Texila International Journal of Academic Research
ISSN: 2520-3088
DOI: 10.21522/TIJAR.2014.12.01.Art010

Effectiveness of Isoniazid Preventive Therapy among Patients on ART in Federal Medical Centre – Keffi, Nasarawa State, Nigeria: A Retrospective Cohort Study

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Abstract

A 6-month isoniazid as tuberculosis preventive therapy (TPT) for people living with HIV (PLHIV) was nationally introduced in Nigeria in 2014. However there has been limited research on the effectives of IPT specific to facilities like FMC – Keffi. This study is, therefore, conducted to evaluate the impact of IPT on the reduction of TB incidence in patients on ART in FMC-Keffi. A retrospective cohort study was conducted on HIV patients who commenced ART from October 2014 to September 2021. A data extraction script was used to extract data from the patient charts on the Electronic Medical Record (EMR). The effectives of IPT on TB incidence was assessed using the total person years, incidence rate ratio, and a multivariate regression model at 5% significance level. A sample size of 581, which included 444 exposed to TPT and 137 unexposed to TPT among PLHIV on ART records. We followed them up for a total of 2,361.66 -person-years of observation. The adjusted odds ratio (AOR) was 0.03 (95% CI: 0.00–0.26, p = 0.006). The results indicated that PLHIV on ART who received and completed a 6-month course of IPT (Exposed group) significantly reduced TB incidence by up to 97% in odds ratio (AOR) compared to does who didn't receive IPT. This study provides strong evidence that TPT significantly reduces the risk of TB in people living with HIV who are on ART. The findings emphasize the need to scale up TPT coverage, particularly for high-risk groups.

Keywords: *ART, IPT, PLHIV, Tuberculosis.*

Introduction

Tuberculosis (TB) is one of the main opportunistic infections in people living with HIV(PLHIV) and reports show that the risk of developing TB in PLHIV is 20–37 times higher than in those without HIV [1]. It was reported that PLHIV also have a significantly increased risk of developing extrapulmonary TB (40–80%) compared to those without HIV (10–20%) [2]. Furthermore, TB-related mortality accounts for 26% of the globally reported HIV deaths [3]. It was estimated that about one-fourth of the world's population is latently infected with mycobacterium tuberculosis [4]. In PLHIV, the lifetime risk of progression from latent TB infection to active disease is about 30% compared to the 10% risk in the general population [5]. According to the WHO global tuberculosis (TB) report, Africa had an estimated 212 total tuberculosis incidences and 42 HIV-positive tuberculosis incidence rates per 100,000 populations in 2021 [6]. Nigeria ranks 6th among the WHO TB high-burden countries and contributes 4% to the global TB burden. In 2021, it was ranked among the ten high-burden countries with low levels of treatment coverage and contributed to the number of multi-drug-resistant and rifampicin resistant TB globally [6]. The highest

Received: 27.12.2024 ***Accepted: 21.01.2025*** ***Published on: 31.01.2025***
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coinfection prevalence of 34.3% was recorded among the North Central States of Nigeria [7]. Nasarawa State is in North Central Nigeria and Federal Medical Center-Keffi Contribute to the diagnosis of approximately 43% of all reported TB cases in the state.

IPT involves the use of isoniazid, an anti-TB medication, to prevent the progression of latent TB infection to active disease. WHO guidelines strongly recommend IPT for PLHIV, regardless of CD4 count, as part of a comprehensive TB prevention strategy. The synergistic effects of IPT and ART have been shown to significantly reduce TB incidence among PLHIV, enhancing their overall health outcomes [26]. The World Health Organization (WHO) and the Nigerian national HIV guidelines recommends the use of a 6–36-month course with isoniazid (INH) as tuberculosis preventive treatment (TPT) to reduce the incidence of active TB in PLHIV [8, 9]. Several studies of different designs, including a meta-analysis, conducted between 2014 and 2020, confirmed the considerable protective effect of isoniazid preventive therapy (IPT) in PLHIV compared to those unexposed [10, 11]. This practice has not been generally accepted in the treatment of HIV patients as some physicians doubt its efficacy and fear the possibility of the development of resistance to INH [12]. Resistance to isoniazid in incident cases of TB has been reported in Africa and globally [13]. Development of resistance could worsen TB treatment outcomes [14]. Conclusions on the impact of IPT on all-cause mortality have, however, been conflicting [10, 11, 15]. In Nigeria, where both TB and HIV are endemic, IPT has been identified as a cost-effective intervention for TB prevention. Several studies have evaluated its impact. Lagos State: A retrospective study reported a significant reduction in TB incidence among PLHIV who completed a six-month IPT course [27]. Northern Nigeria: An observational study showed a 67% reduction in TB incidence among ART patients who received IPT [28]. A report from NTBLCP in 2020 emphasized the role of IPT in achieving Nigeria's TB elimination targets, despite challenges such as poor adherence and low coverage [29].

