Increased Risk of TB and Persistent Immune Deficit with Delayed ART: A Randomized Trial from Haiti

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Background

- For HIV-infected patients with a CD4 count < 350 cells/mm^3, early initiation of antiretroviral therapy (ART) improves immediate survival, decreases the risk of HIV transmission, and prevents opportunistic infections compared to delaying ART until after the CD4 count falls below 200 cells/mm^3 [1-6].
- The long-term effects of early versus delayed ART are uncertain.

Objective

- Determine the effects of early versus delayed ART on long-term immunologic recovery and the risk for incident tuberculosis (TB).

Methods

- Open label randomized controlled trial of ART-naïve HIV-infected adults with no history of AIDS and a CD4 count between 200 and 350 cells/mm^3.
- Participants were randomized to receive either immediate ART or defer initiation of ART until their CD4 counts were below 200 cells/mm^3.
- The primary comparisons were:
  - CD4 counts over time, assessed by generalized estimating equations.
  - Incident tuberculosis during five years of follow-up. TB risk was assessed by Cox proportional hazards regression models.
- Incident tuberculosis cases were defined by American Thoracic Society criteria[7].
- Participants in the deferred-treatment arm who had not met criteria for initiating ART by June 2009 were started on ART at the recommendation of the Data Safety Monitoring Board. Clinical follow-up and data collection continued with both groups on ART until January 1, 2012.
- The study was conducted at Les Centres GHESKIO in Port-au-Prince, Haiti and is registered at ClinicalTrials.gov study number NCT00120510.

Participants

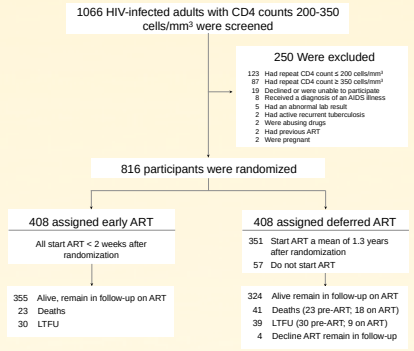


Figure 1. Enrollment, randomization and follow-up.
ART denotes antiretroviral therapy, LTFU denotes lost to follow-up.

Results

Immunologic recovery over 5 years

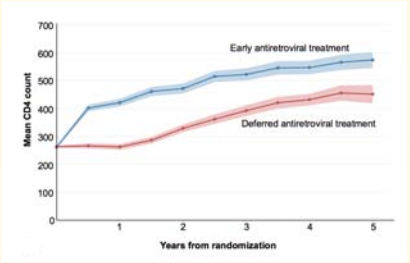


Figure 3. Mean CD4 counts over-time derived from the generalized estimating equation model are plotted from the time of randomization. Shaded areas represent the 95% confidence intervals (CI). After 5 years, the mean CD4 count in the early group was significantly higher than in the deferred group; 574 cells/mm^3 (95% CI 545 to 603) versus 451 cells/mm^3 (95% CI 419 to 484; p<0.0001)

Results

Probability of tuberculosis free survival

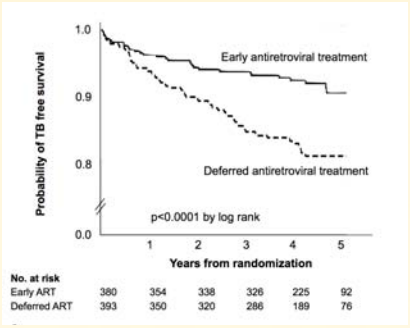


Figure 2. Kaplan-Meier estimates of the probability of tuberculosis free survival from the time of study randomization.

- Deferring ART increased the risk of TB during the first 5 years after randomization. **Hazard Ratio 2.44** (95% CI 1.56-3.70).
- The increased TB risk persisted for at least 3 years after the initiation of ART. **Hazard Ratio 1.69** (95% CI 1.01-2.78).

Predictors of incident tuberculosis: time dependent multivariate analysis

Variable	Hazard ratio (95% CI)	p-value
Baseline HIV Clinical Stage[a]		
Stage 1	1.00 (reference)	
Stage 2	1.33 (0.79-2.25)	0.28
Stage 3	2.26 (1.21-4.21)	0.01
CD4 (per 50 cell/mm^3 decrease)	1.30 (1.16-1.43)	<0.0001
BMI (per 1 unit decrease)	1.16 (1.09-1.23)	<0.0001

Abbreviations: CI, confidence interval; BMI, Body-mass index.
a. The HIV clinical stage of was assessed according to the World Health Organization staging system that ranges from stage 1 (no symptoms) to stage 4 (AIDS).

Conclusion

In this randomized controlled trial of HIV-infected adults with a CD4 count of 200 – 350 cells/mm^3:

- The TB incidence rate was 2.5 times higher in the deferred treatment group compared to the early treatment group.
- Participants who delayed ART initiation for an average of 1.3 years had a lower mean CD4 count over 5 years of follow-up than participants who initiated ART immediately.
- The increased TB risk in the deferred treatment arm strongly correlated with lower CD4 counts..

Short delays in ART initiation for HIV-infected adults with CD4 counts of 200 – 350 cells/mm3 can result in long-term (5 year) immune dysfunction and persistent increased risk of tuberculosis.

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