Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 25 (2021) 100269

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Low level of tuberculosis preventive therapy incompletion among people living with Human Immunodeficiency Virus in eastern Uganda: A retrospective data review

Paul Lwevola [a], Jonathan Izudi [a,b,c], Derrick Kimuli [d], Alimah Komuhangi [a], Stephen Okoboi [a,c,*]

[a] Institute of Public Health and Management, Clarke International University, Kampala, Uganda
[b] Department of Community Health, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda
[c] Infectious Diseases Institute (IDI), Makerere University College of Health Sciences, Kampala, Uganda
[d] Directorate of Socio-Economic Surveys, Uganda Bureau of Statistics, Kampala, Uganda

ARTICLE INFO

Keywords:
Tuberculosis
HIV
Isoniazid preventive therapy
Tuberculosis preventive therapy
Uganda

ABSTRACT

Introduction: In most developing countries, tuberculosis (TB) is the leading cause of mortality among people living with the Human Immunodeficiency Virus (PLHIV). Uganda implements TB preventive therapy (TPT) using Isoniazid but data are limited about TPT incompletion. We, therefore, assessed the magnitude of TPT incompletion and the associated factors among PLHIV in a large rural referral health facility in rural eastern Uganda.
Methods and materials: We conducted a retrospective data review for PLHIV initiated on TPT between October 2018 and September 2019. The outcome variable was TPT incompletion defined as the failure to finish 6 consecutive months of Isoniazid or failure to finish 9 months of Isoniazid without stopping for more than 2 months at a time. We descriptively summarized numerical data using frequencies and percentages and compared differences in the outcome with independent variables using the Chi-square or fisher's exact, and the Student's t-tests. We used a generalized linear model to assess factors independently associated with TPT incompletion, reported using adjusted odds ratio (aOR) and 95% confidence interval (CI).
Results: We enrolled 959 participants with a mean age of 41.1 ± 13.8 years, 561 (58.5%) were females, 663 (69.1%) married, 538 (56.1) travelled 5–10 km from their place of residence to the ART clinic, 293 (30.6%) had disclosed HIV status, 362 (37.7%) had been on ART for 5–9 years, and 923 (96.2%) were on first-line ART regimen. We found 26 (2.7%) participants had incomplete TPT. Non-adherence to ART clinic visits (aOR, 2.81; 95% CI, 1.09–7.73), history of switch in ART regimen (aOR, 9.33; 95% CI, 1.19–52.39), patient representation (aOR, 4.70; 95% CI, 1.35–13.99), and one unit increase in ongoing counselling session (aOR, 0.67; 95% CI, 0.46–0.91) were associated with TPT incompletion.
Conclusion: We found low rates of TPT incompletion among PLHIV in rural eastern Uganda. Non-adherence to ART clinic visits, patient representation, and history of switch in ART regimen is associated with a higher likelihood of TPT incompletion while ongoing counselling is associated with a reduction in TPT incompletion. The health system should address non-adherence to ART clinic visits and patient representation, through ongoing psychosocial support.

1. Introduction

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) co-morbidity remains the commonest cause of morbidity and mortality from infectious diseases globally and in sub-Saharan Africa [1]. Infection with HIV accelerates the risk of progression from TB infection to TB disease following exposure to Mycobacterium TB [2]. TB/HIV co-infection results in increased mortality due to rapid decline in immune functioning [3].

Uganda is categorized among the top 30 TB/HIV high-burden countries because it contributes at least 1,000 TB/HIV incident cases per year [4]. In 2019, people living with HIV (PLHIV) accounted for a third of the total number of TB cases notified and more than half of TB-related deaths in Uganda [5]. Among PLHIV, TB continues to cause

* Corresponding author at: Infectious Diseases Institute, College of Health Sciences, Makerere University, Uganda.
E-mail addresses: akomuhangi@ciu.ac.ug (A. Komuhangi), okoboi25@gmail.com (S. Okoboi).

https://doi.org/10.1016/j.jctube.2021.100269

Available online 28 August 2021

substantial morbidity and mortality despite being preventable and curable. The estimated risk of developing active TB disease among PLHIV who have latent TB infections is 20–40 times higher than among those who are HIV-negative [1]. Even among PLHIV who have been initiated on lifelong antiretroviral therapy (ART), the risk of developing active TB disease is higher despite the protective effect of ART when compared to those who are HIV-negative [6–8]. Accordingly, in 2011, the World Health Organization (WHO) recommended the scale-up tuberculosis prevention among PLHIV enrolled to care [9]. Isoniazid is the main drug used for TB Preventive Therapy (TPT) particularly in resource-limited settings such as Uganda. In Uganda, TPT consists of an oral administration of 6–9 months of Isoniazid tablets without breaking for more than two consecutive months [10]. The dual implementation of TPT and ART among PLHIV has been shown to significantly lower the risk of developing active TB disease by about 89% [6–8], thereby reducing the incidence of TB disease [11,12] and averting TB related deaths.

