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

RESPOND International Cohort Consortium of Infectious Diseases

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Background and Objectives

- Tuberculosis (TB) is the most frequent HIV/AIDS-related cause of death worldwide.
- TB preventive treatment (TPT) is recommended for people with HIV (PWH) irrespective of the degree of immunosuppression or antiretroviral treatment (ART) status.
- However, the benefit of TPT in a low TB/HIV incidence setting is unclear and in many European countries, latent TB infection is not routinely investigated, and TPT is not routinely used either.
- Finally, ART has been shown to reduce the risk of TB by 70%.

- Objectives
- To determine the incidence of TB by time after initiation of ART within the RESPOND study[1] which covers mainly low TB prevalence European countries
- To identify patient-related risk markers of TB development

Methods

Inclusion
- RESPOND individuals first starting ART (INSTI, boosted PI or NNRTI based regimen) after January 1st 2012

Exclusion
- Individuals with HIV-RNA < 200 copies/ml prior to ART,
- Those without a HIV-RNA or CD4 cell count measurement 12 months prior to ART or 6 months after ART initiation
- Prior TB diagnoses

Outcome
- TB diagnosis

Statistical Analysis
- Individuals were followed until the first TB diagnosis, death, last visit or December 2020
- Incidence rates of TB were assessed for consecutive time intervals (0-3, 3-6, 6-12 and > 12 months)
- Risk factors for developing TB within or after 6 months of ART were evaluated using Poisson regression models.
- Variables considered: age, gender, ethnicity, BMI, country of origin, HIV transmission risk group, smoking status, ART regimen (INSTI, PI, NNRTI), prior use of isoniazid monotherapy, baseline CD4 cell count and HIV-RNA measurements (taken as the closest measurement 6 months prior and 2 weeks after ART initiation), prior AIDS events, prior non-AIDS event including cardiovascular disease, diabetes, malignancies, end stage liver disease and end stage renal disease.
- Each variable was considered in a univariable model and if statistically significant ($p < 0.05$) was included in multivariable models. Subsequently, factors that lost statistical significance ($p<0.05$) in multivariable models were removed.

Results

- A total of 8441 PWH who initiated ART in 2012 or later were included.
- PWH were generally young, male, men having sex with men, originating from Europe and only 6.3% came originally from Africa (**table 1**).
- People predominantly started ART in the period 2012-2017, at high CD4 levels (median CD4 count of 356 cells/mm^3 (IQR190-512)) and without prior AIDS diagnoses. For approximately half of the patients, the initial ART regimen was based on a boosted protease inhibitor.
- Non-AIDS comorbidities were uncommon, as 1% or less had been diagnosed with either myocardial infarction, diabetes, non-AIDS malignancies, end stage lever disease or end stage renal disease.
- PWH followed in Eastern Europe were almost exclusively originating from Europe and started ART in later calendar years.

- A total of 66 TB events were diagnosed during 35,383 person-years of follow-up, resulting in an incidence rate of 1.87/1,000 person-years (IQR1.46-2.37). The incidence rates of TB varied substantially and incidence rate was highest in the first six months after starting ART (**figure 1**).
- As the TB incidence rate was 10-25 -fold higher in the first 6 months compared with the period thereafter, we restricted more detailed analysis to the initial 6 months after ART initiation.
- Within the first 6 months, 42 PWH were diagnosed with TB. In univariable models, female gender, black ethnicity, African origin, care/follow-up in Northern or Eastern Europe, CD4 cell count <200 cells/mm3 and HIV-RNA >100,000 cp/ml (or missing HIV-RNA) were all associated with higher risk of TB, whereas men having sex with men (MSM) were at lower risk of being diagnosed with TB compared with other HIV transmission risk categories.
- In a multivariable model, care/follow-up in Northern or Eastern Europe, African origin, other transmission categories than MSM, baseline CD4 cell count <200 cells/mm^3 and baseline HIV-RNA >100,000 cp/ml (or missing HIV-RNA) remained significantly associated with a higher risk of TB in the first 6 months after ART initiation (**figure 2**).