ART has been shown to independently reduce TB risk by restoring immune function in PLHIV. When combined with IPT, the reduction in TB incidence is more pronounced. Isoniazid preventive therapy (IPT) combined with antiretroviral therapy (ART) reduced the risk of developing active tuberculosis (TB) in people with HIV by almost 90% compared with no treatment in a South African study [30]. Despite its proven effectiveness, IPT implementation in Nigeria faces several challenges such as adherence (non-completion of the six-month IPT course remains a significant barrier) [31], Health System constraints: Inadequate supply chains and lack of trained healthcare workers limit IPT uptake (31), stigma and Awareness (Fear of stigma and low awareness among patients contribute to poor adherence to IPT protocols).

However, in 2014, a 6-month INH as TPT for PLHIV was programmatically introduced in Nigeria [16]. Following its launch and widespread implementation, the intervention was taken up by PLHIV in a number of Nigerian tertiary institutions, including the Federal Medical Center in Keffi, Nasarawa State. While evidence from other regions in Nigeria is promising, adverse reactions linked to INH and other unidentified factors have been reported in certain cases and, there is limited research specific to facilities like FMC – Keffi. Localized studies are crucial to understand contextual factors influencing IPT effectiveness, such as healthcare infrastructure, patient demographics, and adherence patterns. As a result, the effectiveness of INH in preventing TB has been an issue for physicians and PLHIV. This study is, therefore, conducted to evaluate the impact of IPT on the reduction of TB incidence in patients on ART in the Federal Medical Centre-Keffi, Nasarawa State, Nigeria

Materials and Methods

Study Area: This study will be conducted at Federal Medical Centre – Keffi, Nasarawa state located in north-central Nigeria. The facility contributes to the diagnosis of approximately 43% of all reported TB cases in the state. Federal Medical Centre - Keffi is a tertiary level hospital that provides comprehensive HIV/AIDS care including HIV testing and counselling (HTC), Adult and Pediatrics ART and prevention of mother-to-child transmission of HIV (PMTCT). The HIV/TB services in the hospital are fully integrated – patients who are receiving TB care are routinely screened for HIV, and those receiving HIV care are screened routinely for TB before commencing HIV antiretroviral treatment. The hospital provides free sputum acid fast bacilli (AFB) testing, Gene Xpert testing, and free tuberculosis and HIV treatment in accordance with the national treatment guidelines [17].

Study Design: Retrospective study using secondary data from the facility Electronic medical record, Nigeria medical record system (NMRS).

Study Population: The study population consisted of HIV-positive patients who were taking ART. The records were extracted from patients who started ART at the Federal Medical Centre in Keffi, Nasarawa State, between October 2014 and September 2021. Figure 1 shows the process of the inclusion and exclusion criteria to determine the cohort of patients selected for the study.

Inclusion Criteria: All HIV positive patients on ART, determined not to have active TB disease at time of ART commencement will be included.

Exclusion Criteria: All patients who had been diagnosed with TB or treated for TB before ART commencement, and those with unknown TB status at commencement will be excluded from the study. Also, patients without records of follow-up visits after the beginning of ART, and those who were transferred in with incomplete records will be excluded.

Exposure and Outcome Measurement: The main exposure of interest was confirmed completion of a 6-month course of daily INH 300 mg tablet for adults and 10 mg/kg for children as TB preventive therapy. Based on clinical records, PLHIV who had completed the 6-month course of IPT during the study period were considered as exposed and those who never took IPT were categorized as non-exposed. Both the exposed and unexposed groups were on ART. The primary endpoints were incident TB, diagnosed according to the national guideline at any time during the study period and the duration of protection of TB by IPT [9].

Sample Method: A design effect (DEFF) with estimated TB incidence among ART cases at 40%, and absolute precision of 2% will be used to determine the sample size. A systematic random sampling will be used to select the records to include in the study.

Sample Size: A sample size of 581 PLHIV on ART will be enough to evaluate the TB incidence and duration of protection of TPT among PLHIV exposed and unexposed to TPT in Federal Medical Centre – Keffi, with 40% relative precision.

