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Highlights

- The TB risk after antiretroviral treatment (ART) initiation in Europe is studied.
- TB peaked within 3 months post ART (14.41/1000 PY).
- TB was linked to certain baseline risk factors.
- TB risk declined over time but remained above European background.
- Thorough TB risk assessment essential at ART onset.

Risk of tuberculosis after initiation of antiretroviral therapy among persons with HIV in Europe

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Abstract

Objectives

Tuberculosis (TB) risk after initiation of antiretroviral treatment (ART) is not well described in a European setting, with an average TB incidence of $25/10^5$ in the background population.

Methods

We included all adult persons with HIV starting ART in the RESPOND cohort between 2012 and 2020. TB incidence rates (IR) were assessed for consecutive time intervals post-ART initiation. Risk factors for TB within 6 months from ART initiation were evaluated using Poisson regression models.

Results

Among 8441 persons with HIV, who started ART, 66 developed TB during 34,239 person-years of follow-up [PYFU], corresponding to 1.87/1000 PYFU (95% confidence interval [CI]: 1.47-2.37). TB IR was highest in the first 3 months after ART initiation (14.41/1000 PY (95%CI 10.08-20.61]) and declined at 3-6, 6-12, and >12 months post-ART initiation (5.89 [95%CI 3.35-10.37], 2.54 [95%CI 1.36-4.73] and 0.51 [95%CI 0.30-0.86]), respectively. Independent risk factors for TB within the first 6 months after ART initiation included follow-up in Northern or Eastern Europe region, African origin, baseline CD4 count <200 cells/mm^3, HIV RNA >100,000 copies/mL, injecting drug use and heterosexual transmission.

Conclusions

TB IR was highest in the first 3 months post-ART initiation and was associated with baseline risk factors, highlighting the importance of thorough TB risk assessment at ART initiation.

Introduction

Tuberculosis (TB) is the most frequent infection in low- and middle-income countries and the leading cause of death globally among persons with HIV.[1] In 2022, 671,000 TB cases and 167,000 TB-related deaths were reported globally among persons with HIV [1].

TB also remains a public health issue in the European region since vulnerable populations, including migrants, injecting drug users, and immunocompromised individuals such as persons with HIV, are at risk of TB. In the World Health Organization (WHO) European Region, 230,000 new and relapse TB cases were reported in 2021, corresponding to an average TB incidence of 25/100,000 population and increased by 1.2% compared with 2020 [2]. Furthermore, persons with HIV accounted for 13% of TB cases in this region, and ART coverage was only 80.1%, well below the WHO target of universal antiretroviral therapy (ART) coverage [2].

The incidence of newly diagnosed HIV in the WHO European region was 12/100,000 in 2021 [3]. Heterosexual contact and injecting drug use (IDU) were the most prevalent reported HIV transmission modes. Almost one-fourth of newly diagnosed persons with HIV originated from high TB incidence areas. Late diagnosis remains challenging since 54% of newly diagnosed had CD4 cell count below 350 cells/mm^3, and TB made up 10% of AIDS-indicator conditions in 2021.

ART and TB preventive treatment (TPT) have been proven to reduce TB incidence and mortality among persons with HIV [4–6]. Various international guidelines advocate routine latent TB infection (TBI) screening for all persons with HIV at the time of HIV diagnosis, regardless of their epidemiological TB risk, and TPT for those diagnosed with TBI [7,8]. The benefits of TPT in a low TB incidence setting (<10 cases/100,000 per year) are, however, unclear and this, combined with the low accuracy of TBI tests, especially in the context of HIV-related immunosuppression, has

resulted in a low level of guideline adoption in clinical practice in many European countries [9,10]. Due to increasing proportions of TB/HIV coinfection in the WHO European Region, it is crucial to continue efforts in TB surveillance and targeted interventions to improve the linkage between the HIV and TB care cascades [2].

Within the International Cohort Consortium of Infectious Disease (RESPOND) cohort study, which covers countries with variable TB prevalence, ranging from low in Western Europe to high in Eastern Europe[11] we aimed to quantify the risk of TB in persons with HIV, including its risk factors and temporal distribution, after initiation of ART.

Methods

Study design and population

We used data from the RESPOND study, a collaboration focusing on HIV and other infectious disease research. Full study details including the type of data being collected have been published elsewhere [11]. Briefly, the consortium was formed in 2017 and consisted of 19 cohorts from Europe and Australia. Persons with HIV were eligible if they were over 18 years old, were integrase strand transfer inhibitor (INSTI)-naïve on January 1, 2012, and had both a CD4 cell count and HIV viral load measurement 12 months prior to or within three months after enrolment/initiation of INSTI.