- Among the 24 PWH who were diagnosed with TB at least 6 months after ART initiation,
  - 10 of 24 were diagnosed in the following 6 months.
  - 10 of 24 were diagnosed in Eastern Europe, only 2 PWH were originally from Africa.
  - 9 of 24 were diagnosed at CD4 <200 cells/mm^3 and 5 were diagnosed at HIV-RNA >100,000 cp/ml.
  - 12 of 24 were diagnosed with TB while responding to ART by having a CD4 count >200 cells/mm^3 and HIV-RNA <100 cp/ml. Of these, 8 had initiated ART at least 12 months before the TB diagnosis, suggesting that they were newly infected with *Mycobacterium tuberculosis*.

Table 1 Baseline characteristics of 8841 PWH starting ART

		No TB No. (%) n = 8375	TB No. (%) n = 66 (42*)
Gender	Male	6930 (82.7)	45 (68.2)
	Female	1424 (17.0)	21 (31.8)
	Oth/Unknown	21 (0.3)	0 (0)
HIV transmission risk group	MSM	4822 (57.6)	14 (21.2)
	IDU	546 (6.5)	12 (18.2)
	Heterosexual	2472 (29.5)	32 (48.5)
	Other	138 (1.6)	3 (4.5)
	Unknown	397 (4.7)	5 (7.6)
Ethnicity	White	5879 (70.2)	40 (60.6)
	Black	678 (8.1)	16 (24.2)
	Other	440 (5.3)	4 (6.1)
	Unknown	1378 (16.5)	6 (9.1)
Origin	Europe	5543 (66.2)	34 (51.5)
	Americas	399 (4.8)	4 (6.1)
	Africa	517 (6.2)	11 (16.7)
	Asia	307 (3.7)	2 (3)
	Unknown	1609 (19.2)	15 (22.7)
Region	Western Europe	3558 (42.5)	15 (22.7)
	Southern Europe	2386 (28.5)	11 (16.7)
	Northern Europe	1325 (15.8)	20 (30.3)
	Eastern Europe	1106 (13.2)	20 (30.3)
ART starting age	median (IQR)	38 (31, 47)	41 (36, 51)
Baseline log10 HIV-RNA	median (IQR)	4.78 (4.20, 5.34)	5.32 (4.90, 5.81)
Baseline CD4	median (IQR)	357 (192, 513)	137 (46, 313)

* EPTB = extrapulmonary TB
Baseline is defined as ART initiation date. Baseline HIV-RNA and CD4 are the most recent value 6 months prior to ART initiation

