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Isoniazid Preventive Therapy for Tuberculosis in People Living with HIV: A Cross Sectional Study in Butebo, Uganda

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ABSTRACT

Background: Despite evidence that isoniazid preventive therapy (IPT) can reduce the risk of tuberculosis (TB) disease among People Living with Human Immunodeficiency Virus (PLHIV), uptake of IPT is low in many resource-limited settings. This study determined the level of IPT uptake and its associated factors amongst PLHIV.

Materials and Methods: This was a retrospective quantitative study amongst PLHIV who do not have active TB and enrolled in 2019 - 2020 for anti-retroviral therapy (ART) in Butebo district, Uganda. Data related to demographic factors (age, sex, religion, marital status, employment status, education level, area of residence, household density), health facility factors (pre-IPT counseling), community factors [distance from Health Center (H/C), incurred costs to reach H/C], and IPT drug-related factors [frequency of Isoniazid (INH) refill, INH stock-outs] were collected from four health facilities using a checklist. The data was analyzed into descriptive statistics and relationships determined using Chi-square tests.

Results: Among eligible PLHIV (272), 34.2% achieved IPT uptake. The mean duration between HIV diagnosis and the start of IPT was 4.31 years, with IPT Uptake among males (37.0%), females (32.8%), married (39.5%), and Christians (35.4%). Factors that affect the rate of IPT uptake include employment, education, residence, costs to reach H/C, and pre-IPT counseling. The IPT completion rate was 97.8%. All the cases who had regular INH refill completed IPT compared to 60.0% with the irregular refill, while 97.8% did not experience INH stock-outs and completed IPT.

Conclusion: Pre-IPT counseling was the most significant contributing factor for IPT uptake. IPT uptake may be scaled up by integrating IPT services in routine HIV care, enhancing counseling for IPT and supervision and monitoring, training of health workers, and improving logistical supplies at the health centers.

Keywords: Tuberculosis; HIV/AIDS; IPT

Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: LO, SK, YAK. Data curation: LO. Formal analysis: LO, KDK. Investigation: LO. Methodology: LO. Project administration: LO. Resources: LO, SK. Software: LO, SK. Supervision: SK, YAK. Validation: KDK. Visualization: LO, KDK. Writing - original draft: LO, KDK. Writing - review & editing: LO, KDK, SK, YAK.

Disclosure

This article is a condensed form of the first author's master's thesis from the Graduate School of Public Health Yonsei University.

INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is one of the leading ten causes of morbidity and mortality throughout the world [1, 2]. In 2019, Africa accounted for 24.5% of the 10 million global TB burden with over 1.4 million cases notified and 608,000 deaths [3]. Tuberculosis aside, its syndromic appearance is common and leads to multiple complications and even death among those with compromised body immunity. Poor immunity in Africa can be associated with several factors but the human immunodeficiency virus (HIV) is commonly noted by most researchers as a comorbidity to TB [3]. Mortality from HIV and TB co-infection was estimated to represent over 211,000 deaths in 2019 [3]. One of the surest ways to reduce this impact is the use of preventive therapy [isoniazid (INH)] for TB among persons diagnosed with HIV. The percentage of People Living with HIV (PLHIV) who were newly enrolled on Isoniazid Preventive Therapy (IPT) was 60.0% in Uganda in 2019 [3]. The IPT reduces the case mortality of TB by 60.0% and up to 55.0% among PLHIV [3, 4]. The World Health Organization (WHO) recommends the use of INH given daily for six months [3-5]. PLHIV who do not have active TB are advised to take IPT [3].

In 2017 the United States Centers for Disease Control and Prevention reported that HIV prevalence in Uganda was 5.7%, and the burden of TB was 201 per 100,000 people [5, 6]. In addition, over 40.0% of PLHIV were co-infected with TB [5]. Due to the high burden posed by the co-infection of TB and HIV in Uganda, the Ministry of Health in 2014, through their policy guidelines for health workers indicated that PLHIV should be screened and have IPT given to all those without active TB [6]. To eventually have a significant reduction in the burden of the disease and the subsequent adoption made by Uganda, WHO aided program made an ambitious objective to ensure that IPT coverage reaches above 90.0% by the year 2035 [7]. This objective was cognizant of previous studies that estimated that between 2003 and 2012, only 0.5% of newly diagnosed people with HIV were put on the IPT, with an overall estimated prevalence of coverage to be 39.0% [7]. This low coverage is likely to hinder achieving the WHO target of reducing TB incidence and mortality by 90.0% by the year 2035 [4]. The case is not only peculiar to Uganda as it was estimated in 2019 that, only 49.0% of HIV-positive people newly enrolled in anti-retroviral therapy (ART) care received IPT globally [8].