Participants consented to share data with RESPOND according to local or national guidelines. Individuals were pseudonymised by the participating cohort using a unique identifier before data transfer to the RESPOND coordinating centre in Copenhagen, Denmark, where all data were stored on secured servers. Data management was by current legislation and under approval by The Danish Data Protection Agency (j.nr.: RH-2018-15, 26/1/2018), currently under the EU's General Data Protection Regulation (EU) 2016/679.

Definitions

In our study, individuals were eligible if they were started an initial ART regimen, defined as an INSTI-, boosted protease inhibitor (PI)-, or non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimen after January 1, 2012. Follow-up began at the initiation of ART (baseline) and ended at the first date of TB diagnosis, date of last visit, death, or December 31, 2020. Individuals with an HIV RNA <200 copies/ml prior to the reported date of starting ART were excluded, as were those with a prior TB diagnosis before the ART initiation. Additionally, individuals were excluded if they lacked CD4 count or HIV-RNA data within the 12-month period preceding or the 6-month period following the initiation of ART (baseline). For individuals included in the analysis, baseline CD4 count and HIV-RNA level were defined as measurements obtained 0-6 months prior to initiation of ART. If no measurements were available within this this window, the data were categorized as 'missing').

The outcome was TB disease, with the diagnosis, encompasses both pulmonary and extrapulmonary forms, made according to local criteria by the treating clinicians.

In the analyses, we had included Australia in Northern Europe.

Potential bias

The RESPOND data set did not include detailed information on routine TB screening or TB investigations prompted by clinical findings. However, data on TB diagnoses is collected in a standardized manner within the RESPOND study. Additionally, data on TBI screening and TPT were not captured for the entire cohort, which may have contributed to a reduction in TB incidence. It is important to note that clinical practice related to the use of TPT varied between participating RESPOND study sites.

Study size

We did not perform a formal sample size calculation for this study. However, our cohort is extensive, covering multiple countries across the European continent, which provides a broad and diverse population. Additionally, the study benefits from a long follow-up period and a sufficient number of events to ensure robust statistical power. We have also performed comprehensive multivariable analyses to accurately identify factors related to the outcomes.

Statistical analysis

Age, sex, HIV transmission risk group, ethnicity, geographical origin, geographical region of care, ART starting year and age, baseline HIV RNA and baseline CD4 cell count (defined as a pre-ART CD4 cell count or HIV RNA measured within 6 months before ART initiation) were stratified by whether they developed TB or not and described as numbers and percentages for categorical variables or medians and interquartile ranges (IQR) for continuous variables.

Incidence rates (IR events/1000 person-years of follow-up, PYFU) and 95% confidence intervals (95% CI) of TB disease were estimated for consecutive time intervals after starting ART; 0-3, >3-6, >6-12, and >12 months, to ascertain if there was a time-dependent effect.

Poisson regression was used to calculate the incidence rate ratios (IRR) of developing TB within the first 6 months after ART initiation. As potential risk factors, we considered age, gender, ethnicity, country of origin, body mass index (BMI), HIV transmission risk group, tobacco smoking status, ART regimen (INSTI, PI, NNRTI), prior use of TPT, baseline CD4 cell count and HIV RNA measurements (taken as the closest measurement 6 months prior to ART initiation), prior AIDS events, prior non-AIDS events.

Variables that were statistically significant in univariable models ($p < 0.05$), were included in multivariable models, and subsequently, variables that lost statistical significance in multivariable models were removed. Unknown/missing data was included as a separate category for the specific variable.

All statistical analyses were performed using Stata software (version 17.0; StataCorp, College Station, Texas, USA).

Results

Between January, 2012, and December, 2020, 8441 ART-naïve persons with HIV initiated ART and were included for analysis after exclusion of 1345 (13.7%) due to missing CD4/HIV RNA (n=638), HIV RNA <200 copies/mL (n=537) or prior TB (n=170) (Figure 1). Baseline characteristics of those included in the analyses were generally comparable to those excluded (Table S1). In general, the 8441 individuals were young (median age 38 years, IQR 31-47), male (82.6%), men having sex with men (MSM) (57.3%) and originating from Europe (66.1%); only 6.3% originated from Africa. The median CD4 cell count was 356 (IQR 190-512) cells/mm^3. Overall, 3573 (42.3%), 2397 (28.4%), 1345 (15.9%) and 1126 (13.3%) persons with HIV were in care in Western, Southern, Northern and Eastern Europe, respectively. Forty-one percent of persons with HIV started ART before the year 2015, and approximately half started an initial INSTI-containing ART regimen. Among those with data available, two-thirds had a body mass index <25 kg/m^2, approximately 50% were tobacco smokers, and 11% had prior AIDS diagnoses. There were some regional differences, and persons with HIV in care in Eastern Europe almost exclusively originated from Europe and started ART in later calendar years **(**Table 1).