Uganda launched the nationwide rollout of TPT implementation in 2018 but there are wide variations in the uptake of TPT within regions and districts. In, eastern Uganda, there was a massive increase in the number of PLHIV initiated on TPT but completion rates stagnated below the desired target of 95% [13].

Buyende district, one of the rural districts in eastern Uganda, has a TPT completion rate of 72% according to program data, which is 23% below the Uganda Ministry of Health (MOH) target of 95%. However, data are limited to explain the TPT incompletion among PLHIV. Accordingly, we, therefore, assessed the magnitude of TPT incompletion and the associated factors among PLHIV at Kidera Health Centre, a large referral HIV clinic in Buyende district. This data is important in providing evidence-based for planning and designing context-relevant interventions to scale up the completion of TPT in the district and similar settings in sub-Saharan Africa.

2. Methods and materials

2.1. Study design and population

We conducted a retrospective data review for PLHIV initiated on TPT between October 2018 and September 2019 at Kidera Health Centre IV in Buyende district, eastern Uganda. This period was deliberately selected to coincide with the scale-up and country-wide implementation of TPT by the Uganda MoH and to provide representative data for Buyende district and other similar districts in the country. We reported the findings following the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guideline [14].

2.2. Study setting

This study was conducted at Kidera HC IV, the largest and one of the HIV clinics in Buyende district in rural eastern Uganda. Regarding the socio-demographic and economic characteristics of the district [15], the total population is 323,067 and 50.9% of the population are females while 2.6% are people aged $\geq$ 65 years. 87.6% of the population work while slightly more than a half (51.3%) live in semi-permanent dwelling units.

39,372 (64.5%) of the households in the district are located $\geq$ 5 km to the nearest public health facility while more than a quarter (26.5%) of the population aged 10 years and above own a mobile phone. <2% of the households have access to piped water while 84.1% use borehole water. 57, 193 (93.5%) households are engaged in crop growing and the predominantly grown crops include maize, beans, millet, and sweet potatoes. Coffee and matooke are grown on a smaller scale. Also, 42,945 (70.2%) households are engaged in livestock farming.

Located in Kidera sub-county, Budiope County in the western Buyende District, Kidera HC IV also serves as the referral health facility for the district and has a catchment population of 60,000 people. The health facility provides promotive, preventive, curative, and rehabilitative health services and has 37 staff, representing 77% of the required staffing capacity. About 62% of PLHIV that were initiated on TPT between October 2018 and September 2019 in Buyende district had sought care at Kidera HC IV. The health facility serves a wide range of people among which includes mobile fishing and sugarcane plantation workers neighboring the shores of Lake Kyoga. Furthermore, the health facility provides care to 32% of PLHIV in the district.

2.3. TPT screening and eligibility criteria for adults and adolescents living with HIV

The Uganda National TB and Leprosy Control Program (NTLP) recommends TPT using a 6 months regimen of Isoniazid (100 mg) as monotherapy for all adults and adolescents living with HIV, and for under-five child contacts of patients with active TB, the dosage of Isoniazid recommended is 10 mg/kg per day. The target population for TPT includes PLHIV, child contacts of people with pulmonary TB, people with immunosuppression such as diabetics, and PLHIV in congregate settings such as prisoners, health workers, and internally displaced persons. Before TPT is initiated, active TB is usually excluded by screening for TB using the four symptom screening tool.

The screening is important to avoid monotherapy for TB disease as doing so results in drug resistance. The four symptoms screened to exclude active TB include current cough, fever, weight loss, or night sweats. The TB screening is usually done by either a trained Community Linkage Facilitator or a Healthcare Worker. After screening, those who do not report any one of the four symptoms are presumed as unlikely to have active TB so they are started on TPT irrespective of the degree of immune suppression, ART status, and pregnancy. In our setting, Tuberculin Skin Test (TST) is not a requirement for initiating TPT in PLHIV.

Pre-TPT counselling is also offered for those eligible and the messages are focused on the proper use of Isoniazid, frequency and duration of TPT, and the recognition and reporting of any side effects. In addition, follow-up TPT counselling is also offered to clients whenever they return for either TPT or ART refills, usually addressing side effects and any other concerns related to TPT as well as assessing tolerability. For PLHIV with any one of the four symptoms, TB disease is presumed and instead of TPT initiation, an evaluation is performed for TB disease and other diseases. The evaluation for TB disease is done through TB diagnosis using either sputum smear microscopy or GeneXpert, and for people with advanced HIV disease, a urine sample is collected for lipoarabinomannan (LAM) test to rule out active TB disease.

