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Lower Tuberculosis Incidence Among People With Human Immunodeficiency Virus Who Completed Isoniazid Preventive Therapy in Ukraine, a High-Burden Multidrug-Resistant Tuberculosis Setting: A Retrospective Cohort Study

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Abstract

Background. Evidence shows that isoniazid preventive therapy (IPT) reduces tuberculosis (TB) incidence among people with human immunodeficiency virus (HIV) with additive benefit beyond antiretroviral therapy alone, but its effectiveness in settings with high multidrug-resistant TB (MDR-TB) burden is unclear. We assessed the relationship between IPT and TB incidence among people with HIV (PWH) in Ukraine, a high-burden (32.6%) MDR-TB setting, and whether its effectiveness is maintained among virologically suppressed persons.

This work is written by (a) US Government employee(s) and is in the public domain in the US.

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Author contributions. J. D. S. and N. S. S. conceptualized the study. S. R., O. Sa., L. H., I. D., E. B., and N. P. collected the data. S. P. and S. R. curated the data. O. So., N. S. S., J. D. S., F. M., and S. P. developed the methodology. O. So., N. S. S., J. D. S., F. M., and S. P., with supervision from S. R., O. Sa., L. H., I. D., E. B., and N. P., conducted the formal analysis. S. P. and S. R. accessed and verified the data. O. So., N. S. S., J. D. S., and S. P. drafted the manuscript. O. So. and S. P. contributed to data visualization. All authors critically reviewed and revised the final manuscript.

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Methods. We analyzed national surveillance data for HIV and TB collected between 2018 and 2022. Complete IPT (n = 40 733) was defined as receipt of ≥ 146 days of therapy and no IPT (n = 91 022) as < 28 days of therapy. We modeled TB incidence and death using Poisson regression adjusting for covariates related to receipt of IPT and TB incidence. The secondary outcome was multidrug resistance, and sensitivity analyses explored the influence of virologic suppression.

Results. Of 131 755 PWH who met inclusion criteria, 9089 (5.5%) died. Unadjusted TB incidence was 1.91 cases per 100 person-years in the No IPT group and 1.01 cases per 100 person-years in the Complete IPT group (adjusted incidence rate ratio [aIRR], 1.99). MDR-TB occurred in 29.1% and 30.7% of TB cases in the Complete and No IPT groups, respectively. Among virologically suppressed PWH, persons with no IPT had a higher TB incidence (aIRR, 1.38) than those who completed IPT.

Conclusions. Completing IPT as part of a public health intervention can significantly reduce TB incidence among PWH, even in settings with high-burden MDR-TB and among the virologically suppressed.

Keywords

tuberculosis; multidrug resistance; HIV; epidemiology

Tuberculosis (TB) is the leading cause of morbidity and mortality among people with human immunodeficiency virus (HIV) worldwide. Isoniazid preventive therapy (IPT) reduces the incidence of active TB disease among people with HIV (PWH) when given alone for 6 months or when combined with rifapentine in shorter regimens [1–5]. Although TB preventive treatment (TPT) has been recommended by the World Health Organization (WHO) for PWH for nearly 2 decades, uptake has been limited. Following the commitment by the United States President’s Emergency Plan for AIDS Relief (PEPFAR) at the 2018 United Nations High-Level Meeting on TB, TPT has been scaled up among PWH worldwide. As of 2022, 12.5 million PWH have received TPT through PEPFAR-supported programs [6]. Still, there remains a knowledge gap regarding the use of IPT for PWH living in settings with high rates of multidrug-resistant TB (MDR-TB).

Each year, approximately half a million people develop MDR-TB. WHO currently recommends TPT for select high-risk household contacts of MDR-TB index cases using levofloxacin, with or without an additional drug (eg, ethambutol and/or ethionamide) [7–9]. While there have been some studies of MDR-TB preventive treatment using isoniazid, all have been among close contacts [10, 11]. There are no data on the use of IPT among PWH in high-prevalence MDR-TB settings who are not close contacts but instead are receiving IPT as part of preventive care. In these settings, PWH may potentially have a latent infection with drug-susceptible or drug-resistant TB strains, but there are currently no tests to determine drug sensitivity of latent TB infections. As such, it remains unclear whether PWH in high-burden MDR-TB settings will benefit from IPT as a programmatic intervention for HIV care.