A total of 66 TB disease diagnoses were made during 35,383 PYFU, resulting in an IR of 1.87/1,000 PYFU (95%CI: 1.47-2.37). When comparing individuals with and without TB disease,

the former were more commonly in care in Eastern Europe (30.3 versus 13.2%), women (31.8% versus 17%), heterosexual (48.5% versus 29.5%), with a history of IDU (18.2 % versus 6.5%), of African origin (16.7% versus 6.2%) and had lower baseline CD4 cell count (median 137 [IQR 46-313] versus 357 [IQR 192-513]). Of patients with TB, 44% had extrapulmonary localisation.

The risk of TB was highest in first 3 months after starting ART (n=30, [45.5%], IR 14.41/1000 PYFU [10.08-20.61]), declined thereafter, and was lowest beyond one year after ART initiation (IR 5.89 [3.35-10.37), 2.54 [1.36-4.73] and 0.51 [0.30-0.86] per 1000 PY in the time intervals 3-6, 6-12, >12 months after ART initiation, respectively (Figure 2a and b).

The TB IR varied substantially over time and was 10 to 25-fold higher in the first 6 months compared with the period beyond 12 months after starting ART. During the first 6 months after ART initiation, 42 (63.6%) persons with HIV were diagnosed with TB. In univariable models, the variables associated with higher rates of TB were: women (IRR 2.27 [95%CI 1.35-3.81]), black ethnicity (IRR 3.52 [1.97-6.28] compared with white ethnicity), care/follow-up in Northern or Eastern Europe (IRR 3.52 [1.80-6.87]) and 4.88 [2.50-9.54], respectively compared with Western Europe), African origin (IRR 3.51 [1.78-6.92] compared with European origin), CD4 cell count <200 cells/mm^3 (8.40 [3.93-17.92] and HIV RNA $\geq$100,000 copies/mL (IRR 3.15 [1.76-5.62]), IDU (IRR 7.45 [3.45-16.11]), and heterosexual transmission (4.45 [2.38-8.34]) compared with MSM (Table S2). In the multivariate models, variables that remained significantly associated with a higher rate of TB were: African origin (3.58 [1.32-9.71]) compared with European origin, care/follow-up in Northern or Eastern Europe (2.89 [1.28-6.53]) and 3.33 [1.21-9.14]), respectively compared with Western Europe), low CD4 cell count (4.51 [2.01,10.12] for <200 compared with $\geq$200 cells/mm^3) and high or missing baseline HIV RNA (3.21 [1.34-7.71] for $\geq$100,000 cp/ml and 3.94 [1.15-13.52] for missing compared with HIV RNA <100,000 cp/mL, respectively) (Figure 3).

Looking at the period beyond 6 months after ART initiation, 24 (36.4%) persons with HIV developed TB, 10 (41.7%) were diagnosed in the following 6 months and 14 (58.3%) beyond one year from ART initiation. Half of these individuals (n=12/24) were not successfully treated for HIV at the time of TB diagnosis, defined as CD4 cell count <200 cells/mm^3 and/or with detectable HIV RNA >100 copies/mL. Ten individuals were diagnosed in Eastern Europe, and 5 had a history of IDU (Table 2).

Discussion

Among persons with HIV who start ART, the TB IR was 10-25 fold higher during the first 3-6 months compared with the period beyond the first 12 months. However, even in the latter period, the TB IR remained higher than in the general population in the European WHO Region (51/100,000 versus 25/100,000) [2]. We identified persons with HIV who received care in Northern or Eastern Europe, of African origin, with a baseline CD4 cell count <200 cells/mm^3, and HIV RNA ≥100,000 copies/mL (or missing HIV RNA) as independent risk factors for TB development within the first 6 months after initiation of ART.

