow goodness of fit test.

3. Results

3.1. Demographic and clinical characteristics of PLHIV initiated on TPT in four regional referral hospitals, Uganda, 2019–2021

A total of 24,206 records of PLHIV were abstracted. Of these PLHIV, only 342 (1 %) were lost to follow-up, 10,047 (42 %) 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 >50 years, 24,204 (99.99 %) were enrolled in the HIV/ART clinic, and 23,677 (98 %) were on isoniazid and pyridoxine (Table 1).

3.2. Factors associated with TPT LTFU among PLHIV in four regional referral hospitals, 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).

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).

4. Discussion

In this study, we analyzed the factors associated with TPT LTFU among PLHIV in four regional referral hospitals in Uganda. Although the loss to follow-up after TPT initiation in this study is very low compared

Table 1
Characteristics of People Living with HIV initiated on Tuberculosis Preventive Treatment in four regional referral hospitals, Uganda, 2019–2021.

Characteristic	Frequency (n = 24,206)	Percent
Regional Referral Hospital		
Masaka	10,047	42
Mbale	5,653	23
Mubende	4,902	20
Jinja	3,604	15
Sex		
Female	15,962	66
Male	8,244	34
Year of TPT initiation		
2019	17,671	73
2020	3,755	16
2021	2,780	12
ART Status at TPT Initiation		
On ART for ≥3 months	20,740	86
On ART for <3 months	1,531	6
Not indicated	1,935	8
Age group*		
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
≥50	4,986	21
Point of entry		
HIV/ART Clinic	24,204	99.99
TPT Regimen		
INH	23,677	98
Q-TIB (CTX + INH + Vit B6)	529	2
Status 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 (≥85–95 %)	255	1
Poor (<85)	5	0.02
Not indicated	1,686	7

*Median age (range) = 40 (1–90) years.
[†] stopped by health workers (31).

Table 2
Bivariate analysis of factors associated with loss to follow-up after Tuberculosis Preventive Treatment Initiation among people living with HIV in four regional referral hospitals, Uganda, 2019–2021.

Characteristics	TPT Status at the end of treatment				*p*-value
	Completed		LTFU[†]		
	n = 22,723	%	n = 232	%	
Sex					0.009 *
Female	15,090	99	173	1	
Male	7,633	99	59	1	
Age group					<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	
TPT Regimen					0.019 *
INH	22,199	99	232	1	
Q-TIB (CTX + INH + Vit B6)	524	100	0	0	
Regional Referral Hospital					<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	
Average adherence levels [‡]					<0.001 *
Good (>95 %)	21,293	99.8	34	0.2	
Fair (≥85–95 %)	249	99	2	1	
Poor (<85)	5	100	0	0	
Year of TPT initiation					0.172
2019	16,638	99	176	1	
2020	3,541	99	39	1	
2021	2,544	99	17	1	
ART Status at TPT Initiation					<0.001 *
On ART for ≥3 months	19,587	99	126	1	
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 who completed and 36 who were lost to follow-up.

to the nationwide loss to follow-up, PLHIV enrolled in the HIV/ART clinics of the four RRHs represent a smaller portion of all PLHIV who have ever been enrolled in ART/HIV clinics in Uganda [24]. However, the causes of LTFU after TPT initiation are similar in all hospitals. Findings from this study will help in addressing the problem of loss to follow-up after TPT initiation among PLHIV in Uganda. This study showed that having been newly started on ART and being middle aged (20–24 years and 25–29 years) were associated with increased odds of LTFU after initiation of 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 [17,20,26–29]. This occurrence could be attributed to stigma [30], poor adherence [31], and a lack of understanding of the role of TB prevention in the absence of symptoms [19]. 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 [17]. 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 [32].

