RESPOND International Cohort Consortium of Infectious Diseases

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

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# Introduction

- Tuberculosis (TB) is the most frequent HIV/AIDS-related cause of death worldwide[1].
- TB preventive treatment (TPT) is recommended for people with HIV (PWH) irrespective of the degree of immunosuppression or antiretroviral treatment (ART) status[2].
- However, the benefit of TPT in a low TB/HIV incidence setting is unclear and in many European countries, latent TB infection (LTBI) is not routinely investigated, and TPT is not routinely used either.
- Finally, ART has been shown to reduce the risk of TB by 70%[3].


1. Global Tuberculosis reports 2021, WHO
2. WHO consolidated guidelines on tuberculosis, 2020
3. Lawn et al, Int J Tuberc Lung Dis, 2011

# Objectives

- To determine the incidence of TB by time after initiation of ART within the International Cohort Consortium of Infectious Disease (RESPOND)[1] study which covers mainly low TB prevalence European countries

- To identify patient-related risk markers of TB development

1. Neesgaard et.al. Microorganisms, 2020

# Methods

- Data
  - The RESPOND study[1], a collaboration focusing HIV and other infectious disease research formed in 2017
  - Consists of 17 cohorts from Europe and Australia
  - Prospective follow-up started from 01/10/2017
  - Retrospective data collected back to 01/01/2012

1. Neesgaard et.al. Microorganisms, 2020

# Methods

- Inclusion
  - ART naïve RESPOND individuals first starting ART after 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

1. Neesgaard et.al. Microorganisms, 2020

# Methods

- Outcome
  - Any TB diagnosis
- Statistical Analysis
  - Individuals were followed from ART initiation (baseline) until the first TB diagnosis, death, last visit or December 2020
  - Incidence rates of TB were assessed for consecutive time intervals from baseline (0-3, 3-6, 6-12 and > 12 months)
  - Risk factors for developing TB within 6 months of ART initiation were evaluated using Poisson regression
  - Descriptive statistics were used to categorize TB cases beyond 6 months

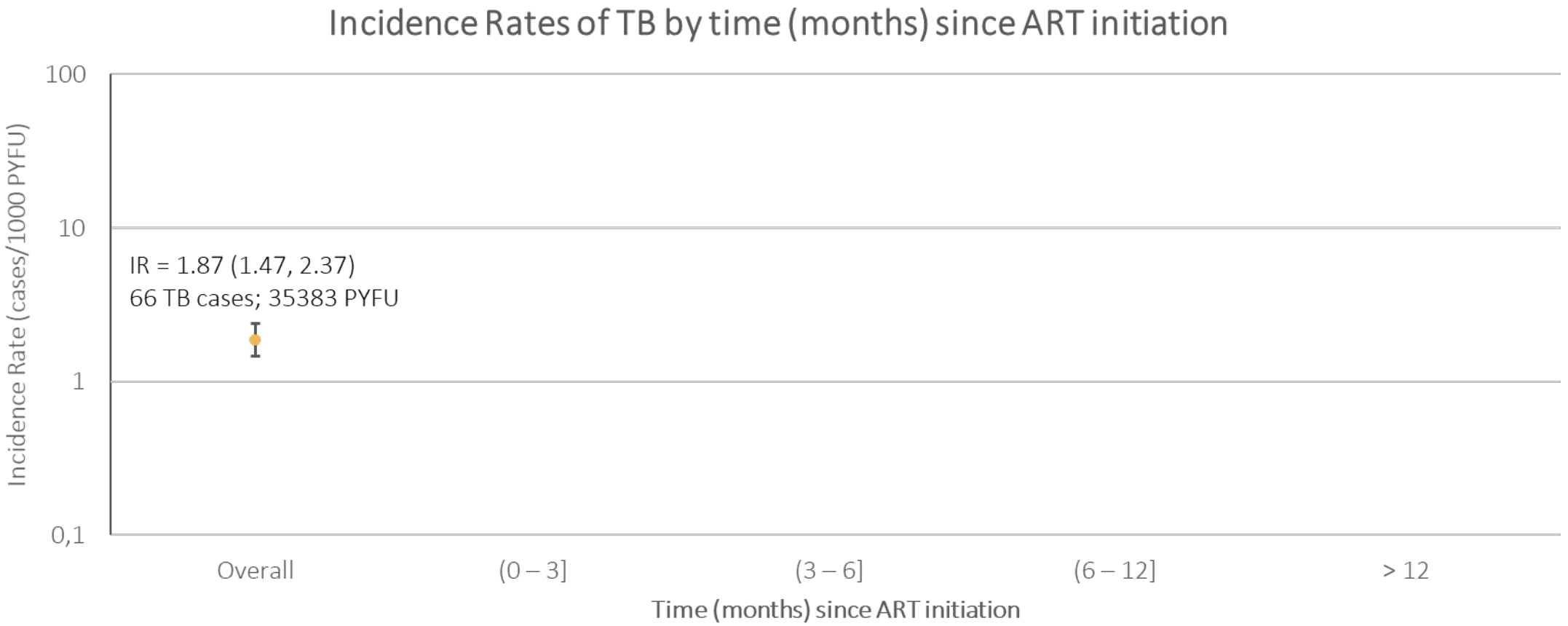
# Results

| | | No TB<br>No. (%)<br>n = 8375 | TB<br>No. (%)<br>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) |