Study Tools Various Schedules, Checklists: A structured data extraction script prepared for this purpose was used to collect historical data of patients from the EMR of the HIV care clinic. The data collection tool comprises the study participants' sociodemographic characteristics, treatment or exposure details, and treatment outcomes available on the NMRS. In instances where records are missing or incomplete, the data collectors update the records using the patient charts or folders.

Pretesting: Two data collectors were hired, and a one-day orientation workshop was held to familiarize them with the study's objectives, data collection methodology, and data collection tools. The data collectors' role is to update the EMR with information from patient charts or folders that are not fully captured on

the NMRS. Prior to data collection, the data extraction sheet was distributed to five experts in clinical pharmacy, medicine, health records (M&E), and epidemiology to ensure content validity. A three-day pre-test was conducted to collect historical data, and the results were used to improve the comprehensiveness of the data collected on the NMRS and ensure consistency of the data abstraction process and data collection approach. Before beginning the enrollment process, the data collectors screened all PLHIV clinical cards for eligibility, and cases that did not meet the eligibility criteria were immediately excluded from the study.

Data Collection: Retrospective data collected from the ART register, patient case notes and TB register at the facility would be entered into the EMR and the patient level data will remain on the local server at the facility.

Utilizing the data extraction scripts, information was obtained from the patient charts or folders. Sociodemographic information (sex, age, education level, employment status, marital status, and place of residence) as well as clinical information (date of HIV confirmation, date of ART initiation, WHO clinical stage, initial weight and height, TB status at enrolment, baseline CD4 count, previous ART, ART adherence) were all retrieved from the data. Additionally, I was able to obtain data regarding the start date of INH, the date INH was finished, compliance with INH, and the type of ART regimen (first line or second line) at the end of the study or the point of censorship. Additionally obtained were details regarding the patient's exposure status, outcome status, person-time contributed to follow-up, and whether the patient experienced ART treatment failure at any point during the follow-up period. The person-time of observation that each participant contributed to the study was computed and expressed in months. The number of months of observation from the conclusion of the 6-month IPT to the end of the study, or until the participant left the study for any reason, or until they developed the outcome of interest (TB), whichever came first, was the person-time contributed for the exposed participant. In contrast, the person-time contributed for the unexposed participant was calculated in terms of months from the start of ART to the completion of the study, or until the participant left the study or contracted tuberculosis. For both IPT and non-IPT, the personal time that each participant contributed was calculated and added up.

Statistical Analysis: Data was extracted from the facility EMR database using a structured query language (SQL) script and exported into Microsoft Excel and analyzed using R 4.0.4 [18]. The Data cleaning, transposing, mapping, classification and analysis was carried out using R 4.0.4. Descriptive statistics including percentages, frequencies, number needed to treat, mean (SD), and median (IQR) were computed as appropriate. Participants with missing data in specific variables of interest were not included in the analysis of a specific variable. The incidence rate of TB was computed using descriptive statistics and, as the cohort was dynamic, the incidence rate of active TB in exposed and unexposed with person-time (years) in the denominator was used as a measure of frequency. Chi-square test of independence and multivariate logistic regression were used to identify factors that are associated with incident TB. Rate ratio or hazard ratio with 95% confidence interval was used as a measure of association or impact of IPT on the prevention of TB. For all statistical tests, a two-sided alpha level of 0.05 was used to determine statistical significance.

Ethical Considerations: The Research and Ethics Committee of FMC-Keffi, Nasarawa State, granted me ethical approval (FMC/KF/HREC/027101/24). The computer containing the data was password-protected. Given that the study was retrospective in nature, informed consent from the patients was not required.