Previous European studies have reported similar or even higher TB IR in persons with HIV concomitantly or during ART, 2.9/1,000 PY (95%-CI 2.6 – 3.4) in a Danish cohort study from 2021, and 1.2/1,000 PY (0.9-1.4) and 6.5/1,000 PY (5.2-7.9) in Western and Eastern Europe in the EuroSIDA study from 2011 [12–14]. A Swiss study reported a declining prevalence of both TBI (4.6%) and TB (0.1/1000) [15]. The gradual decrease in TB IR observed in our study following the start of ART is consistent with finding from the Danish and Swiss HIV cohorts, which observed a significant decline over time after the initiation of ART, paralleling CD4 cell count recovery [13,15]. Older reports from the multi-national studies CASCADE and ART-CC found similarly high initial TB IR after ART initiation, of 4.3 and 4.7/1,000 PY within the first year or first three

years after the start of ART, respectively, and decreasing thereafter [16,17]. An initial increase in the TB IR following ART initiation was observed, most pronounced among those starting ART at CD4 cell counts <50 cells/mm^3, followed by marked decreases with longer time after ART initiation. This could be due to a corresponding steep CD4 cell count increase, as there is an inverse association between CD4 cell count and the risk of TB, with roughly a 10-fold higher risk at a current CD4 cell count <200 cells/mm^3 compared with >500 cells/mm^3 [13,14,16,17].

The higher TB IR during the first three months after ART initiation may be a result of "unmasking" subclinical TB due to paradoxical immune reconstitution inflammatory syndrome or reactivation of TBI [18], highlighting the importance of clinicians undertaking a thorough TB risk assessment prior to ART initiation to diagnose TB disease timely. However, the TB diagnostic workup might be particularly challenging for persons diagnosed with advanced HIV-infection, as did a quarter of the participants in our study, due to the paucibacillary nature of the disease, and low sensitivity of genotypic diagnostic tests, smear and culture among persons with HIV with advanced disease [19,20]. Therefore, despite a thorough investigation a substantial number of TB cases may remain undiagnosed [1].

The WHO recommends that adults and adolescents with HIV, who are unlikely to have TB, should receive TPT as part of a comprehensive package of HIV care when TBI is suspected, or testing is unavailable [8]. This recommendation is based on solid evidence from international randomized trials from TB high-prevalent countries but none from TB low-prevalent countries [21–23]. However, observational evidence from TB low-prevalent countries supports use of TPT [12,15,24–27]. The European AIDS Clinical Society guidelines recommend consideration of routine chest X-rays in persons from high TB prevalence populations and refer to national guidelines to consider ethnicity, CD4 count and ART usage to define indications for TBI screening [28].

Our findings on risk factors for TB diagnosis in the first months after ART initiation, such as African origin and late HIV diagnosis are consistent with previous studies [13,14,16,17]. Surprisingly, care provision in Northern and Eastern Europe was associated with a higher risk of TB diagnosis, despite the latter being a high TB prevalence area. One possible explanation for the higher risk in Northern Europe is the earlier identification of TB cases. However, it may also be due to a higher levels of *M. tuberculosis* exposure in certain vulnerable sub-populations, not fully captured in the adjusted model. Such vulnerable sub-populations represent a higher share of social or behavioral factors such as people originating from high prevalence countries, newly arrived refuge populations, people with unregistered but ongoing IDU, people with economic deprivation, homeless, sex workers, prisoners, and people staying in shelter facilities [13,29,30]. Intensified strategies and testing activities for early HIV diagnosis will reduce the number of late HIV presenters, allow timely ART initiation and, consequently, prevents the associated higher risk of developing TB.

Of note, persons with HIV with documented CD4 cell count and HIV RNA responses to ART initiation were still at risk of TB disease more than 12 months after ART initiation, and the TB IR remained higher than the background population. This difference could in part due to overlapping risk groups for HIV and TB, e.g., unsuccessful ART, IDU, and origin in high-prevalence countries. These findings highlight the possibility of active transmission of *M. tuberculosis* in this population, and monitoring should be based on the presence of the risk factors mentioned above.

The study had several limitations, including most importantly lack of detailed information regarding work-up for exclusion/identification of TB disease, TBI including TPT, and limitations intrinsic to the observational design, where no conclusion could be made regarding causality. Data on TBI screening and TPT were not captured for the entire cohort, potentially contributing to a reduction in observed TB incidence. Additionally, a significant portion of the cohort was excluded from the

analysis. However, our analysis indicated that the baseline characteristics of those included were generally comparable to those excluded. The strengths of the study included the multi-center international design, standardized data collection and robust data quality. Our results may be difficult to generalize to all HIV populations, as RESPOND centers in Europe are often university-affiliated and may not reflect the situation in settings with less expertise and more difficult-to-treat populations.

To conclude, we observed high TB IR in the first 3-6 months after ART initiation in persons with HIV in Europe, which highlights the importance of a thorough TB risk assessment when starting ART. Presenting to care with a low CD4 cell count, a high HIV RNA level, and coming from a high TB endemic area were factors significantly associated with increased risk. The risk of TB declined with time after ART initiation but remained higher than in the general population in most European countries. Intensified efforts for early HIV diagnosis are needed to allow timely initiation of ART and avoid pronounced immunodeficiency. Finally, it is crucial to implement strategies that allow detection of those at higher risk of developing TB to provide TPT, reduce the risk of TB disease whereas a more watchful waiting might be adopted for persons with HIV at lower risk of TB.