There are several factors that are associated with the low patronage and coverage of IPT among PLHIV. This study is imperative to identify those factors that influence the poor uptake of IPT among PLHIV in Butebo district, Uganda. To improve IPT coverage and reduce the burden of TB, the challenges associated with the IPT uptake among eligible PLHIV must be identified and solved [9]. Butebo is a new district in Eastern Uganda that was established in 2017. Because of this, its health system is still developing and lacks programmatic indicators to scale up utilization of IPT for TB among its PLHIV. Also, in Uganda, there appears to be some lack of information on the prevalence of IPT in PLHIV and the factors that influence this low coverage. Data is central in the measures that are instituted by health authorities to mitigate the double impact posed by HIV and TB in these low resource settings. This study is therefore important to assess the prevalence of uptake of IPT and associated factors that affect PLHIV in Uganda.

MATERIALS AND METHODS

1. Study design and population

This was a retrospective quantitative study that determined the level of IPT uptake and the factors contributing to the completion of IPT among eligible PLHIV enrolled in care from January 2019 through December 2020 in Butebo, Uganda. The study primarily relied on hospital-based patient records on IPT among PLHIV in Butebo.

2. Ethics statement

Ethical clearance for this study was obtained from the Yonsei Severance Hospital Institutional Review Board (IRB number is Y-2020-0107), and the need for informed consent was waived by the committee.

3. Study area and population

The study was conducted in Butebo, a rural district in eastern Uganda with a population of about 150,000 people. The district Health Centres (H/C) (4 out of 13) provide comprehensive TB screening, basic diagnostics (sputum smear, Xpert MTB/RIF assay; Cepheid, Sunnyvale, CA, USA), and treatment services for PLHIV. The H/C that provide these services are the Butebo H/C IV, Kakoro H/C III, Nagwere H/C III and Kabwangasi H/C III. These clinics perform the service following Uganda's Ministry of Health guidelines. Each TB treatment facility had two qualified staff working in TB/HIV Clinics. The two workers are trained in TB management to provide counseling to PLHIV about IPT. INH is provided free of charge to PLHIV in Uganda after screening to rule out active TB. Eligible PLHIV is offered the opportunity to choose the healthcare facility they wish to receive IPT and ART.

4. Study population

The study population mainly constituted PLHIV in Butebo district without active pulmonary TB and meeting the inclusion criteria. The inclusion criteria were that a participant had to be enrolled on ART in the designated clinic, and those who were diagnosed with active pulmonary TB were excluded. The four study sites were selected using convenience sampling out of the 13 health care facilities in the district because they provided the IPT services to PLHIV.

5. Data collection techniques and tools

A matrix was developed and guided the collection of relevant data for this study using primary patient records. The primary patient records included the IPT, TB, and ART registers or cards for PLHIV. A research assistant completed the checklist together with the health worker providing IPT care. Prior to the data collection, the research assistant from the four study sites received training facilitated by the principal investigator on research ethics, the study tool, and operational definitions of variables. During the collection, data codes were marked by serial numbers of the checklist used for the extraction and enabled the ability to trace back to specific cases when necessary. The collected data was stored in a personal computer under the guidance of the principal investigator, and access was only granted to only the researchers. The parameters that were mainly extracted included the uptake of IPT as the primary outcome variable. The IPT Completion status was a consequential dependent variable. Independent variables include demographics (age, sex, religion, marital status, employment status, education level, area of residence, household density), health facility factors (pre-IPT counseling), community factors (distance from H/C, incurred costs to reach H/C), and IPT drug-related factors included frequency of INH refill, INH stock-outs. The primary outcome variable for this study was IPT uptake and IPT uptake referred to patients

receiving IPT after diagnosis of HIV and was measured on a dichotomous scale of 'yes' and 'no'. The completion of IPT is defined as the patient who had taken the whole six months course of IPT and was measured on a dichotomous scale of 'yes' and 'no'.

6. Statistical analysis

Data were checked to ensure that all information was properly identified and completed. Errors and omissions detected were discussed and adjusted accordingly. Statistical Package for the Social Science (SPSS) version 25 (IBM Corp., Armonk, NY, USA) was used for data analysis. A preliminary analysis using frequencies was done to identify and rectify concerns associated with missing data. Association between variables was analyzed by performing a chi-square test between the sociodemographic variables with the IPT uptake and IPT completion. The test of association was statistically significant at an alpha level of 0.05.