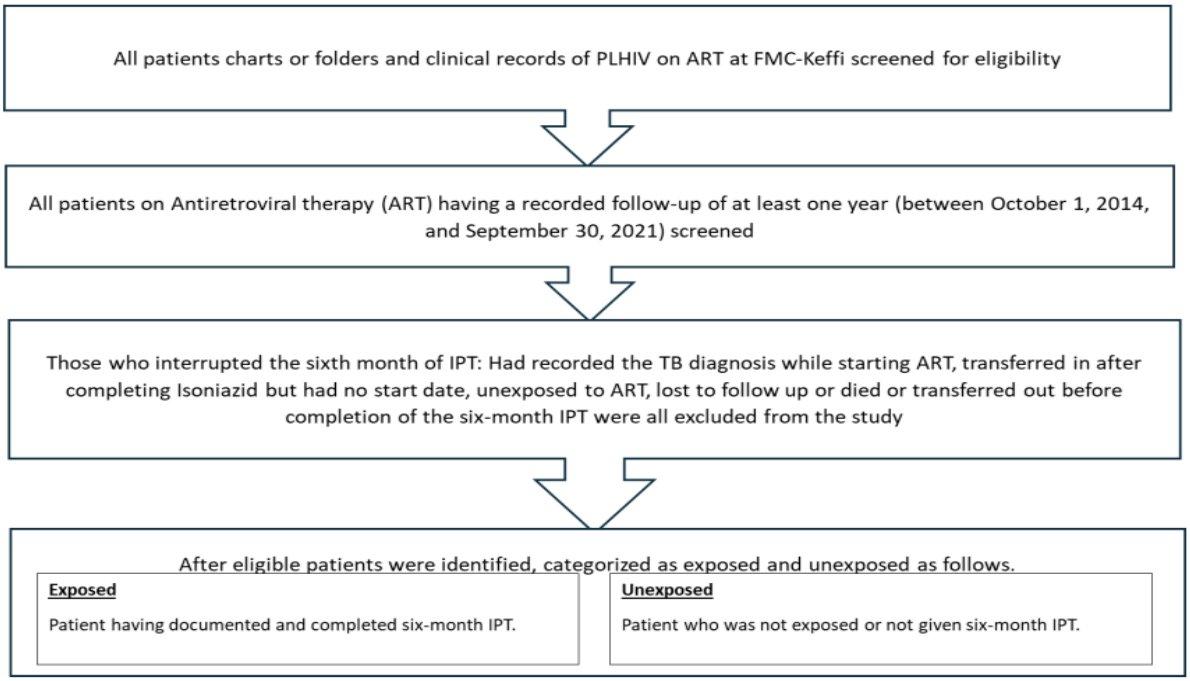

Figure 1. Study Participant Selection Process

a. *Study participants selection process on effectiveness of isoniazid preventive therapy (IPT) among patients on ART in FMC-Keffi, Nasarawa State*.

Results

The socio-demographic and clinical characteristics of respondents in this study revealed significant insights into the dynamics of tuberculosis (TB) prevention and disease outcomes among individuals exposed to tuberculosis preventive therapy (TPT) compared to those who were not. Additionally, the data allowed for an in-depth understanding of how these characteristics related to the development of TB.

TPT Exposure and Associated Characteristics

The socio-demographic and clinical profiles of 581 respondents, stratified by their receipt of tuberculosis preventive therapy (TPT). Of the respondents, 137 did not receive TPT, while 444 were on TPT. Key characteristics are discussed below and shown in Table 1.

Sex Distribution: Both groups had a majority of female participants. Among those exposed to TPT, 70% were female, a proportion similar to the unexposed group (69%). This consistency indicates no gender-based disparity in TPT exposure.

Age Patterns: The median age was slightly higher in the TPT-exposed group (39 years, IQR: 32–46) compared to the unexposed group (37 years, IQR: 26–45). Interestingly, younger individuals (<15 years) were more common in the unexposed group (15%) than in the exposed group (6.5%), while the reverse was true for those aged 26–55 years (81% in the exposed group vs. 69% in the unexposed group). This age distribution suggests that younger individuals may have been less prioritized for TPT, possibly due to perceived lower risks or challenges in access.

Weight Differences: The median weight at baseline was higher in the exposed group (61 kg, IQR: 49–70) compared to the unexposed group (55 kg, IQR: 30–67). This observation may reflect better overall health or different clinical prioritization criteria for TPT initiation.

WHO HIV Staging: Most participants in both groups were classified as WHO HIV Stage 1, with a slightly higher proportion in the

exposed group (62%) than in the unexposed group (59%).

HIV Viral Load: The median HIV viral load for the overall cohort was 20 copies/mL with an interquartile range (IQR) of 20 to 130 copies/mL. Among those exposed to tuberculosis preventive therapy (TPT), the median viral load was 20 copies/mL (IQR: 20 to 81 copies/mL), indicating better viral suppression compared to the unexposed group, which had a higher median viral load of 23 copies/mL (IQR: 20 to 3,940 copies/mL). The proportion of missing values for HIV viral load was substantial, with 222 observations missing overall, distributed as 162 in the exposed group and 60 in the unexposed group.