Conflicts of interest

JN received honoraria for presentations from Oxford Immunotec and ViiV and working on the advisory board of Gilead Sciences and ViiV. OK received honoraria for presentations at meetings supported by Merck, unconditional research grants from Gilead and travel support from Gilead and Viiv. HG, JR are employees of ViiV Healthcare, Gilead Sciences, respectively. The remaining authors declared no conflicts of interests.

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Ethical Approval Statement

The study is approved by the Danish Data Protection Agency (j.nr.: RH-2018-15, 26/1/2018), currently under the EU's General Data Protection Regulation (EU) 2016/679.

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APPENDIX

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Figure 1: Flow chart showing the selection of patients in RESPOND used in the analysis.

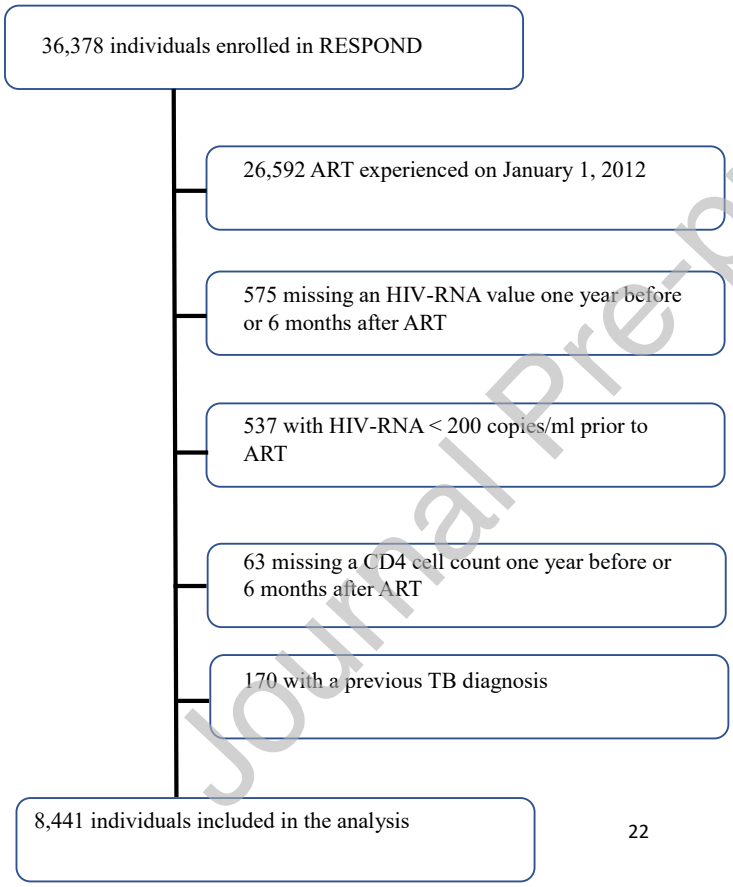
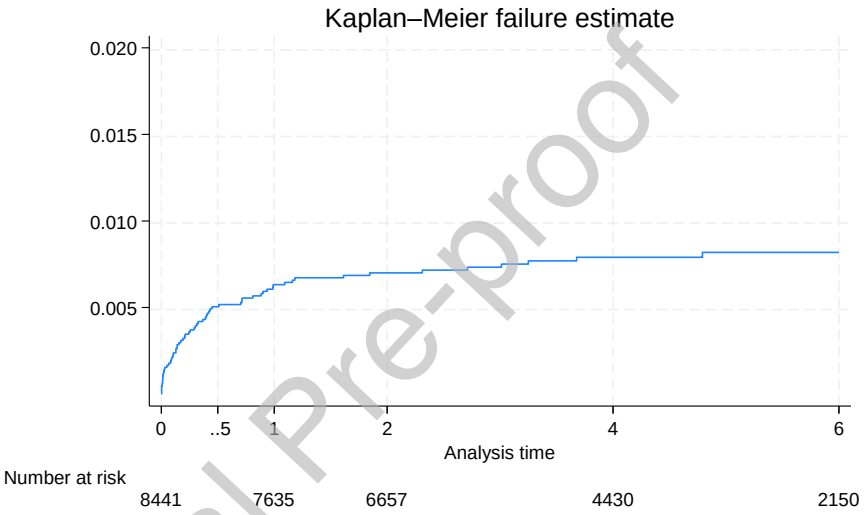


Figure 2a. Development of tuberculosis according to time after initiation of ART: results for 8441 PWH who started antiretroviral therapy; 2b. Incidence rates of tuberculosis in consecutive time periods after initiation of antiretroviral therapy.