RESULTS

Among four health centers, 272 participants were enrolled: 115 (42.3%) in Butebo, 51 (18.8%) in Kakoro, 55 (20.2%) in Kabwangasi, and 51 (18.8%) in Nagwere. **Table 1** shows the baseline characteristics of the participants.

Table 2 shows the status of IPT uptake for each of the H/C. The overall IPT uptake rate was 34.2%. The mean duration from HIV diagnosis up to IPT initiation was 4.31 ± 3.78 years. The

Table 1. Demographic characteristics

Variables	Responses	Frequency	Percentage (%)
Sex	Female	180	66.2
	Male	92	33.8
Health centre	Butebo	115	42.3
	Kabwangasi	55	20.2
	Kakoro	51	18.8
	Nagwere	51	18.8
Employment status	Employed	10	3.7
	Unemployed	262	96.3
Marital status	Divorced	32	11.8
	Married	157	57.7
	Single	55	20.2
	Widowed	28	10.3
Religion	Christian	212	77.9
	Muslim	59	21.7
	Other	1	0.4
Highest educational level	None	21	7.7
	Primary	195	71.7
	Secondary	53	19.5
	Tertiary	3	1.1
Residence	Rural	243	89.3
	Urban	29	10.7
Household density	2 people	2	0.7
	3 people	46	16.9
	4 people	58	21.3
	5 people	62	22.8
	6 people	73	26.8
	7 people	22	8.1
	8 people	8	2.9
	10 people	1	0.4

Table 2. IPT uptake by health center

Health center	Mean (SD) time to uptake (year)	IPT uptake within a year (N, %)	IPT uptake after a year (N, %)	No IPT uptake (N, %)	Rate of IPT uptake (N, %)
Butebo (N = 115)	5.00 (± 4.21)	8 (7.0)	19 (16.5)	88 (76.5)	27 (23.5)
Kakoro (N = 51)	4.63 (± 3.82)	7 (13.7)	17 (33.3)	27 (52.9)	24 (47.1)
Kabwangasi (N = 55)	3.80 (± 3.19)	8 (14.5)	12 (21.8)	35 (63.6)	20 (36.4)
Nagwere (N = 51)	3.59 (± 3.75)	10 (19.6)	12 (23.5)	29 (56.9)	22 (43.1)
Total (N = 272)	4.31 (± 3.78)	33 (12.1)	60 (22.1)	179 (65.8)	93 (34.2)

IPT, isoniazid preventive therapy; SD, standard deviation.

number of patients who took up IPT within one year from HIV diagnosis was 33 (12.1%), and the highest proportion was in Nagwere H/C with 10 (19.6%) and while the lowest ratio was in Butebo H/C having 8 (7.0%). The general IPT uptake at over a year from HIV diagnosis was 60 (22.1%) as the patients and was highest in Kakoro H/C with 17 (33.3%) and while also lowest in Butebo H/C with 19 (16.5%). The participants that did not take IPT Uptake was the majority with 179 (65.8%) patients, and the most significant proportion number was from Butebo H/C, 88 (76.5%), and the lowest number from Kakoro H/C, 27 (52.9%). In general, 93 (34.2%) patients took up IPT from the 272 who were eligible. The distribution of uptake of IPT by each health facility is shown in **Table 2**.

The relationship between IPT uptake and contributing factors is depicted in **Table 3**.

There was no significant relationship between IPT uptake and the gender of participants. In addition, there was no significant relationship of age to IPT uptake as it was shown that only 7 (41.2%) of the participants aged 1 - 12 years were in the IPT Uptake group, which was second only to 28 (41.8%) of the 20 - 35 age group. The most negligible IPT uptake was seen among the cases who were 65 years and over, with only 3 (21.4%).

There was a significant relationship of IPT uptake and employment status as 70.0% of employed were in the uptake category compared to 32.8% who were not employed ($P = 0.015$). There was, however, no significant relationship of marital status and IPT uptake as 25.0% of those categorized to take IPT were divorced. Religion affiliation was not determined to be statistically significant as 35.4% of Christians and 30.5% of Muslims were determined to be in the IPT uptake category.

When education level was analyzed, IPT uptake was highest in cases with tertiary education (66.7%) while the most negligible uptake was among those who had primary education (26.2%). The result was highly significant in this study ($P < 0.001$); it was statistically significant that Urban residence (79.3%) were in the IPT Uptake group compared to 28.8% of those from Rural settings ($P < 0.001$).

Moreover, it was statistically significant that the highest IPT Uptake was in the group that incurred no costs (45.3%) and lower in the group that incurred costs to reach the H/C (28.2%) ($P = 0.005$).