In Ukraine, nearly 1 in 3 people newly diagnosed with TB have MDR-TB, making Ukraine 1 of the highest-burden countries for MDR-TB worldwide [12, 13]. There are an estimated

240 000 PWH in Ukraine [14], and approximately 20% of people with TB have HIV coinfection [15]. Ukraine has been providing IPT to PWH since 2019. We examined whether receipt of IPT was associated with lower TB incidence, including among virologically suppressed PWH on antiretroviral therapy (ART).

METHODS

Study Design

This was a retrospective cohort study of routinely collected national surveillance data on individuals enrolled in HIV and TB care in Ukraine. We identified patients who were newly enrolled or reenrolled in HIV care during January 2018–February 2022.

Data Sources: The HIV Medical Information System (HIV-MIS) [16] is a national electronic medical record managed by the Ukrainian Ministry of Health and utilized by HIV treatment sites nationwide. Aggregate data from HIV-MIS were used for multiple reporting purposes, including national HIV surveillance. Likewise, eTB Manager [17] is a national electronic medical database for TB and has been used at facilities providing TB diagnostic and treatment services. It contains compiled clinical information on all people diagnosed with TB and is used for TB surveillance, regardless of HIV status.

Evaluation of TB Disease and Drug Resistance: PWH were monitored for TB disease through active surveillance at regular HIV care visits where they are asked about TB-related symptoms or health events. No additional training or intervention was done as part of this study; TB screening procedures were at the discretion of the treating clinician.

Individuals reporting TB symptoms were referred for radiography and/or rapid diagnostic test for TB diagnosis [18]. Culture, rapid molecular testing, or sputum smear microscopy was used to diagnose TB depending on availability at healthcare facilities. Resistance to anti-TB drugs was detected by phenotypic drug susceptibility testing or rapid molecular tests (eg, Xpert MTB/RIF). Resistance patterns for each person with confirmed TB disease were categorized as follows: monoresistance, defined as resistance to 1 of 4 first-line TB drugs; multidrug resistance, defined as resistance to at least isoniazid and rifampicin; polydrug resistance, defined as resistance to >1 first-line anti-TB drug other than isoniazid and rifampicin; extensive drug resistance, defined as multidrug or rifampicin resistance plus resistance to any fluoroquinolone and at least 1 group A drug (levofloxacin, moxifloxacin, bedaquiline, and/or linezolid); or rifampicin resistance, based on phenotypic or genotypic methods regardless of the presence or absence of resistance to other TB drugs—including any resistance to rifampicin whether it is mono-, multi-, poly-, or extensive resistance.

Participants

We cross-matched eTB Manager records against HIV-MIS records using name, age, sex, and date of birth to identify patients with HIV who also developed TB during the inclusion period. All individuals with HIV were included regardless of age, place of residence, or healthcare setting. In Ukraine, patients are considered to have completed IPT after at least 146 days; therefore, we excluded PWH who had not been in HIV care for at least 146 days

or completed IPT before the inclusion period began. We also excluded PWH diagnosed with TB disease within 146 days of enrollment in HIV care, began TB treatment before HIV diagnosis, or were on TB treatment at the beginning of the inclusion period.

Procedures

The Public Health Center of the Ministry of Health began scaling up TPT to PWH in 2018. Clinicians prioritized patients newly diagnosed with HIV to receive IPT; as the program expanded, PWH already in care also received IPT. Prior to initiating IPT, PWH were evaluated for active TB disease using the WHO recommended 4-symptom screening [19]. A patient reporting any symptoms was further evaluated and became eligible for TPT once active TB disease was ruled out. Patients were prescribed 6–9 months of isoniazid 300 mg daily, dispensed as 28-day blister packets monthly [18]. While there are other TPT regimens, during the observation period, isoniazid was the only regimen available in Ukraine.

From HIV-MIS, we collected clinical information on HIV diagnosis, including status in care, ART regimen, viral load and CD4 data, and mortality. To evaluate viral suppression history, we analyzed all viral loads 6 months prior to and during the observation period through 28 February 2022 for unsuppressed (>1000 copies/mL) results. We also analyzed information on TB screening, dates of initiation and completion of IPT, and reasons for stopping IPT treatment. From eTB Manager, we collected information on date of TB diagnosis, method of diagnosis, localization of infection, drug resistance pattern, retreatment versus new patient, treatment regimen, treatment outcome, and mortality. Both HIV-MIS and eTB Manager contained data on sociodemographic characteristics and risk factors for HIV and TB, such as self-reported alcohol use and incarceration.