To minimize frequent travels to the health facility, the ART and TPT refill dates are in most cases harmonized or synchronized. Synchronizing ART and TPT refill dates improves adherence to clinic visits as both drugs are dispensed at the same visit. To remind clients about medication pick-ups, the health facility collects data about mobile phone contact numbers, either of the client or a treatment buddy/ or supporter. The reminder calls are made a day before the scheduled appointment date for a medication refill. Similarly, the contacts are used for follow-up especially when one has missed a scheduled clinic appointment date. For ill clients, TPT is delivered at home through home-based care.

2.4. Data collection

We abstracted data from the TB unit and HIV care registers, and patient charts using a standardized data abstraction tool. All patients' identifiable information was de-identified by using the clinical identity. Identifiable information was used to retrieve any missing information from the clinical record but was not recorded in the study database.

2.5. Study variables

The outcome variable was TPT incompletion, defined as failure to finish 6 consecutive months of Isoniazid or failure to finish 9 months of

Isoniazid without stopping for more than 2 months at a time (14). Data about TPT consumption were captured for each month by healthcare providers in the TPT register by recording the quantity dispensed, the date of medication pick-up, and the next TPT refill date. The interval between 2 consecutive refill dates, the most recent and the last date of TPT refill, was computed to establish TPT incompletion.

The independent variables were age which was measured as the number of years lived and later categorized as $\leq$ 24, 25–50, and $\geq$ 50 years; sex was measured as female or male; marital status was measured as single or never married, married, and separated; type of employment was defined as none or without any employment, casual labourer, and self-employed; source of income was measured as "no" if the participant had no income-generating activity or any form of employment otherwise "yes" if there was an income-generating activity; and, distance from the place of residence to the health facility was measured as a self-reported distance in kilometers and then categorized as $<$ 5, 5–10, and $\geq$ 10 km.

Disclosure of HIV status is updated at every clinic visit and was reported as "yes" if the participant's HIV status was known by someone else otherwise "no" if it was not known; functional status was measured as working, ambulant, and bedridden; alcohol consumption was reported "yes" if the participant drinks alcohol otherwise "no" if the participant does not drink alcohol; cigarette smoking was reported "yes" if the participant indicated that he/she smokes otherwise "no" if he/she does not smoke; length of stay on ART was measured in years as the interval between ART and TPT initiation and later categorized as $<$ 5, 5–9, and $\geq$ 10 years; pre-ART counseling was reported "yes" if the participant had received basic information about HIV and ART before treatment initiation otherwise "no" if such information was not received; and, adherence to clinic visits was reported "yes" if the participant had not missed any scheduled ART clinic appointments in the past 6 months otherwise "no". The other independent variables included the current viral load suppression status which was reported as "yes" if the viral load was $<$ 1,000 copies/ul and "no" if the viral load was greater than 1,000 copies/ul; the current ART regimen was reported as "first-line" or "second-line", history of switch in ART regimen was reported as "yes" if the participant had ever experienced a change in ART regimen from the current regimen otherwise "no"; pre-TPT counseling was recorded "yes" if the participant had received health education about the benefits, side effects, and duration of TPT otherwise "no"; representation in the past 6 months was reported "yes" if the participant had sent someone else for TPT pick-up in the last 6 months otherwise "no" if nobody was sent; TPT-related side effects was reported "yes" if the participant had experienced the side effects and "no" if no side effects were reported; and the number of ongoing psychosocial counseling sessions in the past 6 months.

2.6. Data analysis

We descriptively summarized categorical data using frequencies and percentages, and for numerical data, we reported means with respective standard deviations. In the bivariate analysis, we compared differences in TPT incompletion with categorical data using either the Chi-square or Fishers' exact test for large and small cell counts, respectively.

For numerical data, the Student's *t*-test was employed when the data were normally distributed otherwise the Mann-Whitney *U* test was used when the data were skewed. Variables with probability values (p-values) $<$0.05 at univariate analysis were considered statistically significant for multivariate logistic regression analysis. A p-value of$<$0.15 was employed to control for residual confounding and to minimize the exclusion of relevant variables in the final multivariate model. In the multivariate analysis, we computed both crude odds ratio (OR) and adjusted odds ratio (aOR) with the corresponding 95% confidence interval (CI), and variables with a p-value$<$0.05 were considered statistically significant. The final model was parsimonious and characterized with good data fit namely, the lowest Akaike Information Criteria (AIC) of 216, C-statistic or area under the curve of 79.4%, and a statistically non-significant Hosmer-Lemeshow Chi-square statistics of 10.26 ($p = 0.248$).