2a



2b

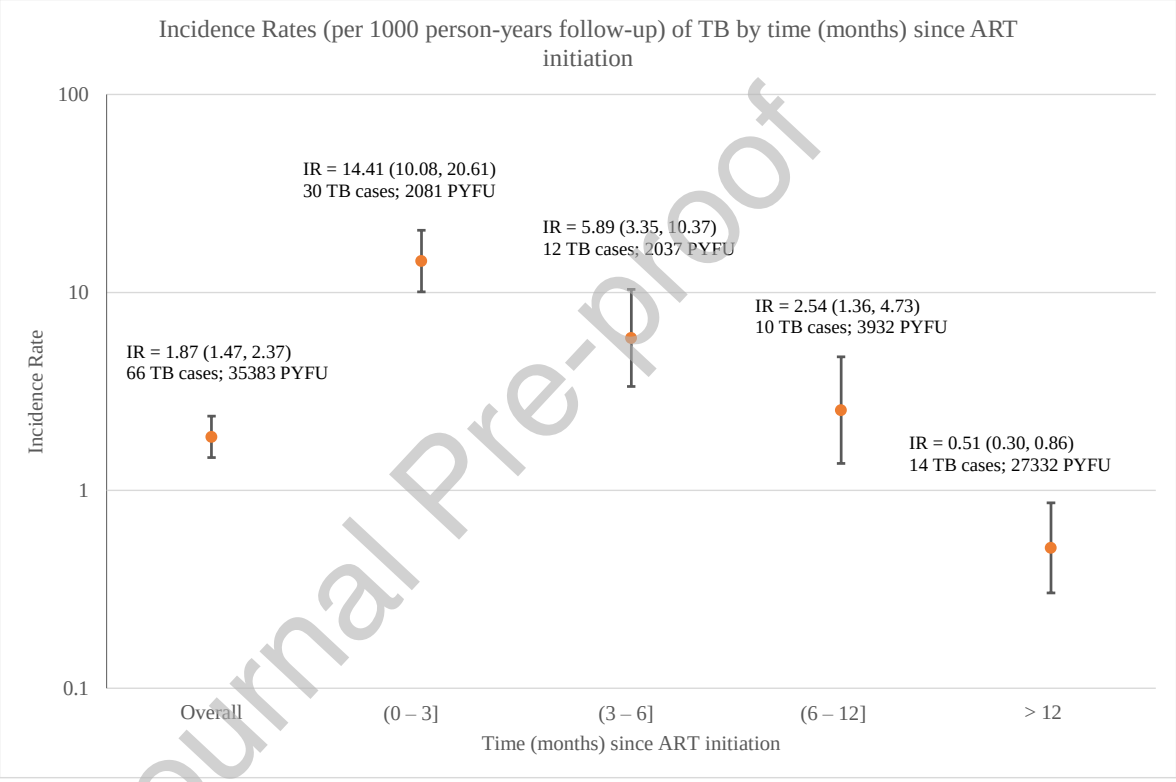


Figure 3. Risk factors for developing TB within 6 months of ART initiation: results of Poisson regression models.