Definitions and Outcomes

Complete IPT was defined as having documentation of isoniazid dispensation for at least 146 days in HIV-MIS. Anyone with <28 days of isoniazid dispensation was categorized as No IPT, and patients who were dispensed between 28 and 145 days of isoniazid were categorized as Partial IPT. Person-time observation began after the last dose of IPT for the Complete and Partial IPT groups. In the No IPT group, person-time began 146 days from HIV diagnosis or 146 days after 1 January 2018, whichever was later. Primary outcomes were diagnosis of active TB disease or death from any cause. The secondary outcome was the designation of MDR-TB disease, defined as those categorized in eTB manager as having “multidrug resistance” or “rifampicin resistance” based on data from sites that use rapid molecular testing [20–22]; phenotypic drug susceptibility testing was not available. Patients with all viral load results <1000 copies/mL starting 6 months prior to and throughout the observation period were categorized as virally suppressed.

Statistical Analysis

We estimated descriptive statistics for baseline demographic and clinical characteristics, stratified by receipt of IPT, and tested for differences using χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The primary analysis used Poisson regression to compare the incidence of active TB disease among PWH who received complete IPT and those who received no IPT. The model adjusted for demographic and

clinical factors related to both IPT status and TB incidence (eg, sex, age, time since HIV diagnosis, CD4 count, viral suppression status and history, ART use, alcohol misuse, history of incarceration) and included an extra dispersion parameter to account for variance in excess of that assumed by the Poisson distribution. We estimated all-cause mortality rates for each IPT group unadjusted and adjusted for the same covariates included in the TB incidence models.

As a supplementary analysis, we fit a model similar to the primary analysis comparing TB incidence for those who received any IPT (ie, those who completed IPT and those who received partial courses of IPT) and those who received no IPT, adjusting for the same demographic and clinical factors. We performed several sensitivity analyses. To address the different lengths of follow-up time for PWH in the Complete IPT and No IPT groups, we repeated the primary analysis, limiting follow-up time to 18 months in each group. We also compared overall TB incidence by IPT status stratified by year of follow-up (2018–2021) and fit a model examining the interaction of IPT status and virologic suppression on TB incidence. All interaction models were also adjusted for demographic and clinical factors. All incidence rates used a denominator of 100 person-years (PY). Models were fit in SAS PROC GLIMMIX using SAS/STAT software version 9.4 (SAS Institute, Cary, North Carolina).

Ethics Statement

The study protocol received ethical approval from the Public Health Center of the Ministry of Health in Ukraine (No. 102). This project was reviewed in accordance with Centers for Disease Control and Prevention human research protection procedures and was determined to be nonresearch.

RESULTS

Between January 2018 and February 2022, 166 365 patients newly entered or reenrolled in HIV care. Of these, 34 610 (20.8%) were excluded, including 6363 (3.8%) with insufficient data to calculate IPT duration or person-time. There were 131 755 (79.2%) individuals included in the analysis (Figure 1). Overall, 40 733 (30.9%) completed IPT and 91 022 (69.1%) had no IPT. At the end of the inclusion period, 9089 (5.5%) patients were known to have died. Of the 48 573 patients who started isoniazid, 83.9% completed at least 146 days of treatment. Among those in the No IPT group, 845 (0.9%) started isoniazid but received <28 days of therapy and were categorized as having received no IPT.

Baseline and follow-up characteristics of the 131 755 patients are shown in Table 1. The median age was 38.7 years (interquartile range [IQR], 33.3–44.5 years) for the No IPT group and 40.4 years (IQR, 34.7–47.0 years) for the Complete IPT group; males accounted for about 54% of both groups. The proportion of PWH with sustained viral suppression was 73.7% (62 309) in the No IPT group and 64.7% (25 005) in the Complete IPT group.