Ethical approval

Our study was approved by Clarke International University Research Ethics Committee (CIU-REC), with the approval number **CLARKE-2020-16.** Besides, we receive administrative approval from the District Health Office.

3. Results

3.1. Characteristics of study participants and TPT incompletion

We enrolled 959 participants, with a mean age of 41.1 $\pm$ 13.8 years and 631 (65.8%) were aged 25–50 years, 561 (58.5%) were females, 663 (69.1%) were married, 423 (44.1%) had not received any formal education, 604 (63.0%) were without any employment, 538 (56.1%) travelled $\geq$ 10 km from their place of residence to the HIV clinic, 293 (30.6%) had disclosed their HIV status, 362 (37.7%) had been on ART for 5–9 years, and 923 (96.2%) were on first-line ART regimen (Table 1). Our data further show that 26 (2.7%) of the 959 participants studied did not complete TPT (Table 1).

Participants who completed TPT had similar average age compared to those who did not complete TPT: 41.2 $\pm$ 13.8 years versus 38.7 $\pm$ 15.1 years, $p = 0.362$. Table 2 further shows that TPT incompletion mainly occurred among participants in the age categories of 25–50 years, females, married, those who ended at a primary level of education, the unemployed, and those without any source of income among others. We observed statistically significant differences in TPT incompletion concerning non-adherence to ART clinic visits in the past 6 months ($p < 0.001$), current viral load suppression ($p = 0.004$), switch in ART regimen ($p = 0.03$), and patient representation for TPT in the past 6 months ($p = 0.004$). On average, the number of TPT counselling sessions received in the past 6 months was significantly low among participants with incomplete TPT compared to those with complete TPT: 1.7 $\pm$ 1.4 versus 3.1 $\pm$ 2.0 respectively, $p < 0.001$.

3.2. Factors associated with TPT incompletion among PLHIV

In the unadjusted analysis (Table 2), TPT incompletion was more likely if the participant was non-adherent to ART clinic visits in the past 6 months (OR, 4.12; 95% CI, 1.87–9.51), had a detectable viral load (OR, 3.21; 95% CI, 1.34–7.20), had a history of switch in ART regimen (OR, 7.69; 95% CI, 1.14–31.25), and had been represented for TPT in the past 6 months (OR, 3.95; 95% CI, 1.28–10.15). TPT incompletion was less likely for every additional number of ongoing psychosocial counselling sessions received by the participant (OR, 0.58; 95% CI, 0.41–0.77). TPT incompletion was less likely among participants aged 25–50 years (OR, 0.62; 95% CI, 0.22–2.17) and $\geq$ 50 years (OR, 0.81; 95% CI, 0.24–3.14) compared to those $\leq$ 24 years. Male sex was associated with a lower likelihood of TPT incompletion compared to female sex (OR, 0.88; 95% CI, 0.38–1.93). However, the association between age and sex with TPT incompletion was not statistically significant.

After adjusting for all statistically significant variables at unadjusted analysis (Table 2), non-adherence to ART clinic visits (aOR, 2.81; 95% CI, 1.09–7.73), previous switch in ART regimen (aOR, 9.33; 95% CI, 1.19–52.39), and patient representation in the past 6 months (aOR, 4.70; 95% CI, 1.35–13.99) were associated with increased odds of TPT incompletion. However, we observed a lower likelihood of TPT incompletion for every additional number of ongoing psychosocial counselling sessions that were provided to each participant (aOR, 0.67; 95% CI, 0.46–0.91).

4. Discussion

The focus of our study is on the magnitude of TPT incompletion and the associated factors among PLHIV in eastern Uganda. Our study shows

Table 1
Differences in TPT completion among people living with HIV.