Distance from the H/C was analyzed and found 63 (35.8%) of those who lived 5 km or less from the H/C took up IPT. This was higher than 30 (31.3%) of those who took up IPT and stayed more than 5 km from the H/C, but this was not statistically significant in this study. It was also statistically significant that people who were counseled for IPT, 81 (100.0%) and those not counseled 12 (6.3%) had IPT uptake ($P < 0.001$).

Table 3. IPT uptake by contributing factors

Variable	IPT uptake status		P-value
	Uptake	No Uptake	
Gender			0.492
Female	59 (32.8)	121 (67.2)	
Male	34 (37.0)	58 (63.0)	
Age (Years)			0.407
1 - 12	7 (41.2)	10 (58.8)	
13 - 19	2 (22.2)	7 (77.8)	
20 - 35	28 (41.8)	39 (58.2)	
36 - 64	53 (32.1)	112 (67.9)	
>65	3 (21.4)	11 (78.6)	
Employment status			0.015
Employed	7 (70.0)	3 (30.0)	
Unemployed	86 (32.8)	176 (67.2)	
Marital status			0.166
Single	14 (25.5)	41 (74.5)	
Married	62 (39.5)	95 (60.5)	
Divorced	8 (25.0)	24 (75.0)	
Widowed	9 (32.1)	19 (67.9)	
Religion			0.604
Christian	75 (35.4)	137 (64.6)	
Muslim	18 (30.5)	41 (69.5)	
Others	0 (0.0)	1 (100.0)	
Education level			<0.001
Primary	51 (26.2)	144 (73.8)	
Secondary	33 (62.3)	20 (37.7)	
Tertiary	2 (66.7)	1 (33.3)	
None	7 (33.3)	14 (66.7)	
Residence			<0.001
Rural	70 (28.8)	173 (71.2)	
Urban	23 (79.3)	6 (20.7)	
Household density			0.451
2 or less	1 (50.0)	1 (50.0)	
3 - 5	61 (36.7)	105 (63.3)	
6 or more	31 (29.8)	73 (70.2)	
Incurred costs to H/C			0.005
Yes	50 (28.2)	127 (71.8)	
No	43 (45.3)	52 (53.7)	
Distance from H/C			0.450
5 km or less	63 (35.8)	113 (64.2)	
>5 km	30 (31.3)	66 (68.7)	
Pre-IPT counseling			<0.001
Yes	81 (100)	0 (0)	
No	12 (6.3)	179 (93.7)	

IPT, isoniazid preventive therapy; H/C, health center.

Table 4 shows the IPT completion status by the Health Center in Butebo district. Almost participants who took up IPT completed the six months course of treatment (97.8%). IPT completion was highest in the three Health Centres of Butebo, 27 (100.0%), Nagwere, 22 (100.0%), and Kakoro, 24 (100.0%). The lowest IPT completion was in Kabwangasi H/C, 18 (90.0%), as shown in **Table 4**.

Table 5 shows IPT completion by INH supply condition. INH supply was relatively stable. Only 5 participants experienced irregular INH refill and only one participant experienced INH stock-outs. For 5 patients with irregular INH refill 2 (40.0%) could not complete IPT while one person with stock-out could not complete INH ($P < 0.001$).

Table 4. IPT completion by health center

Name of Health Center	Total (N)	Completed IPT (N, %)	Not Completed IPT (N, %)	Rate of IPT completion (%)
Butebo	27	27 (100.0)	0 (0.0)	100.0
Kakoro	24	24 (100.0)	0 (0.0)	100.0
Kabwangasi	20	18 (90.0)	2 (10.0)	90.0
Nagwere	22	22 (100.0)	0 (0.0)	100.0
Total	93	91 (97.8)	2 (2.2)	97.8

IPT, isoniazid preventive therapy.

Table 5. IPT Completion status by drug supply

Variable	Completion status		Total	P-value
	IPT Completed	IPT Not Completed		
Frequency of INH refill				<0.001
Regular	88 (100.0)	0 (0.0)	88 (100.0)	
Irregular	3 (60.0)	2 (40.0)	5 (100.0)	
INH Stockouts				<0.001
Yes	0 (0.0)	1 (100.0)	1 (100.0)	
No	91 (98.9)	1 (1.1)	92 (100.0)	

IPT, isoniazid preventive therapy; INH, isoniazid.