Participants who did not receive IPT were followed for 271 039 PY, and those who completed IPT were followed for 69 604 PY (Table 1). The median follow-up time was 3.74 (IQR, 2.35–3.74) PY per person in the No IPT group and 1.53 (IQR, 0.84–2.53) PY

per person in the Complete IPT group. The unadjusted TB incidence rate was 1.91 cases per 100 PY for the No IPT group (95% confidence interval [CI], 1.77–2.07) and 1.01 cases per 100 PY for the Complete IPT group (95% CI, .81–1.25) (Table 2), a rate difference of 0.9 cases per 100 PY. The adjusted TB incidence rate ratio (aIRR) was 1.99 (95% CI, 1.62–2.46) for the No IPT group when compared to the Complete IPT group (Table 3). The unadjusted mortality rate was 2.62 deaths per 100 PY for the No IPT group (95% CI, 2.44–2.81) and 2.79 deaths per 100 PY for the Complete IPT group (95% CI, 2.44–3.19). When adjusted for the same variables, the adjusted mortality rate ratio was 1.11 for the No IPT group (95% CI, .97–1.27) when compared to the group who completed IPT. Among persons who developed TB disease, MDR-TB occurred in 29.1% and 30.7% of TB cases in the Complete and No IPT groups, respectively ($\chi^2 = 0.78$, $P = .3780$).

Patients with a history of imprisonment and self-reported alcohol misuse had 1.95 (95% CI, 1.50–2.53) and 2.07 times (95% CI, 1.56–2.75), respectively, the rate of developing active TB disease when compared to patients without these risk factors. PWH with lower CD4 counts had higher incidences of active TB disease when compared to PWH with CD4 counts ≥ 500 cells/ μ L. Patients who were not virally suppressed had 3.19 times the rate of developing active TB disease compared with patients who were virally suppressed (95% CI, 2.72–3.74) (Table 3).

We tested for interaction of TPT status by year and found it was not significant ($P = .2266$). To explore the impact of differential follow-up time across IPT groups, we limited the follow-up time to 18 months per person. The unadjusted TB incidence rate was 2.44 cases per 100 PY for the No IPT group (95% CI, 2.23–2.67) and 1.15 cases per 100 PY for the Complete IPT group (95% CI, .93–1.43), with an aIRR of 2.22 (95% CI, 1.77–2.77) when adjusted for age, sex, time since HIV diagnosis, CD4 count, viral suppression, history of incarceration, and alcohol misuse.

Among virally suppressed PWH, completion of IPT was associated with a difference of 0.3 cases per 100 PY in TB incidence compared to those who did not complete IPT (Figure 2). For those who were virally suppressed, adjusted TB incidence was 1.1 cases per 100 PY for the No IPT group and 0.8 cases per 100 PY for the Complete IPT group (aIRR, 1.42 [95% CI, 1.25–1.62]). Among those who were not virally suppressed, adjusted TB incidence was 3.8 cases per 100 PY for the No IPT group and 1.5 cases per 100 PY for the Complete IPT group (aIRR, 2.56 [95% CI, 2.26–2.89]; rate difference, 2.3 per 100 PY). TB incidence was lower among virally suppressed than among virally unsuppressed PWH in both IPT groups. The unadjusted MDR-TB incidence rate was 0.59 cases per 100 PY for the No IPT group and 0.29 cases per 100 PY for the Complete IPT group (IRR, 2.13 [95% CI, 1.43–3.18]; Table 2). In a supplementary analysis including patients who received a partial course of TPT, the adjusted MDR-TB IRR was 2.01 for the No IPT group when compared to the group that received any IPT.

DISCUSSION

In Ukraine, a public health intervention that included completion of IPT was associated with a nearly 2-fold lower incidence of TB when compared to PWH who did not receive IPT.

The effect was maintained among PWH who were virally suppressed: TB incidence was 27% lower among virally suppressed PWH who completed IPT. The proportion of MDR-TB among incident TB cases was similar between groups and comparable to the prevalence of MDR-TB (32.6%) in the general population in Ukraine. These findings suggest IPT is an effective intervention to prevent TB among PWH in high MDR-TB settings, regardless of viral suppression status.

While there have been clinical trials of TPT for high-risk contacts of persons with MDR-TB [23–25], this cohort was not limited to contacts of an index MDR-TB case. In our study of a population of PWH, MDR-TB incidence also decreased with receipt of IPT despite national survey data that estimate 37.3% (95% CI: 34.6%–40.1%) isoniazid resistance among new TB patients and 65.8% (95% CI: 60.3%–71.7%) among previously treated patients [13]. There are several possible explanations for this apparent paradox and researchers have raised the possibility that the mechanism by which isoniazid reduces TB disease risk among those with latent infection may differ from its mechanism in active TB disease [26–29]. Isoniazid is known to have potent early bactericidal activity, and because mycobacterial populations in latent TB may be heteroresistant [30], isoniazid could have an effect on isoniazid-sensitive drug-resistant TB strains. Furthermore, at the early stage of infection, when MDR-TB is restricted to the granuloma and bacterial load is low, it is possible that isoniazid is more effective than when MDR-TB is released outside the granuloma and bacterial load is higher.