Characteristics	Levels	TPT completion			P-value
		All (n = 959) n (%)	Yes (n = 933) n (%)	No (n = 26) n (%)	
Age group in years	≤24	104 (10.8)	100 (10.7)	4 (15.4)	0.509
	25–50	631 (65.8)	616 (66.0)	15 (57.7)	
	≥50	224 (23.4)	217 (23.3)	7 (26.9)	
	mean (SD)	41.1 (13.8)	41.2 (13.8)	38.7 (15.1)	0.362
Sex	Female	561 (58.5)	545 (58.4)	16 (61.5)	0.842
	Male	398 (41.5)	388 (41.6)	10 (38.5)	
Marital status	Single	211 (22.0)	205 (22.0)	6 (23.1)	1.000
	Married	663 (69.1)	645 (69.1)	18 (69.2)	
	Separated	85 (8.9)	83 (8.9)	2 (7.7)	
Level of education	None	423 (44.1)	415 (44.5)	8 (30.8)	0.289
	Primary	297 (31.0)	285 (30.5)	12 (46.2)	
	Secondary	121 (12.6)	119 (12.8)	2 (7.7)	
	Tertiary and above	118 (12.3)	114 (12.2)	4 (15.4)	
Employment type	None	604 (63.0)	590 (63.2)	14 (53.8)	0.316
	Casual laborer	212 (22.1)	203 (21.8)	9 (34.6)	
	Formal	25 (2.6)	24 (2.6)	1 (3.8)	
	Self	118 (12.3)	116 (12.4)	2 (7.7)	
Has a source of income	No	604 (63.0)	590 (63.2)	14 (53.8)	0.328
	Yes	355 (37.0)	343 (36.8)	12 (46.2)	
Distance from residence to health facility (km)	< 5	105 (10.9)	102 (10.9)	3 (11.5)	0.806
	5–10	316 (33.0)	306 (32.8)	10 (38.5)	
	≥10	538 (56.1)	525 (56.3)	13 (50.0)	
HIV status disclosed	No	666 (69.4)	646 (69.2)	20 (76.9)	0.401
	Yes	293 (30.6)	287 (30.8)	6 (23.1)	
Bedridden at time of ART initiation	No	951 (99.2)	925 (99.1)	26 (100.0)	1.000
	Yes	8 (0.8)	8 (0.9)	0 (0.0)	
Drinks alcohol	No	951 (99.2)	925 (99.1)	26 (100.0)	1.000
	Yes	8 (0.8)	8 (0.9)	0 (0.0)	
Smokes cigarettes	No	958 (99.9)	932 (99.9)	26 (100.0)	1.000
	Yes	1 (0.1)	1 (0.1)	0 (0.0)	
Length of stay on ART (years)	<5	579 (60.4)	559 (59.9)	20 (76.9)	0.240
	5–9	362 (37.7)	356 (38.2)	6 (23.1)	
	≥10	18 (1.9)	18 (1.9)	0 (0.0)	
	mean (SD)	4.4 (2.6)	4.4 (2.6)	3.3 (2.0)	0.041
Received pre-ART initiation counseling	No	13 (1.4)	12 (1.3)	1 (3.8)	0.302
	Yes	946 (98.6)	921 (98.7)	25 (96.2)	
	No				**<0.001**
Non-adherence to ART clinics in the past 6 months		682 (71.1)	672 (72.0)	10 (38.5)	
	Yes	277 (28.9)	261 (28.0)	16 (61.5)	
Suppressed viral load	Yes	818 (85.3)	801 (85.9)	17 (65.4)	**0.004**
	No	141 (14.7)	132 (14.1)	9 (34.6)	
Current ART regimen	First-line	923 (96.2)	899 (96.4)	24 (92.3)	0.255
	Second-line	36 (3.8)	34 (3.6)	2 (7.7)	
Ever had a switch in ART	No	947 (98.7)	923 (98.9)	24 (92.3)	**0.039**
	Yes	12 (1.3)	10 (1.1)	2 (7.7)	
Received pre-TPT counseling	No	48 (5.0)	46 (4.9)	2 (7.7)	0.378
	Yes	911 (95.0)	887 (95.1)	24 (92.3)	
Ever represented during TPT in the past 6 months	No	901 (94.0)	880 (94.3)	21 (80.8)	**0.004**
	Yes	58 (6.0)	53 (5.7)	5 (19.2)	
Experienced TPT side effects in the past 6 months	No	951 (99.2)	926 (99.2)	25 (96.2)	0.198
	Yes	8 (0.8)	7 (0.8)	1 (3.8)	
Number of ongoing psychosocial counseling sessions in the past 6 months	mean (SD)	3.1 (2.0)	3.1 (2.0)	1.7 (1.4)	**<0.001**

Note: All percentages are column percentages in the form of n/N.

Table 2
Results of factors associated with TPT incompletion.

