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Description of HIV-Infected Persons in Botswana Who Developed Active Tuberculosis during or after Isoniazid Preventive Therapy (IPT): A Retrospective Record Review

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Abstract

Background: Tuberculosis (TB) remains a major cause of morbidity and mortality among people living with HIV, particularly in high TB/HIV burden settings. Botswana introduced Isoniazid Preventive Therapy (IPT) for people living with Human Immunodeficiency Virus (HIV) to reduce the risk of progression from latent TB infection to active TB disease. This study describes IPT programme records and the characteristics and outcomes of HIV-infected persons who developed active TB during or after IPT exposure. **Methods:** A retrospective record review using IPT and TB programme registers from 24 health facilities in eight districts in Botswana. The uploaded dataset contained 1240 IPT-exposed records, classified as IPT completers, IPT defaulters, or persons who developed active TB during or after IPT exposure. Analyses were: 1) IPT programme completion/defaulting classified as completers or defaulters, and 2) TB treatment outcomes classified as g developed TB. Frequencies, proportions, means, medians, and exact 95% confidence intervals were calculated, and modified Poisson regression estimated risk ratios for common binary outcomes. **Results:** Of 1240 IPT-exposed records, 352 (28.4%) were IPT programme completers, 655 (52.8%) were defaulters, and 233 (18.8%) developed active TB during or after IPT exposure. Among the 1007 programme completion/defaulting records, IPT completion was 35.0% (352/1007; 95% CI 32.0 - 38.0). Male sex was associated with lower IPT completion compared with female sex (adjusted risk ratio [aRR] 0.73; 95% CI 0.61 - 0.88). Among 233 developed-TB records, 150 (64.4%) were female, median age was 37 years (IQR 32 - 43), 206 (88.4%) were new TB cases, and 162 (69.5%) had pulmonary TB.

TB treatment outcomes were documented for 196/233 (84.1%) records. Among documented outcomes, 163/196 (83.2%; 95% CI 77.2 - 88.1) completed TB treatment; 17 (7.3%) died, 12 (5.2%) defaulted, 4 (1.7%) failed treatment, and 37 (15.9%) were not evaluated. In adjusted models, sex, age, Antiretroviral Therapy (ART) status, and disease classification were not strongly associated with documented TB treatment success, but incomplete records and missing ART data make this finding uncertain. **Conclusions:** Age showed a small link to treatment success in the sensitivity model, but incomplete records and missing ART data make this finding uncertain. IPT programme non-completion was common and was more frequent among men and younger adults. Among persons who developed TB after/during IPT exposure, most had new pulmonary TB disease, and most with documented outcomes completed TB treatment, but outcome documentation was incomplete. The findings support strengthening IPT adherence support, early follow-up of missed visits, accurate linkage of IPT, ART, and TB registers, and complete documentation of TB treatment outcomes.

Keywords

HIV, Tuberculosis, Isoniazid Preventive Therapy, Treatment Outcomes, Retrospective Record Review

1. Introduction

Tuberculosis remains one of the most important opportunistic infections among people living with HIV. HIV increases the risk of progression from latent Mycobacterium tuberculosis infection to active TB disease and is associated with bad performance of the existing TB diagnostics and high mortality among the coinfected TB patients, particularly when the diagnosis or treatment is delayed. TB preventive treatment, including Isoniazid Preventive Therapy, is therefore a core intervention in comprehensive HIV care when active TB disease has been excluded [1] [2].

TB and HIV coinfection leads to poor TB treatment outcomes. HIV weakens the immune system and makes TB harder to diagnose with unusual symptoms and Laboratory tests. It lowers TB cure and TB success rates, and raises morbidity and mortality rates among the coinfected, as noted by Habitamu *et al.* (2024) and the World Health Organization (2022) [3] [4]. Furthermore, WHO documents that "TB remains the leading cause of death among PLHIV globally, accounting for 167,000 (27%) of global AIDS-related deaths in 2022" and that People Living With HIV (PLHIV) are 12 - 16 times more likely to develop TB disease, have more than two-fold higher mortality during TB treatment compared to people without HIV, and have poorer TB treatment outcomes, such as TB success rate of 79%, (lower than WHO recommendation), TB/HIV coinfection rate of 64%, and a TB diagnosis of 46% before death [5].