We found that the proportion of MDR-TB among PWH who developed TB disease was comparable among those who received IPT and those who did not. If IPT were only effective in PWH with drug-sensitive latent TB infections, the proportion of MDR-TB would have increased among PWH who received IPT and developed TB disease. Furthermore, several studies have previously demonstrated that receipt of IPT does not increase the risk of developing drug-resistant TB [31]. Overall, although one-third of new TB cases in Ukraine have MDR-TB, most TB is drug-sensitive and most PWH are likely to be exposed to a drug-sensitive index case, which may explain the lower overall TB incidence we observed in our analysis. However, for household contacts of a known MDR-TB index case, recent trials [32, 33] have supported the role of levofloxacin TPT in reduction of TB incidence. Because TB transmission is primarily driven by community exposures [34], the proportion of MDR-TB among our cohort of PWH was reflective of the prevalence of MDR-TB in the general population in Ukraine.

To our knowledge, this is the first study to investigate the effects of longitudinal viral suppression on IPT effectiveness. Studies have previously shown the effect of IPT to be independent and additive to that of ART [2]. Here, we used patient-level viral load results as an assessment of HIV control over time, an important risk factor for TB disease. As expected, TB incidence was lower among virally suppressed PWH, but even among PWH who maintained viral suppression, IPT was associated with lower TB incidence. These data suggest that there is an added benefit of treating latent TB, beyond the immune recovery that usually accompanies viral suppression.

This analysis has some limitations. First, PWH were not randomized to receive or not receive IPT, and receipt of IPT may have been correlated with other variables that are also correlated with TB disease. Additionally, we could not control for unmeasurable confounders that may have affected how vigorously newly diagnosed PWH were screened for TB disease in comparison to routinely monitored returning patients. We attempted to address the potential for bias with careful exclusion of groups of patients who did not have an opportunity to complete IPT and be followed over time, and through covariate adjustment in regression models. Further limitations include a large amount of missing data on smoking status, nutritional status, and homelessness—all known risk factors for TB that could not be adjusted for in our regression models. Last, our data source did not include phenotypic data on resistance patterns, so we were unable to determine the prevalence of isoniazid resistance in our cohort.

While we cannot infer causality in an observational analysis, our results are consistently supportive of the benefit of IPT. We conclude that countries with overlapping HIV and MDR-TB epidemics should continue scaling up IPT to all PWH as a population-level intervention. IPT should remain a critical component of care for all PWH who live in high-TB-burden settings, even among those who are on ART and virally suppressed.

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Disclaimer.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Applicable federal law for ethical review includes 45 Code of Federal Regulations (C.F.R.) part 46.102(l)(2), 21 C.F.R. part 56; 42 United States Code (U.S.C.) §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

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Data availability.

No new primary data were collected for this study. Data are owned by the Ukraine Ministry of Health and requests for additional use may be directed to the Public Health Center Head of HIV Treatment Programs Coordination Department (Dr Larysa Hetman, l.hetman@phc.org.ua).