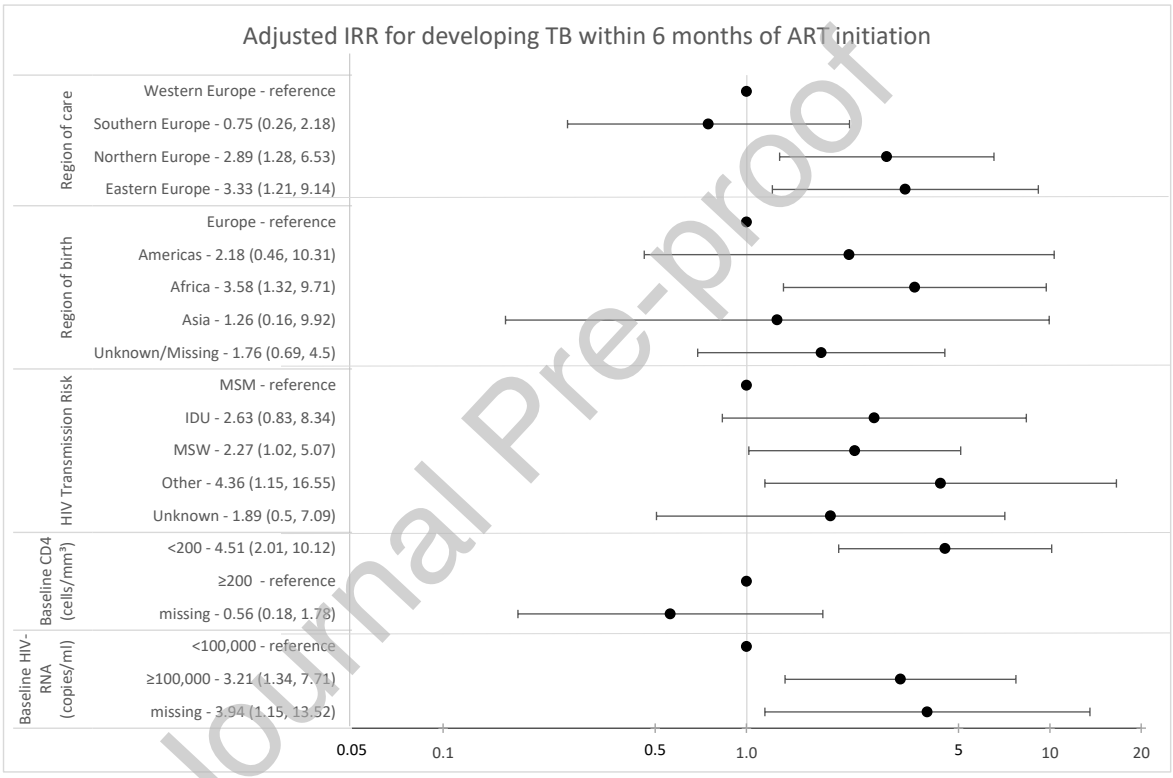


Table 1. Baseline characteristics of 8441 persons with HIV who initiated antiretroviral therapy within the RESPOND Study – according to diagnosis of tuberculosis

		No TB	**TB**	**Total**
		No. (%)	**No. (%)**	**No. (%)**
		n = 8375	n = 66	n = 8441
Gender	Male	6930 (82.7)	45 (68.2)	6975 (82.6)
	Female	1424 (17)	21 (31.8)	1445 (17.1)
	Other/Unknown	21 (0.3)	0 (0)	21 (0.2)
HIV transmission risk group	MSM	4822 (57.6)	14 (21.2)	4836 (57.3)
	IDU	546 (6.5)	12 (18.2)	558 (6.6)
	Heterosexual	2472 (29.5)	32 (48.5)	2504 (29.7)
	Other/Unknown	535 (6.3)	8 (12.1)	141 (1.7)
Ethnicity	White	5879 (70.2)	40 (60.6)	5919 (70.1)
	Black	678 (8.1)	16 (24.2)	694 (8.2)
	Other	440 (5.3)	4 (6.1)	444 (5.3)
	Unknown	1378 (16.5)	6 (9.1)	1384 (16.4)
Geographical region of birth	Europe	5543 (66.2)	34 (51.5)	5577 (66.1)
	Americas	399 (4.8)	4 (6.1)	403 (4.8)
	Africa	517 (6.2)	11 (16.7)	528 (6.3)
	Asia	307 (3.7)	2 (3.0)	309 (3.7)
	Unknown	1609 (19.2)	15 (22.7)	1624 (19.2)
Geographical region of care	Western Europe	3558 (42.5)	15 (22.7)	3573 (42.3)
	Southern Europe	2386 (28.5)	11 (16.7)	2397 (28.4)
	Northern Europe	1325 (15.8)	20 (30.3)	1345 (15.9)
	Eastern Europe	1106 (13.2)	20 (30.3)	1126 (13.3)
Year ART started	2012	1081 (12.9)	13 (19.7)	1094 (13.0)
	2013	1139 (13.6)	9 (13.6)	1148 (13.6)
	2014	1238 (14.8)	14 (21.2)	1252 (14.8)
	2015	1323 (15.8)	11 (16.7)	1334 (15.8)
	2016	1168 (13.9)	6 (9.1)	1174 (13.9)
	2017	1028 (12.3)	6 (9.1)	1034 (12.2)
	2018	767 (9.2)	4 (6.1)	771 (9.1)