In the early HIV pandemic, Botswana had high latent Tuberculosis rates with indurations of 10mm or more, with about 100% of workers in an office outbreak testing positive [6]. Meanwhile, TB notification rates jumped from 199/100,000 in 1999 to a peak of 623/100,000 in 2002, representing a 10% - 15% annual increase [7]. The surge was tied directly to HIV and TB reactivation across Sub-Saharan Africa and globally [8] [9].

Simultaneously, Botswana faced a severe HIV epidemic, ranking one of the highest globally, with approximately 300,000 people estimated to be living with HIV. A national prevalence of 35.4% was estimated from the sentinel surveillance carried out among the tested pregnant women across 22 health districts in 2002 [10]. Coupled with the massive spike in tuberculosis cases, TB-related morbidity and mortality among HIV-infected persons increased substantially, with a coinfection rate of 83% documented in a study on the baseline evaluation of routine HIV testing among TB patients in Botswana [11]. These trends plummeted from 2010, with a coinfection rate of 68% in 2010 [12] and fell further to 44% by 2023 [5]; HIV prevalence among adults aged 15 to 49 fell to 16.6% by 2023, and TB incidence decreased to 244 cases per 100,000 people by 2023 [13]. These downward trends resulted from the intensification of TB and HIV collaborative activities (including IPT) recommended by WHO and represent a huge advancement toward the control of both TB and HIV in the country [4] [14].

To aggressively address these high TB/HIV coinfection rates globally, the WHO and United Nations Programme on HIV/AIDS (UNAIDS) released a policy document in1998, and an interim policy in 2004 (updated in 2012). The key policy landmarks in 1998 Recommended the use of Isoniazid Preventive Therapy for PLHIV to stop latent TB infection from progressing into active TB disease; the 2004 Interim Policy, introduced the collaborative TB/HIV guidelines for a stronger global response on fighting both TB and HIV/AIDS together, while the 2012 updated guidelines, were meant to guide member states and partners to best respond to TB/HIV coinfection [15]-[18].

Subsequently, Botswana adopted a 'Treat All' strategy which provided lifelong ART to all HIV diagnosed individuals regardless of CD4 count [19] [20]. Likewise, the simultaneous use of both ART and IPT is purported to have an additive effect in preventing TB, thereby reducing TB-related morbidity and mortality [1] [21]-[23].

Botswana introduced IPT for HIV-infected persons in 2002 and rolled out the programme nationally to public health facilities. The IPT regimen given included a six-month daily dose of Isoniazid 300 mg (eradicates the dormant TB bacillus lying in the lungs to prevent reactivation), and 25 mg Pyridoxine (to counteract the side effects of INH), following thorough screening and exclusion of active TB disease. A TB screening algorithm was designed and tested for use by all health care workers before enrolling and during the client's repeated visits to the clinic for IPT refill. Physical examination was also supposed to be done to exclude enlarged lymph nodes, which may be suggestive of active extra-pulmonary TB. Also,

a sputum sample was collected for microscopy in case of TB suspicion. The inclusion criteria were that the client had to be HIV positive, 16 years (Botswana's age of consent to HIV testing), and in whom active TB disease had been excluded, and that only one course of this preventive therapy be given in one's lifetime and had been enrolled in IPT at any time between the inception of the IPT programme and 2010. The programme was designed to reduce TB morbidity among people living with HIV by preventing progression to active disease [24].

However, implementation challenges were reported: low adherence levels (65%), incomplete IPT follow-up, missing documentation, and concerns among health workers about active TB exclusion and the possibility of perpetuating INH drug resistance. These programme issues created a need to describe IPT programme completion and to characterize persons who subsequently developed TB after or during IPT exposure. Conversely, these concerns were disputed by WHO, which stated that 'no evidence exists that links IPT to widespread MDR-TB globally' and that "concerns regarding the development of INH resistance should not be a barrier to providing IPT" [25], a claim also supported by Akolo C *et al.* (2006) and Mills *et al.* 2013 who also underscored that symptom screening is a reliable method of excluding active TB disease to prevent enrolling active TB patients into IPT. Furthermore, the importance of closely monitoring IPT clients for possible development of active TB, with thorough investigation of TB suspects followed by immediate termination from IPT once active TB is established, could not be overemphasized. The global scale-up of IPT implementation was also recommended [26] [27].

