Background

- Scale up of combination antiretroviral therapy (ART) has had a profound impact on the development of tuberculosis (TB) in persons with HIV, reducing the risk of developing TB in HIV positive persons on successful treatment by 65-85% 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.
- TB caused nearly 400,000 deaths among people living with HIV in 2013, 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 or after cART initiation.
- Factors associated with the risk of 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.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Type of cohort</th>
<th>Country</th>
<th>TB Incidence in general population (per 1,000 pop)</th>
<th>No. enrolled</th>
<th>No. With TB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDI</td>
<td>Single institution</td>
<td>Uganda</td>
<td>2.1</td>
<td>12,238</td>
<td>1,780 (14.5)</td>
</tr>
<tr>
<td>IMAVH</td>
<td>Single institution</td>
<td>Peru</td>
<td>1.16</td>
<td>3,562</td>
<td>446 (12.5)</td>
</tr>
<tr>
<td>INCMNSZ</td>
<td>Single institution</td>
<td>Mexico</td>
<td>0.22</td>
<td>655</td>
<td>62 (9.5)</td>
</tr>
<tr>
<td>ICoNA</td>
<td>Multicenter</td>
<td>Italy</td>
<td>0.07</td>
<td>7,648</td>
<td>138 (1.8)</td>
</tr>
</tbody>
</table>

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

- TB was diagnosed at first presentation in 1,763 (72%), in 260 (11%) at least 3 months 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)

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 2 - Odds of presenting TB and CD4 cells count at ART initiation

<table>
<thead>
<tr>
<th>CD4 counts (cells/µL)</th>
<th>Uganda</th>
<th>Peru</th>
<th>Mexico</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;200</td>
<td>1.16</td>
<td>0.47</td>
<td>0.23</td>
<td>1.9 (0.7, 5.2)</td>
</tr>
<tr>
<td>200–350</td>
<td>0.28</td>
<td>0.23</td>
<td>0.04</td>
<td>0.34</td>
</tr>
<tr>
<td>&gt;350</td>
<td>0.04</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 3 - Odds of presenting TB and CD4 cells count at ART initiation

- 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 4 - Incidence of TB per person-year by CD4 cells count at ART initiation

<table>
<thead>
<tr>
<th>CD4 counts (cells/µL)</th>
<th>Uganda</th>
<th>Peru</th>
<th>Mexico</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>58.7</td>
<td>11.2</td>
<td>11.1</td>
<td>22.2</td>
</tr>
<tr>
<td>200–350</td>
<td>8.2</td>
<td>3.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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

- Overall 13.1 (95% CI: 11.9-15.0), 9.2 (7.5-11.3), 4.4 (2.7-7.4), 0.8 (0.5-1.3) per 1000 person-years.

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/initiation for cases presented. 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.

References

2. D’Onor, J et al. Lancet HIV. 2017
3. WHO Global tuberculosis report 2018

Acknowledgments

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