Figure 1. Incidences of TB in consecutive time intervals after starting ART

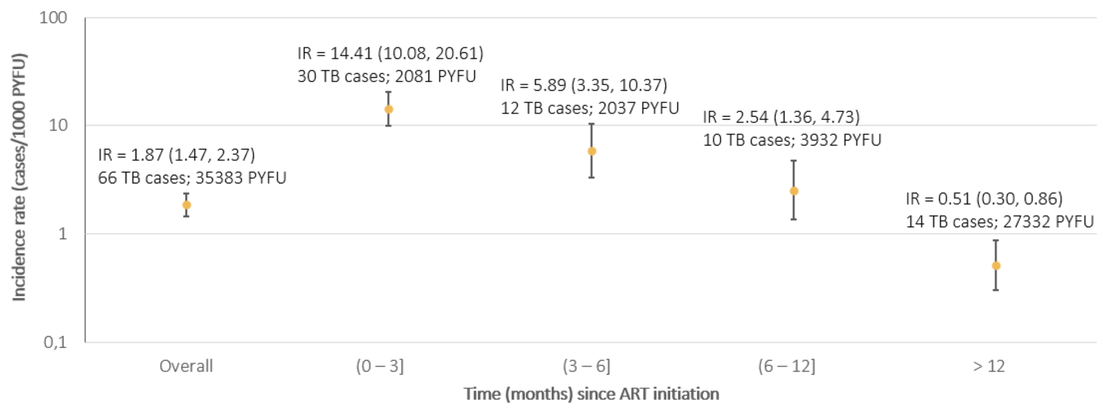
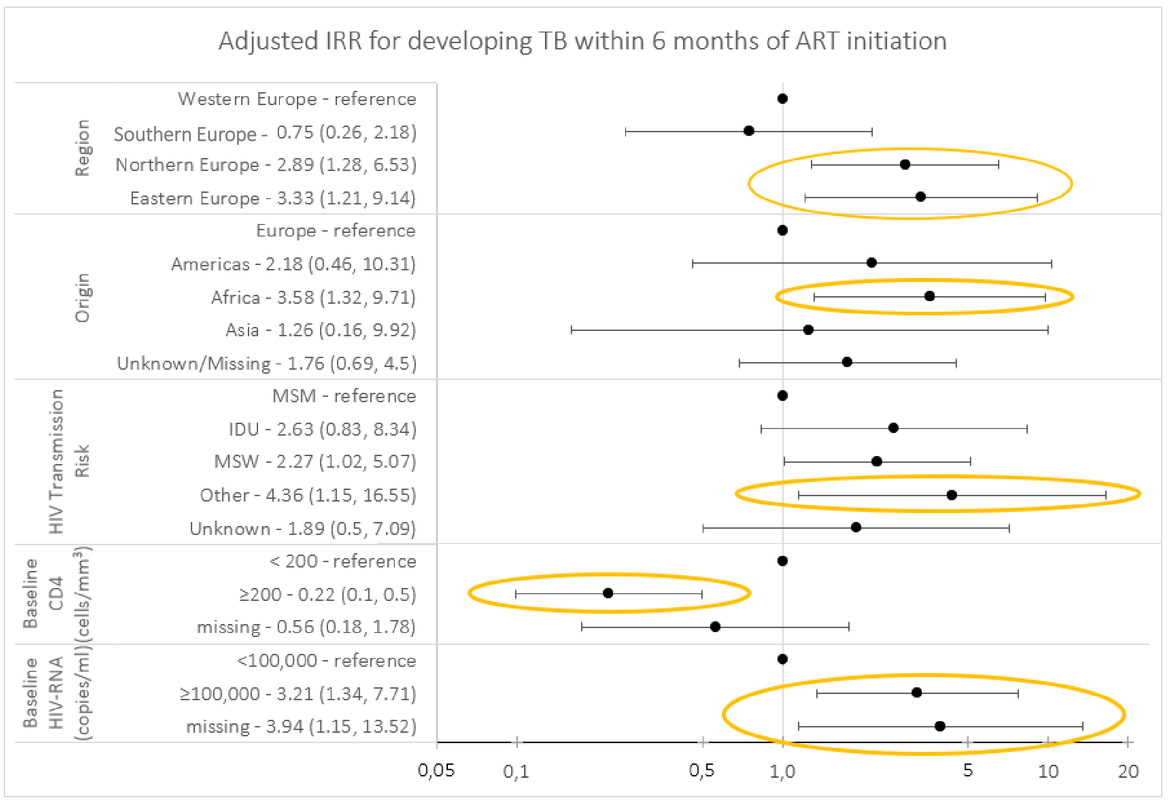


Figure 2. Risk factors for a TB diagnosis within the first 6 months after starting ART



Limitations

Limitations:
- Lack of information regarding workup for TB and LTBI, including TPT
- Due to the design, no conclusion can be made regarding causality

Strengths:
- Multi-center international cohort study
- Standardized data collection

Conclusions

- Overall, TB incidence rates were substantially higher in the first 3 months after the initiation of ART.
- This highlights the importance of a thorough TB risk assessment before starting ART.
- The risk of TB was lower after 6 months of ART but remained higher than in the general population in most European countries (0-9.9 per 10^5).
- This supports directing strategies of careful diagnostics and TPT towards PWH with clear TB risk factors and allows watchful waiting among PWH without risk factors.
- Intensified strategies for early HIV diagnosis are needed.

*References*1Neesgaard et al. Microorganisms, 2020.

Acknowledgements
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The RESPOND Study Group https://www.chip.dk/Studies/RESPOND/Study-Group
RESPOND Scientific Interest Groups https://chip.dk/Research/Studies/RESPOND/SIGs

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