The aim of this study was first, to describe IPT completion and defaulting, and factors associated with IPT completion, among HIV-infected clients enrolled in the Botswana IPT programme in selected facilities; and second, to describe the characteristics, timing of TB after IPT exposure, and TB treatment outcomes among IPT-exposed clients who subsequently developed active TB.

2. Methods

2.1. Study Design and Setting

This was a retrospective cross-sectional record review of data from the IPT and TB programmes at 24 health facilities across eight selected districts in Botswana. The data were collected between 2010 and 2011. Districts were purposively selected; health facilities were selected by convenience within the selected districts; and individual records were included if they met the programme record eligibility criteria. Because of purposive and convenience sampling, the findings should be interpreted as describing the selected programme records rather than providing nationally representative estimates.

2.2. Data Sources and Participants

The selection criteria for the study included records of HIV-positive clients, sixteen years and above, exposed to IPT, who completed the 6-month course of IPT,

failed to complete the 6-month course of IPT, and developed TB either during or after IPT, and were enrolled in IPT anytime between the inception of the IPT programmes and the year 2009. The source dataset contained 1240 IPT-exposed records. Each record was classified into one of three mutually exclusive status groups: IPT completer, IPT defaulter, or developed active TB during or after IPT exposure. All records were HIV-infected and IPT-exposed according to the programme dataset. TB-specific variables were documented in the facility TB register, and data collected included: TB patient category, TB disease classification, ART status at TB treatment, TB treatment outcome, IPT year, and time from IPT to TB, and were analyzed only among records classified as developed TB. The two registers (IPT and TB) were not linked; they were standalone systems. The IPT register was custom-made and used Epi-Info for data analysis, following data extraction from the register. Data could also be extracted and transferred to the TB register, particularly when clients stopped IPT after TB diagnosis.

IPT programme completion was defined using the programme status variable for records classified as completers or defaulters. TB treatment success was defined as treatment completed among developed-TB records with documented outcomes. Non-success, among documented outcomes, comprised death, default, and treatment failure. Records coded as not evaluated were reported separately in the main descriptive analysis and counted as non-success in a sensitivity analysis. Sex was coded as female or male. Age was calculated from the year of birth and categorized using programme-specified bands for the IPT analysis and manuscript-relevant bands for the developed-TB analysis. ART status among developed-TB records was coded as yes, no, or not documented/not tested. TB disease classification was coded as pulmonary or extra-pulmonary TB. Time from IPT to TB was grouped as ≤1 year, 2 - 3 years, and ≥4 years. IPT year was grouped as 2002-2004, 2005-2007, and ≥2008.

Records characterized as IPT completers were those with 6 months of documentation of IPT completion, had 6 months of INH refill visits, and a documented date of IPT completion. Those records named defaulters are those with dates indicating non-completion of the IPT, the last visit date before the completion of the 6-month IPT, and the date the client was terminated from IPT, either because he/she just disappeared of developed TB and was terminated from IPT. Lastly, those named 'developed TB' are records with the date IPT was terminated due to a TB diagnosis, and the date the patient was registered as a TB patient (now in the TB register), and records of TB patients who had a history of PT exposure, either as a completer or defaulter.

2.3. Statistical Analysis

This analysis was conducted using Stata-compatible data preparation and reproducible analysis scripts. Categorical variables were summarized using counts and percentages. Continuous variables were summarized using means, standard deviations, and medians with interquartile ranges. Also, Exact binomial 95% con-

fidence intervals were calculated for key proportions. Two separate analyses were performed.

First, among IPT programme records classified as completers or defaulters, modified Poisson regression with robust standard errors was used to estimate risk ratios for IPT completion. Predictors were selected based on programme relevance and availability: sex, age group, and reason for HIV testing.

Second, among developed TB records, TB treatment success was evaluated among records with documented TB outcomes. Modified Poisson regression with robust standard errors was used because the outcomes were common and risk ratios are more interpretable than odds ratios. The main TB outcome model included sex, age, and TB disease classification. A complete-case model added ART status. A sensitivity analysis counted not-evaluated TB outcomes as non-success. The earlier logistic regression model of IPT completion as a predictor of TB treatment success was not repeated because IPT duration/supply variables were not collected for the developed-TB subgroup in the available dataset. This restriction prevents valid estimation of the association between IPT completion and TB treatment success among developed-TB records.

