Timing and incidence of HIV associated tuberculosis: a 4-country study

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BACKGROUND

- Scale up of combination antiretroviral therapy (ART) had a profound impact on the risk of developing tuberculosis (TB) in persons with HIV, reducing the risk of developing TB in HIV positive persons on successful treatment by 65-84%[1] both in low and high TB burden countries.
- This protective effect is significantly increased in those starting ART with minor level of immunosuppression compared to those delaying ART initiation.[2]
- TB caused nearly 400,000 deaths among people living with HIV in 2017[3], more than a third of all HIV-related mortality. This may reflect still insufficient coverage and /or late initiation of ART.

AIM

- To identify timing and determinants of TB risk for persons with HIV in the context of increasing use of ART in countries with high, intermediate and low TB burden.

STUDY DESIGN AND METHODS

- We included persons enrolled within 3 months of HIV diagnosis/initiation of HIV care from 2006-2016 in observational cohorts in Uganda, Peru, Mexico and Italy.
- TB cases were classified as occurring at first presentation (within 3 months of HIV diagnosis) / during follow-up before cART or during follow-up after cART initiation.
- Factors associated with the risk of having TB at enrolment were identified by multivariable logistic regression.
- Incidence rates of TB from enrolment were calculated, and Poisson regression model was used to identify factors associated with the incidence of TB in the study population

REFERENCES

1. Suthar AB. et al PLoS Med 2017
2. O'Connor J, et al Lancet HIV. 2017
3. WHO Global tuberculosis report 2018

RESULTS

- A total of 24,103 persons with HIV were included from whom an overall of 2,426 TB cases were recorded. Characteristics of the cohort, TB incidence in general population, and number of TB cases from each cohort are reported in Table 1.

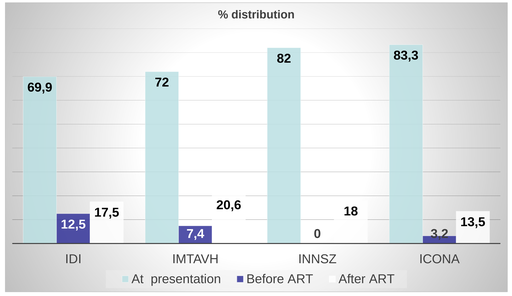
Table 1 – Number of patients enrolled by participating cohorts, TB incidence and TB cases in the four countries

Name	Type of cohort	Country	TB incidence in general population (x1,000 pop)[3]	No. enrolled	No. With TB (%)
IDI	Single institution	Uganda	2.1	12,238	1,780 (14.5)
IMTAvH	Single institution	Peru	1.16	3,562	446 (12.5)
INCMNSZ	Single institution	Mexico	0.22	655	62 (9.5)
ICoNA	Multicenter	Italy	0.07	7,648	138 (1.8)

IDI: Infectious Disease Institue; IMTAvH: Instituto de Medicina Tropical Von Humboldt; INCMNSZ: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; ICoNA: Italian Cohort Naive Antirretroviral

- TB was diagnosed at first presentation in 1,763 (72%), in 260 (11%) at least 3 month after presentation and before ART start, and 432 (18%) after ART initiation. Proportion of cases diagnosed at first presentation ranged from 69.9% in Uganda to 83.3% in Italy. (Figure 1)

Figure 1 - Timing of occurrence of TB relative to HIV diagnosis and ART initiation



- Presentation for HIV care with low CD4$^+$ cell count was a strong risk factor for TB in all countries. Preventive therapy was infrequently reported in these patients (<1%). (Table 3)
- Incidence of TB post ART initiation was high among patients with CD4$^+$ below 200 cells/ml. (Table 4)

- Incidence of TB after cART initiation ranged from 13.3 per 1000 person-years in Uganda to 0.83 in Italy and differed by CD4 cells strata. Incidence declined rapidly during the first year of treatment in all countries. After 12 months of treatment however, it remained higher than the background incidence in each country (Table 5)

Table 3 - Odds ratio of presenting TB by CD4 cells count at enrollment- multivariable logistic regression

CD4 counts cells/µL	Uganda	Peru	Mexico	Italy
<200	1	1	1	1
200 – 350	0.47 (0.39 – 0.56)	0.34 (0.23-0.50)	0.23 (0.08-0.66)	0.34 (0.23-0.50)
>350	0.23 (0.19 – 0.28)	0.28 (0.19-0.41)	0.04 (0.006-0.35)	0.28 (0.19-0.41)

Table 4 - Incidence of TB post ART per 1,000 person-year by CD4 cells count at ART initiation

CD4 counts (cells/µL)	Uganda	Peru	Mexico	Italy
< 200	58.7 (44.1 – 78.1)	11.2 (8.7 - 14.3)	4.4 (2.4-7.9)	0.96 (0.4 - 2.1)
200 – 350	39.41 (31.4 – 49.4)	8.2 (5.2 - 13.1)		1.01 (0.4-2.4)
> 350	12.9 (10.5 – 15.8)	2.7 (1.1 - 6.4)		0.4 (0.1- 1.3)

Table 5 - Incidence of TB per 1,000 person-year by time since ART initiation

	Uganda	Peru	Mexico	Italy
Before ART	21.7 (18.9 – 24.8)	17.8 (12.7-25.1)	----	1.1 (0.3-2.63)
After ART				
Overall	13.3 (11.9 - 15.0)	9.2 (7.5-11.3)	4.4 (2.4-7.9)	0.8 (0.5-1.3)
0–3 months	45.5 (36.8 – 56.2)	46.1 (33.4-63.7)	38.4 (17.2 - 85.5)	1.9 (0.7, 5.2)
4 – 12 months	20.6 (16.2-25.9)	9.99 (6.0-16.6)	12.9 (4.8 - 34.3)	2.3 (1.2, 4.4)
>12 months	7.7 (6.5 – 9.2)	5.2 (3.8-7.1)	0.5 (0.1 - 3.5)	0.3 (0.1, 0.7)

CONCLUSIONS

- Patterns of occurrence of TB were similar, although at a different scale, in the 4 cohorts ; the majority of cases occurred at HIV diagnosis/presentation for cares.
- Low CD4$^+$ count at HIV diagnosis and initiation of cART was the main determinant of TB.
- TB incidence decreased over time on cART, however it remained higher than that of background populations
- Promoting early HIV diagnosis and prompt cART initiation appears to be a key intervention to improve control of the TB-HIV epidemic.
- Other interventions to decrease TB transmission or prevent progression to active TB, including preventive therapy may be needed, at least in some populations. Further studies on their potential impact are needed.

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