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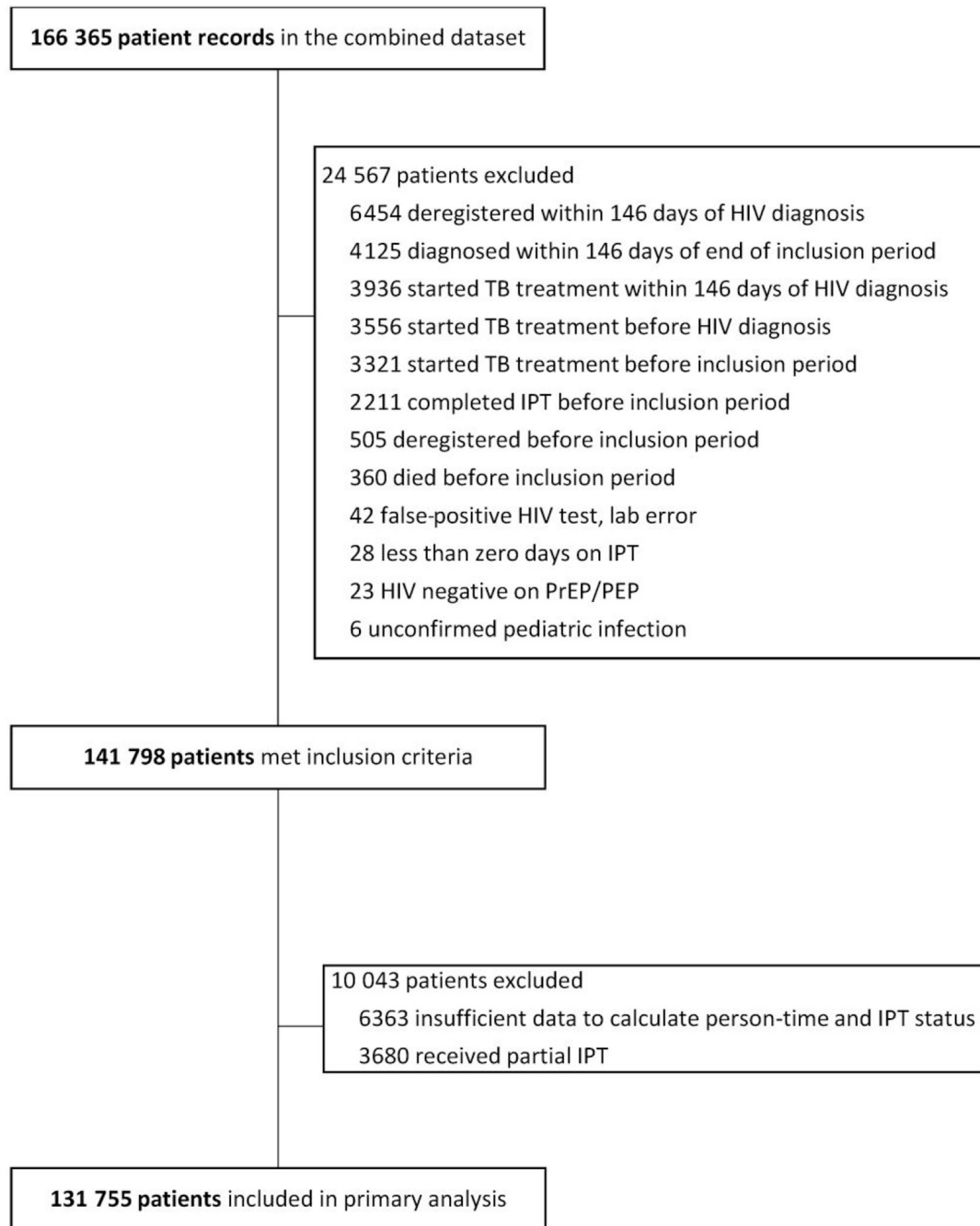


Figure 1.

Study profile. Abbreviations: HIV, human immunodeficiency virus; IPT, isoniazid preventive treatment; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis; TB, tuberculosis.