Duplicate records in the IPT register were filtered by defining parameters such as name and surname, date of birth, and national Identity number, etc, with data verification through other facility registers like the electronic TB register and Dispensary tally sheets from the facility level. Once the duplicates were verified, such records were then removed (data cleaning).

TB was said to have occurred either during or after IPT exposure. For IPT clients that developed TB while still on IPT, the date IPT was stopped due to a confirmed TB diagnosis**, the date the post-IPT** client was put on anti-TB treatment (now a TB patient), and the date the clients are transferred from the IPT register to the TB register were critical for this study and analysis. This was also verified by the variable "reasons for stopping IPT" in the IPT register. For clients who had completed their 6-month course of IPT and developed TB afterwards, the important dates for this study include; the date the post-IPT client was diagnosed with TB (became a TB patient), the date the post-IPT client was started on Anti-TB treatment, now appearing only in the TB register as a TB patient, and complimented by a variable in the TB register "exposure to IPT".

3. Results

3.1. Analytic Populations

We reviewed 1240 IPT-exposed records. Of these, 352 (28.4%) were IPT programme completers, 655 (52.8%) were IPT defaulters, and 233 (18.8%) were classified as having developed active TB during or after exposure to IPT.

3.2. IPT Programme Completion/Defaulting Analysis

Table 1 shows that, among the 1007 records classified as IPT completers or defaulters, 352 completed IPT and 655 defaulted, corresponding to an IPT comple-

tion rate of 35.0% (95% CI, 32.0 - 38.0). The mean age was 38.2 years (SD 10.2), and the median age was 37 years (IQR 31 - 43). Completion was lower among males than females and varied by age group and reason for HIV testing.

Table 1. IPT programme completion summary.

Measure	Value
IPT programme records analyzed	1007
Completed IPT by status	352/1007 (35.0%; exact 95% CI 32.0 - 38.0)
Defaulted IPT by status	655/1007 (65.0%)
Valid age records	1005
Invalid age records excluded from age models	2
Age, mean (SD)	38.2 (10.2) years
Age, median (IQR)	37 (31 - 43) years

Table 2 shows the adjusted modified Poisson regression, where male sex was associated with lower IPT completion compared with female sex (aRR 0.73, 95% CI 0.61 - 0.88; p = 0.001). Compared with clients aged ≤ 26 years, completion was higher among those aged 37 - 46 years (aRR 1.73, 95% CI 1.18 - 2.54) and ≥47 years (aRR 1.68, 95% CI 1.12 - 2.51). Clients tested because of a known HIV-positive partner had higher IPT completion compared with those tested voluntarily (aRR 1.69, 95% CI 1.25 - 2.28).

The regression standard errors accounted for clustering within facilities where data were collected, and the data analysis adjusted error rates to account for groups like facilities or districts. It focuses on clustering, standard errors, and regression models.

Table 2. Adjusted risk ratios for IPT completion among programme completer/defaulter records.

Predictor	Risk ratio (95% CI)	p-value
Male vs female	0.73 (0.61 - 0.88)	0.001
27 - 36 vs ≤26 years	1.39 (0.95 - 2.04)	0.092
37 - 46 vs ≤26 years	1.73 (1.18 - 2.54)	0.005
≥47 vs ≤26 years	1.68 (1.12 - 2.51)	0.012
Illness vs voluntary testing	1.10 (0.90 - 1.35)	0.359
Known HIV-positive partner vs voluntary testing	1.69 (1.25 - 2.28)	<0.001
Other/no reason documented vs voluntary testing	1.28 (0.86 - 1.91)	0.225
PMTCT vs voluntary testing	0.79 (0.56 - 1.11)	0.169

Note: Model used modified Poisson regression with robust standard errors. Outcome: IPT completion among records classified as completer or defaulter.

The analytic denominator for each regression model includes the Sex-Based Model, where the analytic denominator was the total number of male and female clients initiated on IPT who have complete sex data; For the individual risk calculations, (group specifics), the denominator is the total number of female clients (the reference group) and the total number of male clients (the exposure group); for the Age-Based Model: The analytic denominator is the total number of clients across all specified age cohorts with complete age tracking; For the 'Reason for HIV Testing Model', the analytic denominator is the total number of clients who started IPT and have documentation for their motivation to test, and for group specifics, the comparison is anchored by the denominator of voluntarily tested clients (the reference group) compared against the denominator of clients tested due to a known HIV-positive partner.