We found that patients in the 20–24 years and 25–29-year age groups had increased odds of loss to follow-up after initiation of TPT, similar to findings from other studies in Zimbabwe, Malawi, Italy, and the United States [17,33–35]. We could attribute this to the high stigma among younger PLHIV aged 20–29 years compared to the older population, as reported elsewhere [36]. Older PLHIV have developed coping mechanisms and hence have low levels of negative self-image [37,38]. On the other hand, this could be attributed to migration or movement of the young population in search of employment opportunities, as previously reported [39], hence the higher likelihood of loss to follow-up among them. Although the 15–19 years age group is not so different from the 20–24-years age group, the difference in LTFU after TPT initiation could be explained by the fact that most of the adolescents aged 15–19 years depend on their parents for transport and reminders to go to hospital, and most of them stay with their parents [40], which is not the case for most of the 20–24-years age group.

5. Study limitations

The secondary data that we used were limited by the number of possible variables we could use in determining factors associated with

Table 3
Multivariate analysis of factors associated with loss to follow-up after TPT initiation among PLHIV, Uganda, 2019–2021.

Characteristics	TPT Status at the end				AOR (95 % CI)	*p*-value
	Completed		LTFU[†]			
	n	%	n	%		
Sex						
Female	15,090	99	173	1	1.0	
Male	7,633	99	59	1	0.9 (0.6–1.2)	0.38
Age group						
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)	0.32
35–39	4,011	99	20	1	0.6 (0.2–1.7)	0.34
40–44	3,540	99	28	1	1.0 (0.4–2.7)	0.92
45–49	2,977	99	20	1	0.9 (0.3–2.5)	0.88
≥50	4,906	99	28	1	0.9 (0.3–2.3)	0.78
ART Status at TPT Initiation						
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 $p < 0.05$.

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 regional prevalence, socio-economic barriers, and loss of follow-up in lower-level health facilities differed along with associated factors.

6. Conclusions

Although our study had limited coverage, the findings concur with what has been established in other settings. People just starting ART and young adults had higher odds of being LTFU from TPT during 2019–2021 in the four RRHs. Reasons for the LTFU were unclear but may be due to stigma, pill burden, or migration of young workers in search of jobs. 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.

7. Disclaimer

The conclusions, findings, and opinions expressed by the authors contributing to this article do not necessarily reflect the official position of the U.S. Department of Health and Human Services, the Public Health Service, the Centers for Disease Control and Prevention, or the authors' affiliated institutions. The contents of this article are exclusively the responsibility of the authors and do not essentially represent the official views of the US Centers for Disease Control and Prevention, Makerere University, the Uganda Industrial Research Institute, or the Uganda Ministry of Health.

8. Ethics approval and consent to participate

The Office of the Associate Director for Science, US-CDC/Uganda, and the U.S. CDC human subjects review board 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 US-CDC and was conducted consistent with applicable federal law and US-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.

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Author contributions

EJN took the lead in conceptualizing the study idea, data analysis, writing, and editing the manuscript. DL participated in the conceptualization of the study idea, data analysis, and writing of the manuscript. SNK, SMM, AK, ES, RN, RN, SMN, JK, LB, BK, and ARA participated in the conceptualization of the study idea and editing and reviewing of the manuscript. All authors read and approved the final manuscript for publication.

CRediT authorship contribution statement

Edirisa Juniour Nsubuga: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Deus Lukoye:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Steven N. Kabwama:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Stella Martha Migamba:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – review & editing. **Allan Komakech:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Elayete Sarah:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft. **Rose Nampeera:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Rashida Nakazzi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – review & editing. **Saharu Magona Nerima:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – review & editing. **Jireh Kirabo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. **Lilian Bulage:** Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **Benon Kwesiga:** Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **Alex Riolexus Ario:** Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets upon which our findings are based belong to the Uganda Public Health Fellowship Program. For confidentiality reasons, the datasets are not publicly available. However, the datasets can be made available upon reasonable request from the corresponding author (Edirisa Juniour Nsubuga, nsubugaeddiej@musph.ac.ug) and with permission from the Uganda Public Health Fellowship Program.

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