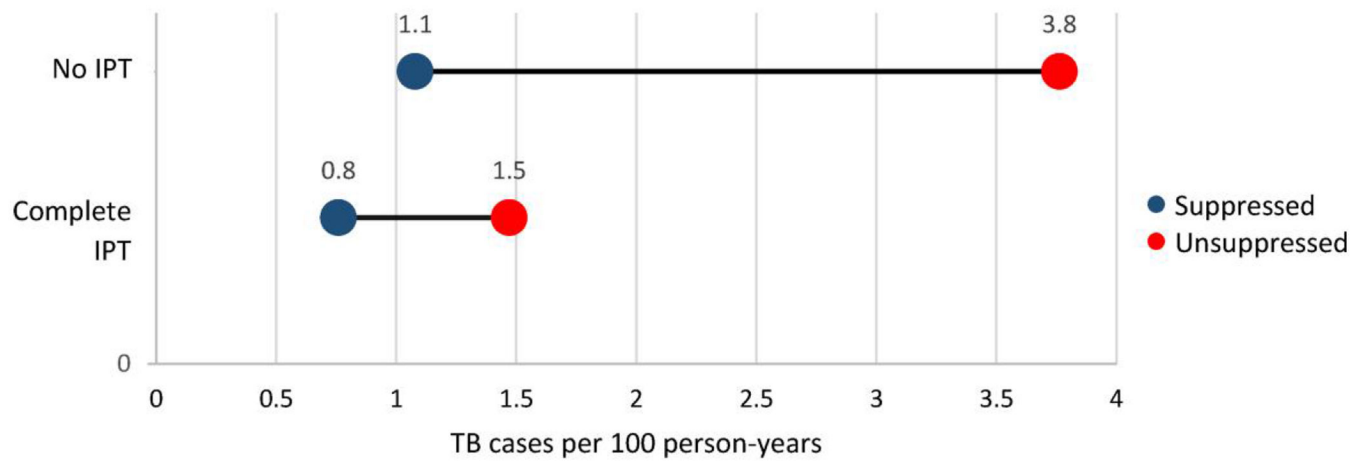


Figure 2.

Adjusted tuberculosis (TB) incidence rate by isoniazid preventive therapy (IPT) group, stratified by virologic suppression. Incidence rates were adjusted for age, sex, time since human immunodeficiency virus diagnosis, CD4 count, viral suppression, incarceration, and alcohol misuse.

Table 1.

Baseline and Follow-up Characteristics

Baseline	No IPT (n = 91 022)	Complete IPT (n = 40 733)	P Value
Sex			.7630
Male	48 854 (53.7)	21 826 (53.6)	
Female	42 168 (46.3)	18 907 (46.4)	
Age, y, median (IQR)	38.7 (33.3–44.5)	40.4 (34.7–47.0)	<.0001
0–14	2350 (2.6)	258 (0.6)	
15–24	3107 (3.4)	1220 (3.0)	
25–34	23 826 (26.2)	9207 (22.6)	
35–44	40 386 (44.4)	17 338 (42.6)	
45–54	16 239 (17.8)	9149 (22.5)	
≥55	5114 (5.6)	3561 (8.7)	
Alcohol misuse	2445 (2.7)	1756 (4.3)	<.0001
Time since HIV diagnosis, y, median (IQR)	3.3 (0.6–7.5)	2.1 (0.4–6.8)	<.0001
<1	26 838 (29.5)	17 149 (42.1)	
1–3	16 438 (18.1)	5687 (14.0)	
3–5	12 326 (13.5)	4526 (11.1)	
>5	35 420 (38.9)	13 371 (32.8)	
CD4 count at diagnosis, cells/μL, median (IQR)	351 (178–560)	278 (131–460)	<.0001
<200	24 947 (28.0)	14 803 (36.7)	
200–349	19 435 (21.8)	9739 (24.2)	
350–499	16 941 (19.0)	7267 (18.0)	
≥500	27 899 (31.3)	8505 (21.1)	
Ever started ART	91 022 (100.0)	40 733 (100.0)	NA
Time on ART, y, median (IQR)	1.9 (0.4–5.1)	1.2 (0.4–4.36)	<.0001
<10	25 668 (30.9)	19 737 (48.6)	
1.0–2.9	20 547 (24.8)	6932 (17.1)	
3.0–4.9	13 637 (16.4)	5196 (12.8)	

Baseline	No IPT (n = 91 022)	Complete IPT (n = 40 733)	P Value
≥5.0	23 103 (27.9)	8732 (21.5)	
Ever incarcerated	4480 (4.9)	919 (2.3)	<.0001
Clinical characteristics at 48 mo			
Active on ART ¹	74 150 (81.5)	35 025 (86.0)	<.0001
Total no. of viral load results, median (IQR)	3 (1–4)	2 (1–3)	<.0001
Virally suppressed ^{2,3}	62 309 (73.7)	25 005 (64.7)	<.0001
Follow-up			
Follow-up time, overall (PY)	271 039	69 604	
PY of follow-up per person, median (IQR)	3.74 (2.35–3.74)	1.53 (0.84–2.53)	<.0001
Incident cases of active TB disease, no.	5188	702	<.0001
Time to TB disease diagnosis, d, median (IQR)	446 (204–773)	261 (135–511)	<.0001
New diagnosis of TB disease	3393 (65.4)	513 (73.1)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy; IQR, interquartile range; NA, not applicable; PY, person-years; TB, tuberculosis.

¹On ART at least 90 days before end of follow-up time.

²All viral loads 6 months prior to and during follow-up time.