Male gender was associated with lower IPT completion rates (30.3%) than female gender (37.9%) (Figure 1).

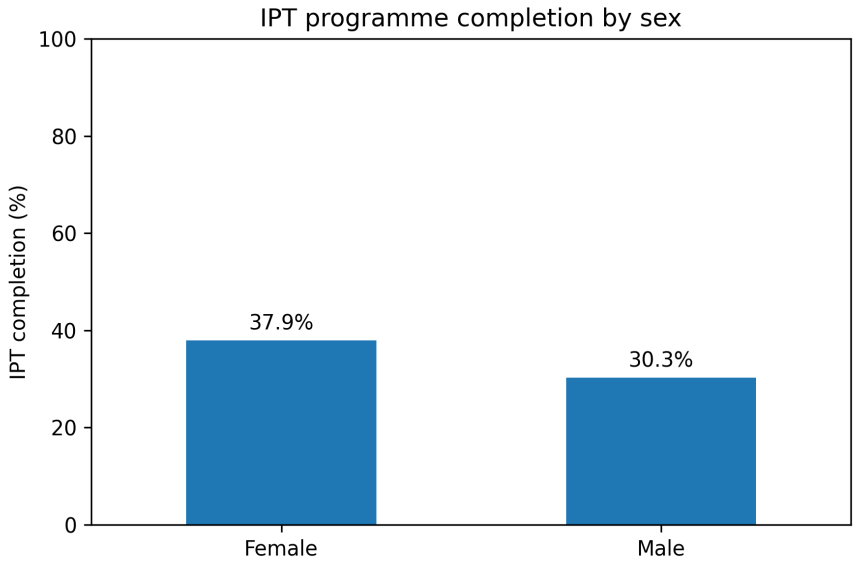

Figure 1. IPT completion by sex among programme completer/defaulter records.

Table 3 shows the characteristics and outcomes among the developed-TB records.

Among 233 records classified as developed active TB, 150 (64.4%) were female and 83 (35.6%) were male. The mean age was 38.2 years (SD 9.1), and the median age was 37 years (IQR 32 - 43). Most developed-TB records were new TB cases (206/233, 88.4%), and most had pulmonary TB (162/233, 69.5%). ART status was documented as yes for 122 (52.4%), no for 65 (27.9%), and not documented/not tested for 46 (19.7%).

The recorded time from IPT exposure to TB was ≤1 year in 79 (33.9%), 2 - 3 years in 101 (43.3%), and ≥4 years in 53 (22.7%). Most IPT exposure years among developed-TB records were between 2005 and 2007 (150/233, 64.4%).

Table 3. Summary of developed-TB records and TB treatment outcomes.

Measure	Value
Developed-TB records analyzed	233
Documented TB outcomes	196/233 (84.1%)
TB treatment success among documented outcomes	163/196 (83.2%; exact 95% CI 77.2 - 88.1)
Not evaluated/missing outcome	37/233 (15.9%)
Sensitivity success, counting not evaluated as non-success	163/233 (70.0%; exact 95% CI 63.6 - 75.8)
Age, mean (SD)	38.2 (9.1) years
Age, median (IQR)	37 (32 - 43) years

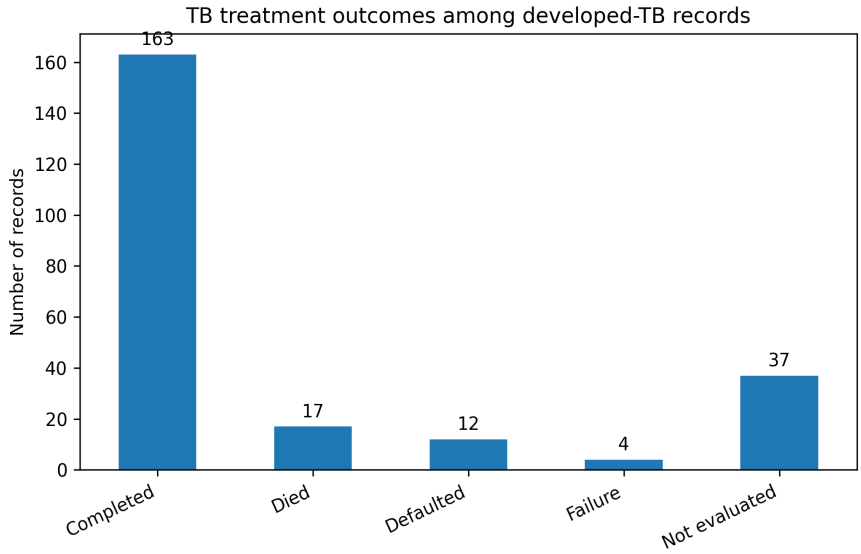

Figure 2. TB treatment outcomes among records classified as developed active TB.