	2019	546 (6.5)	3 (4.5)	549 (6.5)
	2020	85 (1.0)	0 (0)	85 (1·0)
Age at ART initiation, years	median (IQR)	38 (31, 47)	41 (36, 51)	38 (31, 47)
Tobacco smoking status	No	1883 (22.5)	9 (13.6)	1892 (22.4)
	Yes	1712 (20.4)	9 (13.6)	1721 (20.4)
	Missing	4780 (57.1)	48 (72.7)	4828 (57.2)
BMI, kg/m^2	<18·5	191 (2.3)	1 (1.5)	192 (2.3)
	18·5-25	2068 (24.7)	15 (22.7)	2083 (24.7)
	25-30	740 (8.8)	5 (7.6)	745 (8.8)
	>=30	176 (2.1)	0 (0)	176 (2.1)
	missing	5200 (62.1)	45 (68.2)	5245 (62.1)
Baseline HIV-RNA,log10 copies/mL	median (IQR)	4.78 (4.20, 5.34)	5.32 (4.90, 5.81)	4.78 (4.20, 5.35)
Baseline CD4, cells/mm^3	median (IQR)	357 (192, 513)	137 (46, 313)	356 (190, 512)
Pulmonary TB			37 (56)	
Extrapulmonary TB			29 (44)	

ART: antiretroviral therapy

TB: tuberculosis

MSM: men who have sex with men

IDU: injection drug use

BMI: body mass index

IQR: interquartile ranges

Western Europe: Austria, Belgium, France, Germany, Luxembourg, Switzerland

Southern Europe: Argentina, Greece, Israel, Italy, Portugal, Spain

Northern Europe: Denmark, Finland, Iceland, Ireland, Australia, Netherlands, Norway, Sweden, United Kingdom

Eastern Europe: Albania, Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine, North Macedonia, Bosnia-Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia, Slovakia

Table 2. Characteristics of people with HIV who were diagnosed with tuberculosis beyond the first 6 months after starting antiretroviral therapy (n=24)

Age at TB, years	Gender	HIV transmission risk group	Region of care	Geographical region of birth	Months to TB	Baseline CD4	CD4 at TB	Baseline log10 HIV-RNA	log10 HIV-RNA at TB	Site of TB
<40	male	MSM	NE	Americas	6-11.9	missing	<200	missing	<2	extrapulmonary
<40	male	MSM	EE	Europe	6-11.9	<200	<200	[5-6]	[2-4]	extrapulmonary
≥40	male	Heterosexual	NE	Unknown	6-11.9	missing	<200	missing	[5-6]	pulmonary
≥40	male	Heterosexual	NE	Unknown	6-11.9	missing	<200	missing	[5-6]	pulmonary
<40	male	IDU	EE	Europe	6-11.9	[200-350)	missing	[5-6]	[5-6]	extrapulmonary
≥40	male	Heterosexual	EE	Europe	6-11.9	missing	<200	≥6	[2-4]	pulmonary
≥40	male	Heterosexual	SE	Europe	6-11.9	[200-350]	[350-500]	[4-5]	<2	pulmonary
<40	male	Heterosexual	SE	Europe	6-11.9	[200-350]	≥500	[4-5]	<2	Pulmonary
≥40	male	MSM	WE	Asia	12.-23.9	≥500	[350-500]	[4-5]	<2	pulmonary
<40	female	Heterosexual	NE	Africa	12-23.9	[200-350)	[200-350]	[4-5]	<2	extrapulmonary
≥40	male	Unknown	EE	Europe	12-23.9	[200-350)	[350-500]	[5-6]	<2	pulmonary
<40	male	IDU	EE	Europe	12-23.9	<200	<200	≥6	≥6	pulmonary
≥40	female	Heterosexual	EE	Europe	12-23.9	missing	≥500	[5-6]	<2	pulmonary
≥40	male	MSM	SE	Europe	12-23.9	≥500	≥500	[2-4]	<2	extrapulmonary
≥40	female	IDU	EE	Europe	12-23.9	[200-350)	[350-500]	[5-6]	<2	pulmonary
<40	female	Heterosexual	WE	Africa	>24	≥500	≥500	[4-5]	<2	extrapulmonary
≥40	female	IDU	NE	Europe	>24	[200-350)	[350-500]	[4-5]	<2	pulmonary
≥40	male	Heterosexual	SE	Africa	>24	missing	≥500	missing	<2	pulmonary
≥40	female	Heterosexual	WE	Unknown	>24	≥500	≥500	[2-4]	<2	extrapulmonary
≥40	male	Unknown	SE	Americas	>24	[350-500)	<200	[5-6]	[5-6]	lymph node
≥40	male	IDU	EE	Europe	>24	<200	[200-350]	[4-5]	[4-5]	extrapulmonary
≥40	male	IDU	EE	Europe	>24	missing	<200	missing	[2-4]	pulmonary
≥40	male	IDU	SE	Europe	>24	missing	<200	[4-5]	<2	pulmonary
≥40	male	Heterosexual	EE	Europe	>24	<200	≥500	≥6	[2-4]	Pulmonary

EE: Eastern Europe, NE: Northern Europe, SE: Southern Europe, WE: Western Europe

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *[Journal name]* and was not involved in the editorial review or the decision to publish this article.

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