Characteristics	Level	Logistic regression analysis	
		Univariable OR (95% CI)	Multivariable aOR (95% CI)
Age group in years	≤24	1	
	25–50	0.61 (0.22–2.17)	
	≥50	0.81 (0.24–3.14)	
Sex	Female	1	
	Male	0.88 (0.38–1.93)	
Non-adherence to ART clinic visits in the past 6 months	No	1	1
	Yes	4.12 *** (1.87–9.51)	**2.81** * **(1.09–7.73)**
Suppressed viral load	Yes	1	1
	No	3.21 ** (1.34–7.20)	2.37 (0.92–5.78)
Ever had a switch in ART	No	1	1
	Yes	7.69 * (1.14–31.25)	**9.33** * **(1.19–52.39)**
Ever represented for TPT in the past 6 months	No	1	1
	Yes	3.95 ** (1.28–10.15)	**4.70** ** **(1.35–13.99)**
Number of ongoing psychosocial counseling sessions in the past 6 months	1 unit increase	0.58 *** (0.41–0.77)	**0.67** * **(0.46–0.91)**

Note: 1) TPT: Tuberculosis Preventive Therapy; 2) OR: unadjusted odds ratio; 3) aOR: Adjusted odds ratio; 4) All odds ratios are exponentiated coefficients at 5% statistical significance; 5) Statistical significance codes at 5% level: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

that in every 100 PLHIV, less than three do not complete TPT. TPT incompletion is more likely when the participant is non-adherent to ART clinic visits, has experienced a switch in ART regimen, and has been represented during ART clinic visits in the past six months. However, TPT incompletion is less likely as the number of psychosocial and counseling sessions increases. The magnitude of TPT incompletion observed among PLHIV in the present study is much lower than 31% in a cohort of newly diagnosed PLHIV in Cape Town, South Africa [16], 13% in a TB vaccine trial in Tanzania [17], and 11.8% among PLHIV in Kinshasha, Democratic Republic of Congo [18]. The Uganda Ministry of Health recommends a 95% TPT completion rate to prevent TB disease among PLHIV [13]. Our finding implies that the HIV program has met the set target and is on course to ending TB disease among PLHIV. The low TPT incompletion in our setting could be attributable to the provision of routine health education and ongoing psychosocial support to all PLHIV. The same reason explains the lower likelihood of TPT incompletion as the number of ongoing psychosocial counselling sessions in the past 6 months increases. The HIV clinic has trained counselors who provide ongoing psychosocial support and counseling to all PLHIV, at least once every three months. Also, all the staff in the HIV clinic have received basic training in HIV counselling. Psychosocial counselling improves adherence to medications and medical advice hence the low TPT incompletion. This finding is consistent with various studies which report health education and counseling as facilitators of TPT completion [19–22]. Consistent with our findings, PLHIV tends to have better adherence to treatment when they receive ongoing psychosocial counseling and support [23,24]. Our findings reflect TPT incompletion among PLHIV who have started TPT at the health facility and might not be generalizable to those who have never been started on TPT ("missing in care"), and who remain at high risk of developing TB in the district. Therefore, the district TB control program should design deliberate measures for the "missing in care" individuals to enroll on TPT to lower the overall burden of TB in the district.

Our data show that non-adherence to ART clinic visits on one hand, and patient representation, on the other hand, are associated with an increased likelihood of TPT incompletion. Adherence to clinic visits is an important proxy measure for adherence to ART [25,26]. ART clinic attendance is an important component of comprehensive HIV care as it enables service providers to track patient clinical progress and offers a valuable opportunity to receive health information. Adherence to HIV clinic visits is associated with a lower risk of mortality [27], slower progression to HIV disease, suppressed viral load and faster immune recovery [28,29], and decreased risk of hospitalization [30]. Furthermore, adherence to clinic visits is closely linked to good adherence to medications [31]. A recent study reports a high proportion of unsuppressed viral load among participants non-adherent to HIV clinic visits and a high proportion of suppressed viral load among those adherent to the visits [25]. Missed clinic appointments have been linked to unsuppressed viral load and delayed immune recovery [32,33]. These findings emphasize the importance of clinic attendance in achieving good adherence to ART and viral load suppression. Our finding of a high likelihood of TPT incompletion and non-adherence to HIV clinic visits is thus plausibly explained by these reasons. Conversely, patient representation is an alternative to individual clinic visits in the circumstances that the patient cannot attend scheduled clinic visits in person. The patient may thus decide to delegate a representative, mostly a treatment buddy, to collect medications. Although permissible per the Uganda HIV treatment guidelines, the practice results in the loss of benefits of individual clinic attendance such as ongoing counseling and support. Patient representation thus disenfranchises the patient from achieving better treatment outcomes. Consistent with our findings, it is thus not surprising that patient representation is connected to poor adherence to ART [34] and potentially TPT incompletion. Overall, our findings underscore the importance of individualized clinic attendance over patient representation. HIV service providers should therefore enforce measures to improve clinic attendance for all PLHIV.

Our data show a high likelihood of TPT incompletion among participants with a previous history of switch in ART regimens. This finding requires cautious interpretation, as there are no previous studies to corroborate our findings with. Although there are several reasons to explain the switch in ART regimen, one of the most important reasons is treatment failure [35], which largely results from non-adherence to ART. The current findings might therefore be a consequence of the past treatment behaviors. Individuals with a history of poor adherence to ART might currently have poor adherence not only to ART but also other medications hence TPT incompletion.