TB treatment outcomes were documented for 196/233 (84.1%) developed-TB records. Among documented outcomes, 163/196 (83.2%; 95% CI 77.2 - 88.1) completed treatment. In the fully developed TB subgroup, 17 (7.3%) died, 12 (5.2%) defaulted, 4 (1.7%) failed treatment, and 37 (15.9%) were not evaluated.

3.3. Predictors of TB Treatment Success among Developed-TB Records

In the main documented-outcome model (n = 196), sex, age, and TB disease classification were not strongly associated with TB treatment success. In the complete-case model, adding ART status (n = 158), ART status was also not strongly associated with documented TB treatment success (aRR 1.08, 95% CI 0.91 - 1.29). These findings should be interpreted cautiously because ART status was not documented for 46 developed-TB records and because treatment outcomes were not evaluated for 37 records.

The regression standard errors accounted for clustering within facilities where data were collected, and the data analysis adjusted error rates to account for groups like facilities or districts. It focuses on clustering, standard errors, and regression models.

In the complete case analysis, all participant records with a missing value in sex, age, antiretroviral therapy (ART) status, or tuberculosis (TB) outcome were completely excluded from the adjusted regression models and were done as follows: **Exclusion:** Only observations with complete and documented values for every variable included in the multivariable model (the outcome of isoniazid preventive therapy [IPT] completion, plus covariates like sex, age, testing motivation, and clinical status) are analyzed. **Reduction of Sample Size:** Records containing missing data for sex, age, ART status, or TB outcome are dropped from the specific regression analysis, reducing the effective sample size to the count of fully observed cases. **Assumption:** This approach implicitly assumes that data are missing completely at random (MCAR), meaning that the exclusion of incomplete records does not bias the adjusted risk ratios (aRR) or confidence intervals.

4. Discussion

In this study, there were more females (64%) than men (35.6%), which is not consistent with the annual BNTP reports, as shown in Table 1, whereby men are always more in numbers than females, but probably consistent with the fact that more women are infected with HIV than men. The IPT programme analysis demonstrates substantial non-completion: only 35.0% of programme completer/defaulter records completed IPT as shown in Table 2 & Figure 1. Completion was lower among men and younger clients, refer to suggesting that adherence support may need to be intensified early and tailored to groups at higher risk of default. This suboptimal IPT completion rate of 35% is comparable to lower rates experienced regionally, such as 32% and 58% in Uganda and Tanzania, respectively. [28] [29] compared to better-performing regional peers like Zimbabwe (73%), Uganda (83%), and Namibia (89%), though still below the WHO-recommended goal [22] [29] [30]. This 65% default rate in IPT, which is notably high among young adults and males, is comparable to results of IPT studies conducted among the TB/HIV coinfected in Uganda and Malawi [31] [32]. The low completion rates undermine tuberculosis prevention for people with HIV, as such patients lose protection against latent TB activating into active disease, driving up preventable illness among people living with HIV, driving risks of INH drug resistance, and raising healthcare costs [33]. These low completion rates were attributable to high loss to follow-up of clients who missed treatments, suboptimal documentation of patients' records by healthcare workers (HCWs), and overburdened healthcare [34]. Moreover, a study that sought to identify the missing men with tuberculosis has established that challenges related to the health system, community, health worker, and individual, such as: delayed health-seeking, unfavorable facility operating hours, and long waiting times that conflicted with men's work schedules, also purported by WHO Report 2021 [35] [36]. However, Table

2 shows a higher completion rate among older clients and those tested because of a known HIV-positive partner; A view that may be related to the differences in perceived risk among the age groups, the continuous counseling, health education counselling, and the effectiveness of the health care system [34].