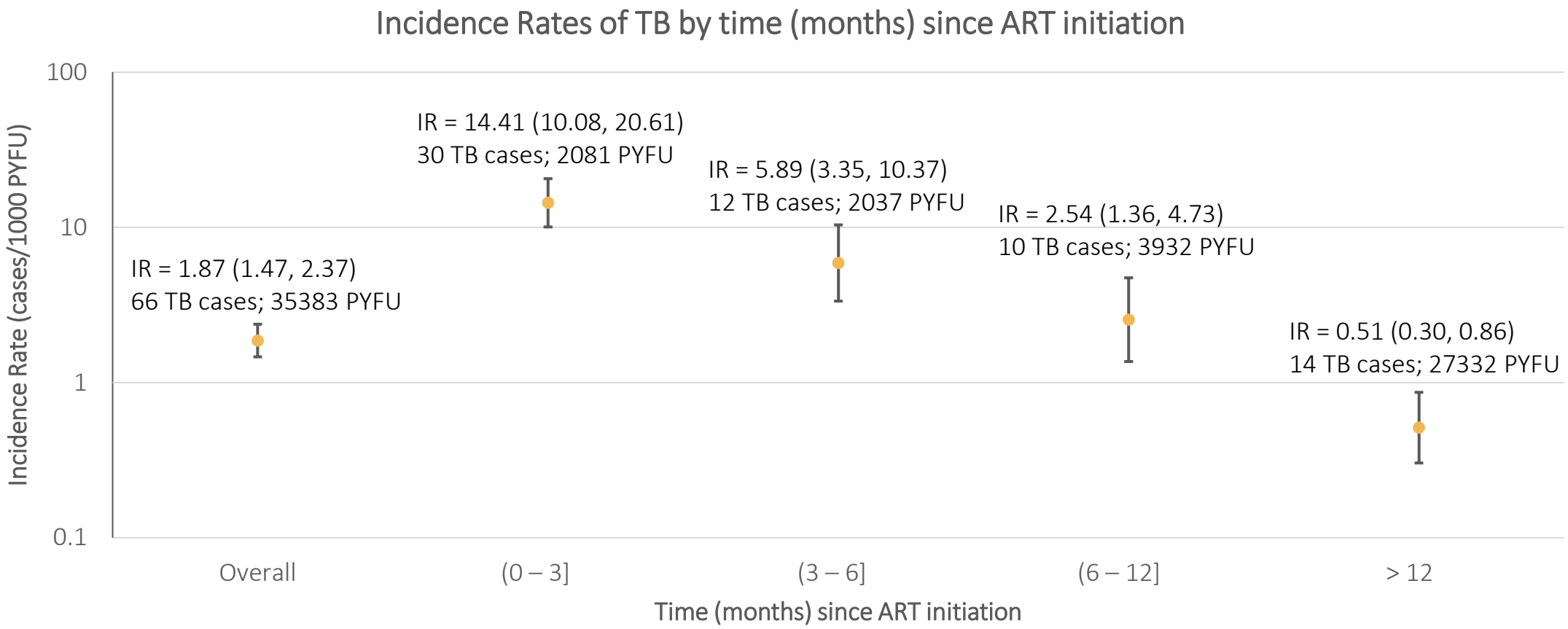
* EPTB = extrapulmonary TB

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

# Results

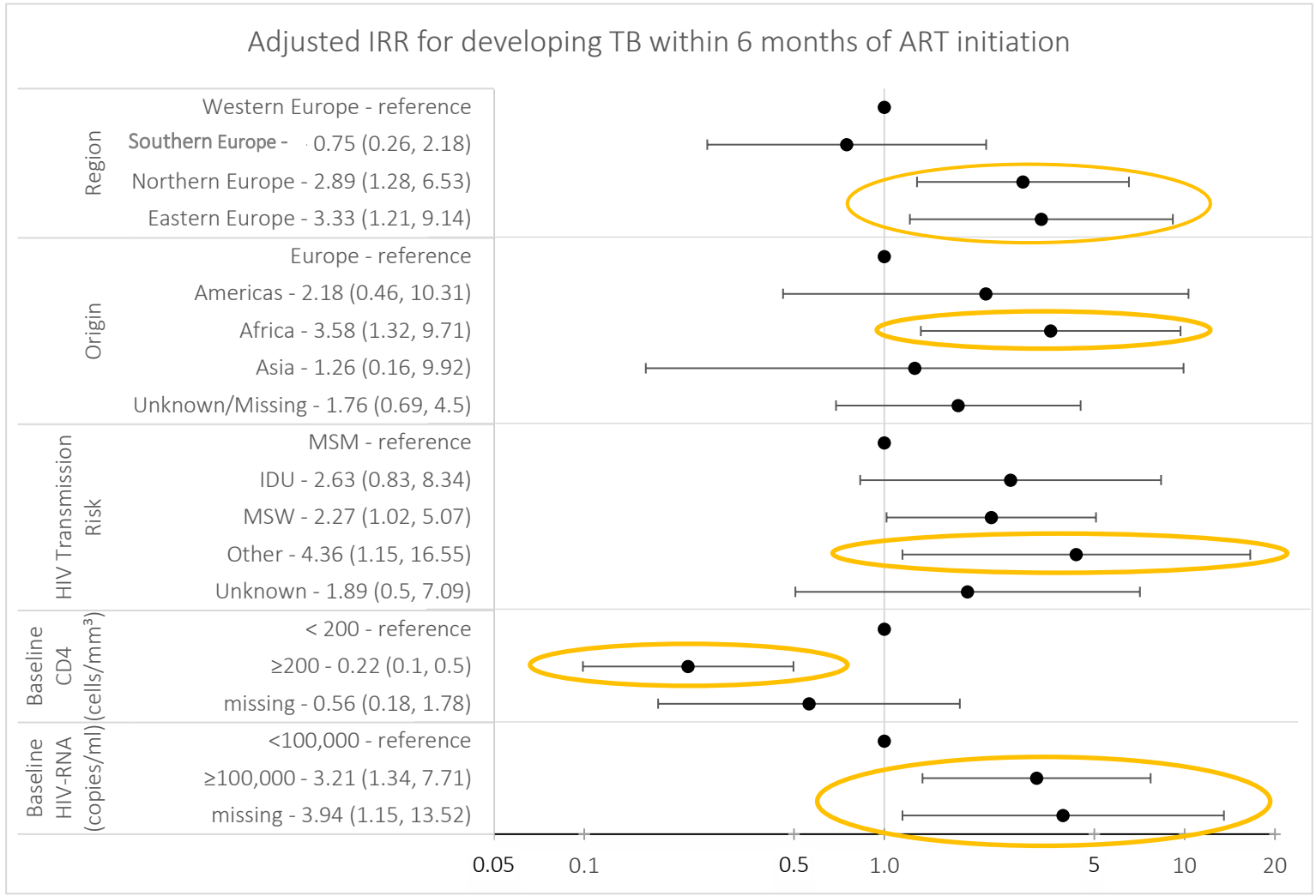

Incidence Rates of TB by time (months) since ART initiation
100
10
1
0,1
Incidence Rate (cases/1000 PYFU)
IR = 1.87 (1.47, 2.37)
66 TB cases; 35383 PYFU
Overall
(0 – 3]
(3 – 6]
(6 – 12]
> 12
Time (months) since ART initiation

# Results


Incidence Rates of TB by time (months) since ART initiation
Incidence Rate (cases/1000 PYFU)
100
10
1
0.1
IR = 1.87 (1.47, 2.37)
66 TB cases; 35383 PYFU
IR = 14.41 (10.08, 20.61)
30 TB cases; 2081 PYFU
IR = 5.89 (3.35, 10.37)
12 TB cases; 2037 PYFU
IR = 2.54 (1.36, 4.73)
10 TB cases; 3932 PYFU
IR = 0.51 (0.30, 0.86)
14 TB cases; 27332 PYFU
Overall
(0 – 3]
(3 – 6]
(6 – 12]
> 12
Time (months) since ART initiation

# Results

- Independent risk factors within 6 months of ART initiation:
  - Northern/Eastern Europe
  - African origin
  - Baseline CD4 cell count ≥200 cells/mm$^3$
  - Baseline HIV-RNA ≥100,000 copies/ml



# Results

- Among 24 PWH diagnosed with TB >6 months after ART initiation
  - 12/24 were diagnosed while responding to ART (latest CD4 count ≥200 cells/mm$^3$ and HIV-RNA <100 copies/ml
  - 10/24 were diagnosed in Eastern Europe and 5 of these had IDU as a transmission risk

## Limitation

- Lack of information regarding workup for TB, LTBI including TPT
- Due to the design no conclusion can be made regarding causality
- Because of the low absolute number of TB cases, it was not possible to construct a risk score

## Strength

- Multi-center international cohort study
- Standardized data collection

# Conclusion

- 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.

# ACKNOWLEDGEMENTS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