5. Study strengths and limitations

Our study has several strengths and limitations to consider in the interpretation of results. Concerning the strengths, our study is the first in eastern Uganda to establish the level of TPT incompletion among PLHIV. Our study has adequate statistical power to detect a difference in the study outcome. For instance, the analysis of the viral load suppression and TPT incompletion data show 82.6% statistical power assuming a 95% CI, 5% precision, and 97.9% (801/818) and 93.6% (132/141) TPT completion rates in the viral load suppressed and non-suppressed categories, respectively. This statistical power is sufficient to detect the existence of any significant difference. The limitations include the use of secondary data, which is limited by the number of possible variables associated with TPT incompletion such as adherence to ART clinic visits. The lack of qualitative data to enrich, explain, or triangulate the quantitative findings is another limitation to consider. TPT incompletion was low in our setting but this might not be generalizable to other studies due to differences in the study setting and study population among others. Other important limitations include the small number of patients with the outcome of interest, which limits the precision of estimates and the ability to conduct sub-analyses. In addition, our analysis is focused on one step of the TPT cascade and doesn't include individuals who weren't screened/offered TPT. Also, we do not have data on participants who were eligible for TPT but did not initiate the treatment. Accordingly, there may still be substantial dropouts at these other points in the process.

5.1. Conclusions and recommendations

Our study shows a low magnitude of TPT incompletion among PLHIV in eastern Uganda. We found Non-adherence to ART clinic visits, a previous switch in ART regimen, and patient representation are associated with an increased likelihood of TPT incompletion while the provision of ongoing psychosocial counselling is associated with a lower likelihood of TPT incompletion. To improve TPT completion rates, the health system should address non-adherence to ART clinic visits and patient representation and should continue to provide ongoing psychosocial support. People who have ever switched ART regimens should be targeted with special interventions to ensure TPT completion.

6. Ethics and consent to participate

Clarke International University Research Ethics Committee approved this study. Clarke International University Research Ethics Committee (CLARKE-2020–8) waived off informed consent for secondary data. No patient identifiers were collected during data abstraction. We confirm that all methods were carried out under relevant guidelines and regulations.

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.

Acknowledgments

We acknowledge the Clarke International University Research Ethics Committee for the wonderful comments and the Research Assistants for their support in data collection.