DISCUSSION

We conducted a retrospective analysis of health center-based patient records to identify the level of uptake of IPT and those factors that influence the IPT uptake for the prevention of TB among PLHIV. In this study, 34.2% of the PLHIV were initiated on IPT in Butebo district, Uganda. Similar findings on IPT uptake were found in epidemiological studies conducted in South India, which reported 33.0% [10], and in Zambia, which reported 30.0% [11]. Despite the slight differences and study designs, the IPT uptake in our study was found to be higher than 6.3%, 18.0%, 22.0% [12], and 26.8% [13] reported in Malawi [14], India, and South Africa [12, 15], respectively. In contrast, in other studies in Ethiopia [16], Gambia [17], Rwanda [18], and Benin [19], there was 64.3%, 89.0%, 89.0%, and 99.0% of IPT uptake, respectively, which were much higher compared to the findings of the current study. In these countries that reported a higher uptake, health authorities have integrated the program into the routine care of all PLHIV, and it is associated with the intake of antiretroviral therapy. The integration of IPT into the delivery of healthcare among PLHIV might explain the high uptake in those countries. Therefore, it is imperative that health care authorities in Uganda institute practical measures to ensure increased uptake of IPT for TB prevention among PLHIV. These measures must target and mitigate the challenges that are associated with IPT uptake and completion. IPT implementation shortcomings need to be discussed at all levels of management, from the H/C to the District level, and centrally at the Tuberculosis Control Program of the Ministry of Health. This integrated approach will be key to mitigate adequately the bottlenecks associated with uptake and completion of IPT. The health care providers should integrate IPT with their routine HIV-AIDS/TB services to capture all potential cases for IPT.

The highest proportion of respondents (66.2%) were female in this study. However, there was a non statistically significant relationship of IPT uptake among gender even though some studies have shown a statistically significant relationship [16-18]. It is believed that females have positive health seeking behaviour in Africa and are possible to be health conscious [16]. The discrepancies in this study finding may be attributable to the fact that the population were mainly people diagnosed with HIV and are likely to have received education on general

health improvement through counselling. Some demographic variables that influenced the uptake of IPT were employment ($P = 0.015$), educational level ($P < 0.001$) and residence ($P < 0.001$). These findings demonstrate that these cadres have a greater likelihood of attending health care services and may have enhanced knowledge on health awareness. These demographic variables were also shown to positively impact respondents' uptake of IPT [16-19]. Therefore, it is imperative that health care interventions target specific populations strata to have the desired impact as the level of use of IPT uptake seems to vary based on certain demographic characteristics. There was a statistically significant relationship of incurring cost ($P = 0.005$) and uptake of IPT. Most of the cases initiated on treatment lived in rural households within 5 km from the health centers, which could have made access to health services more favorable and influenced uptake of IPT. The majority incurred travel costs probably due to the bad nature of the roads, limited means of transport, and long distance to the health facility. In line with this it is also important to institute primary health care interventions that will increase health care access while reducing cost by implementing and testing intervention base studies that will encourage IPT uptake among all cadre. Receiving a pre-IPT counseling was shown to be statistically significant ($P < 0.001$) as those who were counseled took IPT than those who did not receive any form of counseling. The counseling given to people diagnosed with HIV on the prophylactic treatment of TB is important in the eventual uptake. The importance of pre-IPT counseling was also reported in other studies that assessed the factors associated with prophylactic management of TB in HIV-positive people [1, 4, 7, 10, 11, 14]. This emphasizes the need for patients be given pre-IPT uptake counseling after they are diagnosed.

The results show that the IPT completion rate was high. However, the data demonstrate that WHO and Uganda's National Tuberculosis and Leprosy Program recommendations for screening all newly diagnosed PLHIV and initiating them to IPT were still not well implemented in Butebo district [3-5, 16, 19]. Implementations of strategies to aid IPT completion is warranted. Also, primary research should focus on those factors that hinder the completion of IPT.

The research was conducted in Butebo district; thus, the findings might not be generalized to the whole country. A significant limitation of this study is the inability to conduct face-to-face interviews with the study cases to determine their personal and community factors that determined IPT uptake and completion. This was due to the lockdown regulations instituted by the government because of coronavirus disease 2019 (COVID-19). The health workers were also not interviewed to obtain their perspectives about IPT services in the health centers. Additionally, we could not get more detailed information about underlying HIV infection and other co-morbidities.

In conclusions, the rate of IPT uptake was found to be low, although the completion rate among those who took up treatment was high. Poor IPT uptake represents missed opportunities to prevent future tuberculosis cases amongst the PLHIV. Significant gains in IPT uptake may be scaled up by addressing the factors affecting IPT uptake especially pre-IPT counseling, integrating IPT with other routine HIV and TB and community care services, enhancing supervision and monitoring, training health workers, and maintaining regular INH supplies at the health centers. Community HIV/TB counselors and village health teams need to be supported further to conduct health education and home visits to the PLHIV to increase uptake of IPT and to monitor them through the period of treatment.

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