CD4 Count: The overall median CD4 count was 288 cells/µL (IQR: 171 to 522 cells/µL). Participants exposed to TPT had a slightly higher median CD4 count of 306 cells/µL (IQR: 176 to 519 cells/µL) compared to their unexposed counterparts, who's median CD4 count was 265 cells/µL (IQR: 170 to 549 cells/µL), suggesting that individuals with better immunological profiles were more likely to be initiated on TPT. Missing data for CD4 count was also notable, with 420 observations missing overall, distributed as 328 in the exposed group and 92 in the unexposed group.

CD4 Count Category: The CD4 count category distribution revealed that: 29% of the overall cohort had a CD4 count less than 200 cells/µL, with similar proportions in the exposed (28%) and unexposed (31%) groups. 29% had a CD4 count between 200 and 350 cells/µL, evenly distributed across both the exposed (28%) and unexposed (31%) groups. 42% had a CD4 count greater than 350 cells/µL, with a slightly higher proportion in the exposed group (44%) compared to the unexposed group (38%). There were 420 missing observations for the CD4 count category, with 328 in the exposed group and 92 in the unexposed group.

ARV Regimen: The majority of participants in both groups were on the adult first-line ARV regimen, with a higher prevalence in the TPT-exposed group (90%) compared to the unexposed group (76%).

Table 1. Socio-Demographic and Clinical Characteristics of Respondents by Treatment Group

		Tuberculosis Preventive Therapy	
Variable	**Overall**, N = 581[1]	**Exposed**, N = 444[1]	**Unexposed**, N = 137[1]
Sex			
Female	404 (70%)	309 (70%)	95 (69%)
Male	177 (30%)	135 (30%)	42 (31%)
Age Years			
Median (IQR)	39 (32, 45)	39 (32, 46)	37 (26, 45)
Age Category			
<15 years	49 (8.4%)	29 (6.5%)	20 (15%)
16 - 25 years	33 (5.7%)	21 (4.7%)	12 (8.8%)
26 - 55 years	456 (78%)	361 (81%)	95 (69%)
>55 years	43 (7.4%)	33 (7.4%)	10 (7.3%)
Weight (Kg)			
Median (IQR)	59 (45, 69)	61 (49, 70)	55 (30, 67)
(Missing)	231	170	61
Pregnancy Breastfeeding Status			
Breastfeeding	11 (2.8%)	10 (3.3%)	1 (1.2%)
Not Pregnant	369 (94%)	290 (94%)	79 (94%)
Pregnant	11 (2.8%)	7 (2.3%)	4 (4.8%)

(Missing)	190	137	53
WHO_HIV Stage			
1	356 (61%)	275 (62%)	81 (59%)
2	129 (22%)	99 (22%)	30 (22%)
3	87 (15%)	62 (14%)	25 (18%)
4	9 (1.5%)	8 (1.8%)	1 (0.7%)
HIV Viral Load			
Median (IQR)	20 (20, 130)	20 (20, 81)	23 (20, 3,940)
(Missing)	222	162	60
CD4_count			
Median (IQR)	288 (171, 522)	306 (176, 519)	265 (170, 549)
(Missing)	420	328	92
CD4_count_category			
Less than 200	46 (29%)	32 (28%)	14 (31%)
200 – 350	47 (29%)	33 (28%)	14 (31%)
Greater than 350	68 (42%)	51 (44%)	17 (38%)
(Missing)	420	328	92
Regimen Line at Start of ART			
Child 1st line ARV regimen	74 (13%)	43 (9.8%)	31 (24%)
Child 2nd line ARV regimen	1 (0.2%)	1 (0.2%)	0 (0%)
Adult 1st line ARV regimen	495 (87%)	396 (90%)	99 (76%)
Adult 2nd line ARV regimen	1 (0.2%)	0 (0%)	1 (0.8%)
(Missing)	10	4	6
[1]n (%)			

b. *TPT Exposure and associated characteristics among 581 patients*

Characteristics by Tuberculosis Status

Among the 581 respondents, 27 developed TB during the study period, while 554 did not. Examining these groups revealed critical differences seen below and shown in Table 2.

Sex: Females were more likely to develop TB, comprising 74% of TB cases, compared to 69% among those who remained TB-free.

Age: The median age was comparable between the TB and non-TB groups (40 years vs. 39 years). However, age distribution showed slight variations, with TB more frequent in individuals aged 26–55 years (81%) compared to other age groups.

Weight: Participants who developed TB had a lower median weight (55 kg, IQR: 45–67) than those who did not (59 kg, IQR: 45–70), potentially reflecting poorer nutritional or overall health status among TB cases.

