DEVELOPMENT OF TUBERCULOSIS IN HIV-INFECTED PATIENTS RECEIVING SUCCESSFUL HAART

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Background: The incidence of active tuberculosis in HIV-infected patients receiving antiretroviral therapy (ART) is still significantly higher than that observed in the general population. We hypothesized that an optimal immunological recovery may reduce the risk of tuberculosis.
Methodology: Historical cohort study in ART-treated patients without previous diagnosis of tuberculosis. Tuberculosis was diagnosed only if microbiologically proven. Multivariate analyses were performed to identify risk factors associated with tuberculosis.
Results: This study included 1824 patients, with a median follow-up of 473 days. Higher CD4 count gain after ART initiation was a protective factor against active tuberculosis (per each 100 cells/µL increase, OR, 0.683; 95% CI, 0.522-0.894). The maximal protection was observed in patients reaching increments ≥150 cel/µL after 12 months (OR, 0.29; 95% CI 0.11-0.8) or ≥300 cel/µL after 24 months (OR, 0.73; 95% CI 0.71-0.75) of ART. CD4+ cell increase after ART initiation was confirmed as an independent predictor of development of tuberculosis by Cox regression analysis (per each 100 cell/uL at year one, HR 0.63; 95% CI, 0.43 - 0.94; per each 100 cell/uL at year two; HR, 0.57; 95% CI, 0.41 - 0.81). However, there was no association between achieving HIV RNA <50 copies/mL and the risk of active TB (OR, 1.43; 95% CI, 0.68-2.49).
Conclusions: The risk of tuberculosis in patients starting ART is reduced among those with better immunological response and it is unrelated to the virological response.

INTRODUCTION

- The incidence of active tuberculosis in HIV-infected patients receiving antiretroviral therapy (ART) is still significantly higher than that observed in the general population. (Dheda K, J Infect Dis 2004; Girardi E, Clin Infect Dis 2005).
- While risk factors for active tuberculosis have been well characterized in ART-naive people living with HIV, among ART-treated patients this question is less clear (Martín-Echevarría, Int j Tuberc Lung Dis 2011; Moreno, Int j Tuberc Lung Dis 2008)
- **In this retrospective cohort study, we aimed to evaluate whether a poor immunovirological response after ART initiation could be a risk factor for development of tuberculosis.**

METHODS

- Retrospective cohort study in ART-treated patients without previous diagnosis of tuberculosis.
- We included all patients in our prospective database after 1999 starting ART with at least three antiretroviral drugs.
- Tuberculosis diagnosis: only microbiologically proven.
- Multivariate analyses were performed to identify risk factors associated with tuberculosis.
- The magnitude of the association between variables was expressed as odds ratio (OR) or hazard ratio (HR), with its corresponding 95%CI.

RESULTS

Total patients: 1824. **Median follow-up**: 473 days.

Variables	Total	Cases of tuberculosis
Age	33 (28-38)	33 (26-37)
Gender, N (%)		
Women	444 (24.3)	15 (33,3)
Men	1380 (75.7)	30 (66,4)
HIV Transmission category		
Injection drug user	1078 (59.1)	31 (68,9)
Homosexual/bisexual	315 (17.3)	6 (13,3)
Heterosexual	351 (19.2)	6 (13,3)
Other	80 (4.4)	2 (4,4)
CDC Risk category		
A	760 (41.7)	15 (33,3)
B	525 (28.8)	17 (37,8)
C	539 (29.6)	13 (28,9)
CD4+ counts (cells/uL)	207 (90 – 363.8)	
CD4+ T-cell category, N (%)		1 (2,2)
≥500cells/uL	187 (10.2)	12 (26,7)
200-499cells/uL	603 (33.1)	21 (46,7)
<200cells/uL	750 (41.1)	11 (24,4)
Missing values	284 (15.6)	
HIV RNA(log $_{10}$ copies/mL)		
HIV RNA category	4.6 (3.8-5.2)	0
<2log $_{10}$ copies/mL	48 (2.6)	8 (17,8)
2-4log $_{10}$ copies/mL	411 (22.5)	27 (60)
>4log $_{10}$ copies/mL	979 (53.7)	10 (22,2)
Missing values	386 (21.2)	
Tuberculin skin test		
Positive	339 (18.6)	19 (42,2)
Negative	1198 (65.7)	16 (35,6)
Other	287 (15.7)	10 (22,2)
Previous tuberculosis		
Yes	254 (14)	5 (11,1)
No	1570 (86)	40 (88,9)

Higher CD4 count gain after ART initiation was a protective factor

Factor increments	OR (IC95%)	P
Per each 100 cells/µL	0.683 (0.522-0.894).	0,028
CD4 > 150 cel/µL month 12	0,29 (0,11-0,8)	0,011
CD4 > 300 cel/µL month 24	0,73 (0,71-0,75)	0,03

The maximal protection was observed in patients reaching increments ≥150 cel/µL after 12 months or ≥300 cel/µL after 24 months

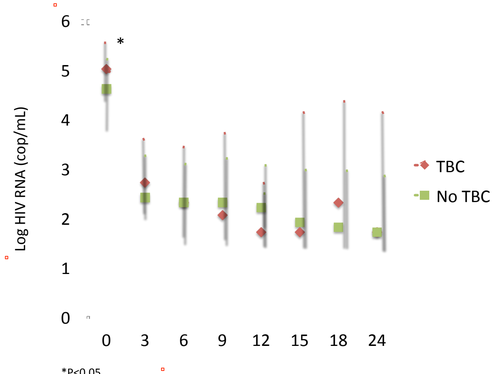
No association between achieving HIV RNA <50 copies/mL and the risk of active TB (OR, 1.43; 95% CI, 0.68- 2.49).

Factors associated with the risk of development of active tuberculosis (Cox proportional risks model)

VARIABLES	HR	IC 95%	P
Baseline CD4 count (per 100 cells increase)	**0.66**	**0.48-0.91**	**0.011**
CD4 count after treatment increase (per 100 cells/at year one)	**0.63**	**0.43-0.94**	**0.028**
CD4 count after treatment increase (per 100 cells/at year two)	**0.57**	**0.41-0.81**	**0.002**
Positive tuberculin skin test	**5.11**	**2.01-12.92**	**0.001**

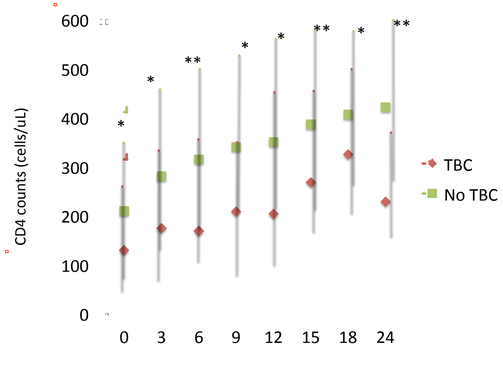
CD4+ cell increase after ART initiation was confirmed as an independent predictor of development of tuberculosis by Cox regression analysis

Changes in plasma HIV RNA during follow-up according to the development of tuberculosis



*P<0.05

Changes in CD4 counts during follow-up according to the development of tuberculosis



*P<0.05
**p<0,001

CONCLUSIONS

- The risk of tuberculosis in patients starting ART is reduced among those with better immunological response and it is unrelated to the virological response.
- Our data have clinical implications, as they suggest that strategies aiming to enhance the immunological recovery might contribute to reduce the risk of tuberculosis.
- Our results emphasize the need of adjunctive strategies in immunological non-responders in order to minimize the residual risk of tuberculosis.