The analysis also revealed that the majority of the TB records as depicted in Table 4, were new TB cases (206/233, 88.4%), most of whom had pulmonary (PTB) TB (162/233, 69.5%), and 122 (52.4%) were on ART; 65 (27.9%) had not yet accessed ART, while 46 (19.7%) had no documented ART status. The high PTB cases of 69.5% remained the dominant clinical manifestation of TB, documented consistently in the BNTP annual reports, which aligns with the standard epidemiological patterns where the lungs are the primary site of reactivation and airborne transmission, inferring that most patients had not previously received anti-tuberculosis therapy, pointing to primary disease progression or recent transmission rather than direct relapse from past treatment failure [37] [38]. The BNTP has constantly documented higher rates of PTB (77.3% to 87.3%) than extrapulmonary tuberculosis (EPTB) (12.7% to 22.7%) across all available historical surveillance and retrospective cohort periods. This also aligns with the WHO global reports that 84% of notified tuberculosis cases are pulmonary and 16% are EPTB [39]. In the main documented-outcome model (n = 196), sex, age, and TB disease classification were not strongly associated with TB treatment success; See Table 2. The sensitivity model and age show an age-connection, indicating that age was linked to treatment success, but with a very small effect size estimate. The challenge is missing outcome records and incomplete ART documentation, which adds to high uncertainty about these results.

Table 4. Characteristics of IPT-exposed records that developed active TB.

Characteristic	Category	N	n (%)
Sex	Female	150	150 (64.4%)
Sex	Male	83	83 (35.6%)
Age group	≤20	2	2 (0.9%)
Age group	21 - 30	44	44 (18.9%)
Age group	31 - 40	107	107 (45.9%)
Age group	41 - 50	55	55 (23.6%)
Age group	>50	25	25 (10.7%)
TB patient category	New	206	206 (88.4%)
TB patient category	Retreatment/repeat	22	22 (9.4%)
TB patient category	Failure	3	3 (1.3%)
TB patient category	Died	1	1 (0.4%)
TB patient category	Missing	1	1 (0.4%)
TB disease classification	Pulmonary TB	162	162 (69.5%)

Continued

TB disease classification	Extra-pulmonary TB	71	71 (30.5%)
ART status	Yes	122	122 (52.4%)
ART status	No	65	65 (27.9%)
ART status	Not documented/not tested	46	46 (19.7%)
Time from IPT to TB	≤1 year	79	79 (33.9%)
Time from IPT to TB	2 - 3 years	101	101 (43.3%)
Time from IPT to TB	≥4 years	53	53 (22.7%)
IPT year group	2002-2004	41	41 (17.6%)
IPT year group	2005-2007	150	150 (64.4%)
IPT year group	≥2008	42	42 (18.0%)
TB treatment outcome	Completed	163	163 (70.0%)
TB treatment outcome	Died	17	17 (7.3%)
TB treatment outcome	Defaulted	12	12 (5.2%)
TB treatment outcome	Failure	4	4 (1.7%)
TB treatment outcome	Not evaluated	37	37 (15.9%)

The 52.4% ART uptake (shown in **Table 4**) documented in this study demonstrates overlapping coverage, which also aligns with the WHO TB/HIV collaborative policy guidelines, though still below the WHO recommendation that all eligible PLHIV be commenced on ART, irrespective of their IPT status. However, a substantial fraction was either not on ART (27.9%) or had unrecorded/untested status (19.7%). This gap emphasizes the historical operational challenges in harmonizing the parallel HIV and TB care programmes. During the same period, efforts were made to fully integrate IPT into both the voluntary testing centers and the HIV clinics, and were met with some reluctance, particularly from medical officers who were skeptical about the possibility of generating INH resistance to one of the anti-tuberculosis drugs. The Challenge of Undocumented ART (see **Figure 2**) often reflects strained clinical record-keeping or missed screening opportunities at the primary care level, such as missing medical records, non-disclosure of prior treatment by patients (which is not supposed to be an issue in Botswana, as patients' ART records are electronically documented, hence making it easy for tracking of patients across the facilities (see **Figure 3**). and unrecorded care transitions or self-transfers. These significantly hinder program monitoring, distort retention metrics, severely skew treatment outcomes, and compromise patient safety [39]-[41].