HIV Characteristics

Participants in advanced HIV stages (Stages 3 and 4) were more likely to develop TB (33% of TB cases) compared to those in Stages 1 and 2 (15% of TB cases). Median CD4 counts were lower in TB cases (237, IQR: 145–605) than in non-TB cases (289, IQR: 175–519), reaffirming the role of immune suppression in TB progression.

Table 2. Socio-Demographic and Clinical Characteristics of Respondents by Tuberculosis Status

			Tuberculosis Status		
Variable	**N**	**Overall**, N = 581[1]	**Developed tuberculosis**, N = 27[1]	**Did not develop tuberculosis**, N = 554[1]	**p-value**[2]
Sex	581				0.6
Female		404 (70%)	20 (74%)	384 (69%)	
Male		177 (30%)	7 (26%)	170 (31%)	
Age Years	581				0.8
Median (IQR)		39 (32, 45)	40 (29, 45)	39 (32, 45)	
Age Category	581				0.9
<15 years		49 (8.4%)	2 (7.4%)	47 (8.5%)	
16 - 25 years		33 (5.7%)	2 (7.4%)	31 (5.6%)	
26 - 55 years		456 (78%)	22 (81%)	434 (78%)	
>55 years		43 (7.4%)	1 (3.7%)	42 (7.6%)	
Weight (Kg)	350				0.7
Median (IQR)		59 (45, 69)	55 (45, 67)	59 (45, 70)	
(Missing)		231	12	219	
Pregnancy Breastfeeding Status	391				>0.9
Breastfeeding		11 (2.8%)	0 (0%)	11 (3.0%)	
Not Pregnant		369 (94%)	19 (100%)	350 (94%)	
Pregnant		11 (2.8%)	0 (0%)	11 (3.0%)	
(Missing)		190	8	182	
WHO_HIV Stage	581				0.10
1		356 (61%)	13 (48%)	343 (62%)	
2		129 (22%)	5 (19%)	124 (22%)	
3		87 (15%)	8 (30%)	79 (14%)	
4		9 (1.5%)	1 (3.7%)	8 (1.4%)	
HIV Viral Load	359				0.3
Median (IQR)		20 (20, 130)	45 (20, 100)	20 (20, 131)	
(Missing)		222	12	210	
CD4_count	161				>0.9
Median (IQR)		288 (171, 522)	237 (145, 605)	289 (175, 519)	
(Missing)		420	20	400	
CD4_count_category	161				0.5
Less than 200		46 (29%)	3 (43%)	43 (28%)	
200 – 350		47 (29%)	1 (14%)	46 (30%)	
Greater than 350		68 (42%)	3 (43%)	65 (42%)	

(Missing)		420	20	400	
Regimen Line at Start of ART	571				0.8
Child 1st line ARV regimen		74 (13%)	4 (15%)	70 (13%)	
Child 2nd line ARV regimen		1 (0.2%)	0 (0%)	1 (0.2%)	
Adult 1st line ARV regimen		495 (87%)	23 (85%)	472 (87%)	
Adult 2nd line ARV regimen		1 (0.2%)	0 (0%)	1 (0.2%)	
(Missing)		10	0	10	
[1]n (%)					
[2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test					

c. *Characteristics by Tuberculosis Status across the different variables*

Incidence Rate Analysis

The incidence rate of TB was significantly lower in the TPT-exposed group compared to the unexposed group; this is shown in Table 3.

TPT-Exposed Group: Among the 444 individuals who received TPT, there were 12 TB cases over 1,785.24 person-years, resulting in an incidence rate of 6.72 per 1,000 person-years.

TPT-Unexposed Group: In the 137 unexposed individuals, 15 TB cases occurred over 576.42 person-years, yielding a much higher incidence rate of 26.02 per 1,000 person-years.

Incident Rate Ratio: The incident rate ratio is approximately 0.26. The IRR of 0.26 indicates that the exposed group has a 74% lower incidence rate of developing TB as compared to the unexposed group.

Table 3. TB Incidence Rates According to TPT Status

TB Preventive Therapy	Number of persons	Number of tuberculosis cases	Total person years	Incidence rate (per 1000 person years)	Incident rate ratio
Exposed	444	12	1,785.24	6.72	1.00
Unexposed	137	15	576.42	26.02	3.87

d. *Incident rate analysis among the exposed and unexposed group*

Crude and Adjusted Odds Ratios

Multivariate regression analysis further highlighted the protective role of TPT as shown below in Table 4.

