

# The risk of tuberculosis following HAART initiation among adults in resource-constrained settings

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## Background

Tuberculosis is a leading cause of morbidity and mortality among HIV-infected individuals.

## Objectives

1. To describe new or recurrently diagnosed and recorded episodes of tuberculosis (TB) during the first year post-HAART initiation among adults in resource-constrained settings.
2. To identify factors associated with a newly recorded TB event during this period.
3. To compare the findings in ART-LINC with those in ART-CC networks.

## Methods

### Study population:

#### The ART-LINC Collaboration

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration is a multinational collaborative observational operational cohort network<sup>1,2</sup>. For this study, 18 centres in 16 countries in Africa, Brazil, India, and Thailand contributed data.

Included in the analysis were all previously ART naive individuals who initiated treatment with a minimum of 3 drugs on a known date, had at least one day of follow-up, were aged at least 16 years, with known gender.

#### The ART Cohort Collaboration (ART-CC)

ART-CC is a pooled network of databases from Europe and North America established in 2001 to monitor prognosis in HAART-era

Egger et al. *Lancet* 2002, Vol.360: 119-29

[www.art-cohort-collaboration.org](http://www.art-cohort-collaboration.org)

### Outcome Measures:

Infections/illnesses included all recorded tuberculosis events, including pulmonary and extra-pulmonary.

To avoid counting prevalent illnesses, events were defined as 'newly diagnosed and/or recorded' if at least 180 days had passed since the last recorded TB episode.

### Statistics:

- Random effects logistic and survival models
  - Adjusted for inter-cohort heterogeneity
- Follow-up time censored at:
  - Time of event
  - Death
  - Last follow-up visit
  - 12 months post-HAART initiation.
- Explanatory variables considered:
  - Age, sex, baseline CD4, initial treatment regimen (NNRTI-based vs. PI-based vs. 'other' triple), and having TB at or pre-HAART, and calendar time.
- Incidence rates (events/PYFU)
  - Presented per 100 person-years

### Publications by the ART-LINC Collaboration:

1. "Cohort Profile: Antiretroviral Therapy in Lower Income Countries (ART-LINC): international collaboration of treatment cohorts" in *International Journal of Epidemiology* 2005; 34:979-986.
2. "Mortality of HIV-1 infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income settings" in *The Lancet* 2006; 367: 817-24.

## Results

There were 4540 individuals in the ART-LINC database who were eligible for analysis, representing 3468 person-years of follow-up and 258 events.

**The incidence of newly diagnosed and recorded tuberculosis events in ART-LINC: 6.12 per 100 person years.**

In comparison, among 17,142 individuals in ART-CC (15,382 person-years), there were 119 events.

**The incidence of tuberculosis events in ART-CC was previously reported to be 0.77 per 100 person years\*\*.**

\*\*The Antiretroviral Therapy Cohort Collaboration *CID* 2005;41:1772-82.

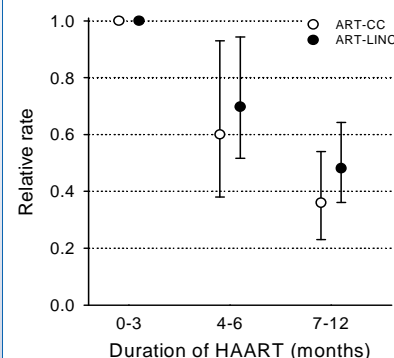
**Table 1. Eight most frequently reported opportunistic infections in ART-LINC vs. ART-CC**

ART-LINC	ART-CC
1. Tuberculosis	1. Mycobacterium Avium Complex (MAC)
2. Kaposi's Sarcoma	2. Kaposi's Sarcoma
3. Candidiasis	3. Cytomegalovirus
4. Bacterial pneumonia	4. Pneumocystis Carinii Pneumonia
5. Cryptococcus	5. Tuberculosis
6. Toxoplasmosis	6. Esophageal Candidiasis
7. Wasting	7. Encephalopathy
8. Mycobacterium Avium Complex (MAC)	8. Toxoplasmosis

**Table 2. Factors associated with new TB events in first 12 months post-HAART, and especially in the first 1-3 months post-HAART initiation**

New Tuberculosis	12 months post-HAART	P-Value	1-3 months post-HAART	P-Value
<b>Age</b>		0.001		0.003
<30 years	1.0		1.0	
30-39 years	0.91 (0.65-1.27)		0.89 (0.55-1.43)	
40-49 years	0.88 (0.60-1.29)		0.61 (0.34-1.12)	
50+ years	0.31 (0.15-0.61)		0.14 (0.03-0.62)	
<b>Sex</b>		0.006		0.132
Female	0.69 (0.53-0.90)		0.74 (0.49-1.10)	
<b>Baseline CD4</b>		0.014		0.250
<25 cells/μL	1.0		1.0	
25-49 cells/μL	0.88 (0.58-1.35)		1.13 (0.61-2.11)	
50-99 cells/μL	1.05 (0.74-1.49)		1.06 (0.62-1.82)	
100-199 cells/μL	0.71 (0.50-1.03)		0.72 (0.41-1.28)	
200-350 cells/μL	0.80 (0.51-1.25)		0.76 (0.38-1.50)	
>350 cells/μL	0.32 (0.14-0.71)		0.35 (0.10-1.17)	
<b>Initial HAART</b>		0.124		0.278
NNRTI-based	1.0		1.0	
PI-based	1.62 (0.88-3.00)		1.25 (0.50-3.11)	
Other triple	1.51 (0.92-2.47)		1.75 (0.90-3.39)	
<b>TB History (vs none)</b>		<0.001		<0.001
Pre-HAART	4.74 (2.43-9.25)		2.78 (0.95-8.16)	
At HAART	4.56 (3.38-6.14)		4.04 (2.56-6.36)	
<b>Calendar Time (per year increase)</b>		<0.001		<0.001
	1.55 (1.35-1.79)		1.68 (1.36-2.09)	

**Figure 1. Decline in relative risk of a post-HAART tuberculosis event over time: ART-LINC vs. ART-CC**



## Limitations and Conclusions

Diagnostic techniques and clinical approaches vary significantly across regions and by centre. For example, some centres systematically screen for TB at a patient's first visit, compared to others who only investigate upon presentation of symptoms. Some centres document opportunistic infections upon laboratory confirmation, while some document upon clinical suspicion. We were therefore unable to accurately distinguish between *de novo* infections and occult infections

In summary, tuberculosis is common in 1st year post-HAART in these resource-constrained settings:

- 5 times as high in ART-LINC compared to high income settings.

Highest risk is in first months following initiation of treatment:

- consistent with high income settings. The relative declines are similar in North and South

## The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration

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