TB/HIV coinfection significantly worsens treatment success by lowering cure rates, evidenced by **Figure 2**, increasing death risks, and complicating drug therapies, including delaying recovery. The two diseases act together in the body to weaken the immune system through HIV, making it harder for TB drugs to work well. In addition, HIV and TB drugs can cause heavy side effects or interact poorly

together. These studies advocated for integrated screening, simultaneous or staged multi-drug regimens, and robust prophylaxis to ensure effective coinfection management [42].

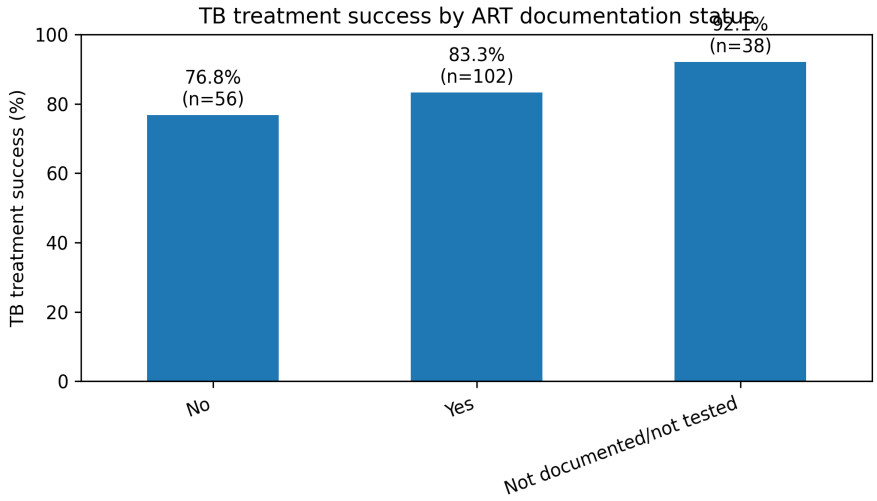

Figure 3. TB treatment success by documented ART status among developed-TB records.

5. Conclusions

In this retrospective record review, IPT programme non-completion was common among HIV-infected IPT-exposed clients in selected Botswana facilities, particularly among men and younger adults. Among IPT-exposed persons who developed active TB, most had new pulmonary TB (**Table 3**), and most with documented outcomes completed TB treatment, but outcome documentation was incomplete. The study supports strengthening early adherence counselling, active tracing after missed IPT visits, documentation of complete ART and TB outcome, and linkage of IPT, ART, and TB information systems. In addition, Etoori D *et al.* (2020) underscored the importance of improving linkages between clinics to reduce patient loss between clinics, and improving record-keeping systems, training and motivation of workers on the need for completeness of data, and that they should take ownership of their data. Finally, training of community health workers may improve sustained motivation and improve their ability to respond appropriately to their clients' needs [43].

6. Strengths and limitations

The findings should not be interpreted as evidence that IPT completion did or did not prevent TB, because the dataset did not include a complete underlying cohort with follow-up time and incident TB ascertainment for all IPT-exposed individuals. Likewise, the analysis cannot determine whether IPT contributed to isoniazid resistance because the dataset did not have drug-susceptibility testing results. Resistance should therefore be discussed as a programme concern requiring appropriate TB screening, follow-up, and drug-resistance surveillance, not as

a direct finding of this analysis.

A key strength of the study is that it uses routine programme records from multiple health facilities and directly addresses an important TB/HIV prevention question in Botswana. The analysis also uses reproducible definitions and separates the programme completion analysis from the developed-TB outcome analysis.

The study has important limitations. Districts and facilities were selected purposively and by convenience, limiting generalizability. Routine programme records had missing and incomplete documentation. IPT duration, number of supplies, and completion dates were not collected for developed-TB records, preventing direct analysis of IPT completion as a predictor of TB treatment outcomes. ART status and TB treatment outcome were incompletely documented among developed-TB records. Drug-susceptibility data were not available, preventing conclusions about INH resistance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Acronyms and Abbreviations

Abbreviation	Definition
ART	Antiretroviral Therapy
ARV	Antiretroviral
aRR	Adjusted Risk Ratio
BNTP	Botswana National Tuberculosis Programme
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IPT	Isoniazid Preventive Therapy
IQR	Interquartile Range
MDR-TB	Multi-Drug Resistant TB
PLHIV	People Living with HIV
RR	Risk Ratio
SD	Standard Deviation
TB	Tuberculosis
TB/HIV	Tuberculosis and HIV
TPT	Tuberculosis Preventive Treatment
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organization