Sex: In the crude analysis, males had a higher odds ratio (OR = 1.26; 95% CI: 0.55–3.28; p = 0.6) for developing tuberculosis (TB) compared to females. This association, however, was not statistically significant. After adjusting for confounders, the odds for males further increased to 3.46 (95% CI: 0.36–90.8; p = 0.3), but the wide confidence interval indicates high variability in the estimate, and the result remained non-significant.

Age Categories: The association between age and incident TB was analyzed across four age categories, using those aged under 15 years as the reference group:

1. Ages 16–25 years: The crude analysis showed a lower odds ratio (OR = 0.66; 95% CI: 0.08–5.73; p = 0.7), suggesting a reduced risk

compared to the reference group, but this result was not statistically significant. The adjusted analysis produced an extremely high odds ratio (OR = 2,053,516,521), with an undefined upper confidence interval (NA) and a p-value > 0.9, reflecting instability in the model and no significant association.

2. Ages 26–55 years: The crude analysis showed an OR of 0.84 (95% CI: 0.13–2.97; p = 0.8), indicating no significant relationship with incident TB. After adjustment, the odds ratio increased to 7.48 (95% CI: 0.00–3,349; p = 0.6), but the result remained non-significant with high uncertainty.

3. Ages >55 years: The crude analysis suggested a potential increased risk (OR = 1.79; 95% CI: 0.17–39.3; p = 0.6), but this result was not significant. The adjusted analysis yielded an extremely high odds ratio (OR = 844,860,815), with undefined confidence intervals and a p-value > 0.9, indicating no meaningful association.

TPT Exposure: PLHIV on ART who received TPT had significantly lower odds of developing TB. The adjusted odds ratio (AOR) was 0.03 (95% CI: 0.00–0.26, p = 0.006), indicating a 97% reduction in odds of TB development compared to the unexposed group after adjusting for other factors. A statistically significant and strong protective relationship between PLHIV on ART who received TB preventive therapy, and their risk of contracting TB is indicated by the p-value (p = 0.006)

WHO HIV Stage: Advanced HIV stages (3 and 4) were associated with increased odds of developing TB in crude models. However, these associations lost statistical significance after adjustment, likely due to overlapping immunosuppressive effects captured by CD4 count variables.

CD4 Count: Lower CD4 counts were associated with a higher likelihood of TB in crude models, but these associations were not statistically significant in the adjusted models.

Table 4. Crude and Adjusted Odds Ratios using Multivariate Regression Model

	Crude Ors				**Adjusted ORs**		
Variable	**N**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**
Sex	581						
Female							
Male		1.26	0.55, 3.28	0.6	3.46	0.36, 90.8	0.3
Age Category	581						
<15 years							
16 - 25 years		0.66	0.08, 5.73	0.7	2,053,516,521	0.00, NA	>0.9
26 - 55 years		0.84	0.13, 2.97	0.8	7.48	0.00, 3,349	0.6
>55 years		1.79	0.17, 39.3	0.6	844,860,815	0.00, NA	>0.9
WHO_HIV Stage	581						
1							
2		0.94	0.35, 2.98	>0.9	0.00		>0.9
3		0.37	0.15, 0.97	0.035	0.00		>0.9
4		0.30	0.05, 5.84	0.3	0.00		>0.9
CD4_Count_ Category	161						

Less than 200							
200 – 350		3.21	0.39, 66.2	0.3	3.00	0.25, 77.4	0.4
Greater than 350		1.51	0.27, 8.50	0.6	0.30	0.02, 4.05	0.4
TB Preventive Therapy	581						
Unexposed							
Exposed		0.23	0.10, 0.49	<0.001	0.03	0.00, 0.26	0.006
[1]OR = Odds Ratio, CI = Confidence Interval							

e. *Crude and adjusted odds ratio to describe the strength and direction of the association between TPT and TB incidence after adjusting for potential confounders.*