References

[1] Murray CJL, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384(9947):1005–70.
[2] Schutz C, Meintjes G, Almajid F, Wilkinson RJ, Pozniak A. Clinical management of tuberculosis and HIV-1 co-infection. Eur Respiratory Soc 2010;36(6):1460–81.
[3] Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G, Hobman TC. Tuberculosis and HIV co-infection. Plos Pathog 2012;8(2):e1002464. https://doi.org/10.1371/journal.ppat.1002464.
[4] World Health Organization, Global Tuberculosis Report 2020. 2020: Geneva, Switzerland. p. 1-2, 6-7,.
[5] Izudi J, Tamwesigire IK, Bajunirwe F. Treatment success and mortality among adults with tuberculosis in rural eastern Uganda: a retrospective cohort study. BMC Public Health 2020;20:1–10.
[6] Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS (London, England) 2007;21(11):1441–8.
[7] Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS (London, England) 2009;23(5):631–6.
[8] Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011;377(9777):1588–98.
[9] World Health Organization, Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resourceconstrained settings. 2011: Geneva, Switzerland.
[10] World Health Organization. WHO consolidated guidelines on tuberculosis. Module 1. 2021; Available from: http://www.ncbi.nlm.nih.gov/books/NBK554956/.
[11] Akolo, C., et al., Treatment of latent tuberculosis infection in HIV infected persons. Cochrane database of systematic reviews, 2010(1).
[12] Zunza, M., et al., Isoniazid for preventing tuberculosis in HIV-infected children. Cochrane Database of Systematic Reviews, 2017(8).
[13] University Research Co. LLC. Regional Health Integration to Enhance Services in East Central Uganda activity. 2021 [cited 2021 Apr 20]; Available from: https://www.urc-chs.com/projects/rhites-ec.
[14] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12(12):1495–9.
[15] Uganda Bureau of Statistics, The National Population and Housing Census 2014 – Area Specific Profile Series. 2017: Kampala, Uganda. p. 19-27.
[16] Oni T, Tsekela R, Kwaza B, Manjezi L, Bangani N, Wilkinson KA, et al. A recent HIV diagnosis is associated with non-completion of Isoniazid Preventive Therapy in an HIV-infected cohort in Cape Town. PLoS ONE 2012;7(12):e52489.
[17] Munseri P, et al. Completion of isoniazid preventive therapy among HIV-infected patients in Tanzania. Int. J. Tuberc. Lung Dis. 2008;12(9):1037–41.
[18] Yotebieng M, Edmonds A, Lelo P, Wenzi LK, Ndjibu PT, Lusiama J, et al. High completion of isoniazid preventive therapy among HIV-infected children and adults in Kinshasa, Democratic Republic of Congo. AIDS (London, England) 2015;29(15):2055–7.
[19] Makanjuola T, Taddese HB, Booth A, Neyrolles O. Factors associated with adherence to treatment with isoniazid for the prevention of tuberculosis amongst people living with HIV/AIDS: a systematic review of qualitative data. PLoS ONE 2014;9(2):e87166.
[20] Mindachew M, et al. Predictors of adherence to isoniazid preventive therapy among HIV positive adults in Addis Ababa, Ethiopia. BMC Public Health 2011;11(1):1–7.
[21] Musayón-Oblitas Y, Cárcamo C, Gimbel S. Counseling for improving adherence to antiretroviral treatment: a systematic review. AIDS Care 2019;31(1):4–13.
[22] Ngugi SK, et al. Factors affecting uptake and completion of isoniazid preventive therapy among HIV-infected children at a national referral hospital, Kenya: a mixed quantitative and qualitative study. BMC Infect. Dis. 2020;20(1):1–11.
[23] Do NT, Phiri K, Bussmann H, Gaolathe T, Marlink RG, Wester CW. Psychosocial factors affecting medication adherence among HIV-1 infected adults receiving combination antiretroviral therapy (cART) in Botswana. AIDS Res. Hum. Retroviruses 2010;26(6):685–91.
[24] Seth P, Kidder D, Pals S, Parent J, Mbatia R, Chesang K, et al. Psychosocial functioning and depressive symptoms among HIV-positive persons receiving care and treatment in Kenya, Namibia, and Tanzania. Prev. Sci. 2014;15(3):318–28.
[25] Lokpo SY, Ofori-Attah PJ, Ameke LS, Obirikorang C, Orish VN, Kpene GE, et al. Viral suppression and its associated factors in HIV patients on highly active antiretroviral therapy (HAART): A retrospective study in the Ho municipality, Ghana. AIDS Res. Treat. 2020;2020:1–7.
[26] Shumba C, Atuhaire L, Imakit R, Atukunda R, Memiah P. Missed doses and missed appointments: adherence to ART among adult patients in Uganda. Int. Scholar. Res. Notices 2013;2013:1–7.
[27] Kimeu M, Burmen B, Audi B, Adega A, Owuor K, Arodi S, et al. The relationship between adherence to clinic appointments and year-one mortality for newly enrolled HIV infected patients at a regional referral hospital in Western Kenya, January 2011-December 2012. AIDS Care 2016;28(4):409–15.
[28] Alamo ST, Wagner GJ, Sunday P, Wanyenze RK, Ouma J, Kamya M, et al. Electronic medical records and same day patient tracing improves clinic efficiency and adherence to appointments in a community based HIV/AIDS care program, Uganda. AIDS Behav 2012;16(2):368–74.
[29] Fong R, Cheng AC, Vujovic O, Hoy JF. Factors associated with virological failure in a cohort of combination antiretroviral therapy-treated patients managed at a tertiary referral centre. Sex Health 2013;10(5):442. https://doi.org/10.1071/SH13043.
[30] Colubi MM, Pérez-Elías MJ, Elías L, Pumares M, Muriel A, Zamora AM, et al. Missing scheduled visits in the outpatient clinic as a marker of short-term admissions and death. HIV Clin Trials 2012;13(5):289–95.
[31] Park WB, Choe PG, Kim S-H, Jo JH, Bang JH, Kim HB, et al. One-year adherence to clinic visits after highly active antiretroviral therapy: a predictor of clinical progress in HIV patients. J. Intern. Med. 2007;261(3):268–75.
[32] Rastegar DA, Fingerhood MI, Jasinski DR. Highly active antiretroviral therapy outcomes in a primary care clinic. AIDS Care 2003;15(2):231–7.
[33] Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann. Intern. Med. 1999;131(2):81–7.
[34] Kunutsor S, et al. Clinic attendance for medication refills and medication adherence amongst an antiretroviral treatment cohort in Uganda: A prospective study. AIDS Res Treat 2010;2010:872396.
[35] Republic of Uganda, Consolidated guidelines for the prevention and treatment of HIV and aids in Uganda. 2020, Ministry of Health.: Kampala, Uganda. p. 20.