³In the No TPT group, 6520 patients are missing viral loads and in the Complete TPT group, 2097 patients are missing viral loads. These patients are not included in the denominators. *P* values for categorical variables are from χ^2 tests; *P* values for continuous variables are from Wilcoxon rank-sum tests.

Table 2.
Rates and Rate Ratios of Active Tuberculosis Disease, Death, and Multidrug-Resistant Tuberculosis Disease

IPT Status	Active TB Disease			Death			MDR-TB Disease		
	No.	Rate	aIRR	No.	Rate	aIRR	No.	Rate	aIRR
No IPT	5187	1.91 (1.77–2.07)	1.99 (1.62–2.46)	7141	2.62 (2.44–2.81)	1.11 (.97–1.27)	1592	0.59 (.51–.68)	2.13 (1.43–3.18)
Complete IPT	702	1.01 (.81–1.25)	Ref	1948	2.79 (2.44–3.19)	Ref	204	0.29 (.19–.44)	Ref

Incidence rate ratios (with 95% confidence intervals) were adjusted for age, sex, time since human immunodeficiency virus diagnosis, CD4 count, viral suppression, history of incarceration, and alcohol misuse. Rates are per 100 person-years.

Abbreviations: aIRR, adjusted incidence rate ratio; IPT, isoniazid preventive therapy; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

Table 3.
Unadjusted and Adjusted Relative Risks of Tuberculosis Disease by Isoniazid Preventive Therapy Status

Variable	Incidence	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
IPT status			
No IPT	1.91 (1.77–2.07)	1.9 (1.51–2.39)	1.99 (1.62–2.46)
Complete IPT	1.01 (.81–1.25)	ref	ref
Sex			
Male	2.25 (2.06–2.46)	1.93 (1.65–2.25)	1.66 (1.41–1.95)
Female	1.17 (1.03–1.33)	ref	ref
Age, y			
0–14	0.6 (.27–1.30)	0.53 (.22–1.25)	0.66 (.28–1.53)
15–24	0.90 (.52–1.56)	0.80 (.41–1.55)	0.74 (.38–1.42)
25–34	1.64 (1.42–1.90)	1.46 (.98–2.17)	1.21 (.83–1.78)
35–44	1.97 (1.78–2.19)	1.75 (1.20–2.56)	1.43 (.99–2.05)
45–54	1.76 (1.49–2.09)	1.56 (1.05–2.34)	1.39 (.95–2.04)
≥55	1.13 (.78–1.63)	ref	ref
Ever incarcerated			
Yes	4.59 (3.59–5.87)	2.81 (2.18–3.64)	1.95 (1.50–2.53)
No	1.63 (1.51–1.76)	ref	ref
Alcohol misuse			
Yes	4.53 (3.42–6.00)	2.73 (2.04–3.66)	2.07 (1.56–2.75)
No	1.66 (1.54–1.78)	ref	ref
Duration of HIV diagnosis, y			
<1.0	2.21 (1.95–2.51)	1.47 (1.24–1.74)	1.18 (.98–1.43)
1.0–2.9	1.69 (1.44–2.00)	1.12 (.92–1.38)	0.93 (.75–1.16)
3.0–4.9	1.57 (1.29–1.91)	1.04 (.83–1.31)	0.97 (.76–1.24)
≥5.0	1.51 (1.34–1.70)	ref	ref
CD4 count at diagnosis, cells/ μ L			
<200	2.76 (2.49–3.07)	2.81 (2.30–3.43)	2.51 (2.03–3.09)

Variable	Incidence	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
200–349	1.69 (1.46–1.97)	1.72 (1.37–2.17)	1.58 (1.25–2.00)
350–499	1.31 (1.09–1.58)	1.33 (1.04–1.72)	1.2 (.93–1.56)
≥500	0.98 (.83–1.17)	ref	ref
ART started at least 90 d before end of follow-up time			
Yes	1.39 (1.27–1.52)	ref	ref
No	3.46 (3.05–3.93)	2.49 (2.13–2.91)	1.15 (.96–1.38)
All viral loads suppressed			
Yes	0.72 (.65–.81)	ref	ref
No	2.61 (2.36–2.88)	3.6 (3.11–4.18)	3.19 (2.72–3.74)

Incidence rate ratios were adjusted for age, sex, time since HIV diagnosis, CD4 count, viral suppression, incarceration, and alcohol misuse. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy; IRR, incidence rate ratio.