Discussion

We set out to evaluate the effectiveness of IPT among PLHIV on ART reviewing the incidence of TB among PLHIV on ART who received IPT and those who had not received IPT among patient on ART from October 2014 to September 2021. The study found that ART patients who had received the 6-month course IPT and completed treatment (exposed group) had a reduced risk of developing TB. WHO HIV stage and CD4 count were associated with higher likelihood of developing TB but were not statistically significant. The incidence of TB among the participants who received IPT was low as seen from other studies [15, 19]. This could be due to the high level of implementation of IPT among PLHIV on ART in Nigeria [20]. The WHO's guidance and global reports on TB and HIV co-infection also backs the significant reduction of TB incidence when IPT is combined with ART for PLHIV. This approach is recommended as part of the comprehensive TB prevention strategy [21]. The protective effect of IPT is well-supported, with research showing that those who completed the 6-month regimen had a lower incidence of TB, and their CD4+ T cell count improved significantly as reported in a systematic review study in Ethiopia [22]. The six-month course of isoniazid independently lowers the incidence of TB by 97% among HIV patients on ART. The lowering of incidence of TB by INH in this study is comparable to findings in a meta-analysis highlights that IPT, particularly when combined with ART, significantly reduces TB incidence in PLHIV. This research supports the claim that IPT reduces TB risk by up to 76% [23]. The rate of developing tuberculosis among the exposed compared to the unexposed was significantly lower. Our study population were patients who were already on ART. Being on ART substantially reduce the risk of TB among HIV patients. The period of observation was much higher for those who had received INH prophylaxis compared to those who had not. However, the result also indicate that 6-month isoniazid confers additional protection against TB on PLHIV who had been on ART among those who received IPT.

PLHIV who were in an advanced stage of HIV and those who had low CD4 count to their antiretroviral treatment were at greatest risk of developing TB. The relationship between advanced HIV disease and the development of TB is probably due to severe immunosuppression associated with the advance HIV infection and CD4 count (low CD4 count). Tuberculosis infection is also one of the opportunistic infections observed at this stage of HIV infection. The relationship between TB, advanced HIV and low CD4 count to ART are in keeping with other studies [24]. Patients with advanced HIV disease and those with low CD4 count on ART should be identified early and ensure they are placed on

IPT to protect them from developing active TB. Interestingly, younger individuals (<15 years) were more common in the unexposed group (15%) than in the exposed group (6.5%), this age distribution suggests that pediatrics and adolescents may have been less prioritized for TPT, possibly due to perceived lower risks or challenges in access. The recommendation given in a study (Taking tuberculosis preventive therapy implementation to national scale: the Nigerian PEPFAR Program experience) stated that the provider-to-client stage of TPT implementation be driven by the HIV program and that cross-communication between the two programs (TB and HIV) be improved [25]. This will ensure the right IPT regimen is provided for pediatrics and adolescents looking at their corresponding weight since INH is mainly procured by the NTBLCP under the TB program.

The study had the following limitations: Among PLHIV on ART with at least a year of documented follow-up on either ART alone or ART and IPT, this observational study assessed the efficacy of a completed 6-month IPT (Exposed group). Therefore, the results of this study could not be applied to individuals who died or were lost to follow-up without at least a year of documented follow-up. The study cohort of patients who initiated or started ART from October 2014 to September 2021, the role out of IPT in Nigeria started in 2014, but adoption by health facility was delayed until 2016-2017, therefore leading to patients who had TB before the intervention (IPT), as such including these cohorts of patients to either group would give a false result, thereby reducing the transparency of the research study. Patients were considered unexposed if they had IPT for fewer than six months. The difference between the exposed and unexposed may have been influenced by the amount of isoniazid received, and depending on the TB diagnosis of others—some of whom may have had a clinical diagnosis—may have resulted in a different incidence than the gold standard of having a confirmatory TB diagnosis. I worked with the ART and TB Clinic to compare their data with my findings in order to reduce this.

Salient recommendations on the problems studied: We recommend that HIV program managers should optimize placing PLHIV with advanced HIV stages and those with lower CD4 count on IPT. The current guideline of test and treat should be strengthened to avoid deterioration of the patient WHO clinical stage. Those identified at an advanced stage of the disease should be specifically targeted for intervention to low their risk of developing TB.

Future efforts should address gaps in TPT access, particularly among younger populations and those with lower baseline weights, to ensure equitable protection against TB. These findings also underscore the importance of integrating weight and immunological status into clinical decision-making for TB prevention

Conclusion

The incidence rate of TB among HIV patients who had received IPT was 6.72 per 1000-person-year of observation, while that among HIV patients who had not received IPT the incidence was 26.02 per 1000-person-year of observation. This study provides strong evidence that TPT significantly reduces the risk of TB in individuals living with HIV. The findings emphasize the need to scale up TPT coverage, particularly for high-risk groups such as those with advanced HIV stages or lower CD4 counts.

Conflict of Interest

There is no conflict of Interest.

Acknowledgements

I would like to acknowledge my super mum, beloved Chinweoke, Mr. Abel Umoru, Dr. Nifarta Andrew and Mr. Kenneth for their encouragement, guidance and support during the implementation of this study and the manuscript writing process.

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