# Background and Overview

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<tr>
<td>Funding Source</td>
<td>Supported by the French National Agency for Research on AIDS and Viral Hepatitis, National Institutes of Health, and the National Institute of Allergy and Infectious Diseases, Division of AIDS</td>
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| Introduction/Brief Background | • In 2007, it was estimated that there were 33 million people living with human immunodeficiency virus (HIV) infection¹.  
  • Tuberculosis (TB) is a major cause of death in persons infected HIV².  
  • Delayed initiations of therapy as well as early initiation of therapy have each have their own unique associated benefits and risks².  
  • Current World Health Organization (WHO) guidelines recommend that all HIV-infected individuals with active TB receive antiretroviral therapy (ART) as soon as TB treatment is tolerated, generally within 2-8 weeks³.  
  • The optimal timing for the initiation of ART in patients with HIV and TB co-infection remains unclear¹. |
| Objective | To determine whether the earlier initiation of ART (2 weeks after onset of tuberculosis treatment), as compared with later initiation (8 weeks afterward), could reduce the mortality among patients with advanced immunodeficiency (CAMELIA trial) |
| Study Design | • Prospective, randomized, multicenter, open-label, superiority trial with no placebo  
  • Total of 661 patients enrolled in the study  
  • Earlier group (ART at two weeks after beginning TB treatment) N=332  
  • Later group (ART at eight weeks after beginning TB treatment) N=329  
  • Randomization in a 1:1 ratio  
  • No significant differences in baseline characteristics of the study groups  
  • Patients were evaluated by on-site clinicians at 2, 4, 8, 10, 14, 18, 22, 26, 34, 42, and 50 weeks after initiation of TB treatment and then again at weeks 58 and 78, then again every 6 months until the end of collection  
  • Collection ended 50 weeks after the last patient was enrolled (May 13, 2010)  
  • TB therapy: isoniazid, rifampin, ethambutol, and pyrazinamide for two months  
  • TB therapy: isoniazid and rifampin for the remaining four months  
  • If resistance was documented, treatment was modified based on WHO guidelines  
  • ART: stavudine, lamivudine, efavirenz  
  • ART: after one year, considered switching stavudine to zidovudine and switching efavirenz to nevirapine  
  • Prophylaxis: trimethoprim-sulfamethoxazole and fluconazole  
  • CD4 counts and viral loads were measured at 8, 26, 50, and 78 weeks then every 6 months thereafter  
  • Reviewed by the ethics review boards of the Cambodian government, the Immune Disease Institute, and Medecins sans Frontieres. |

## Selection and Enrollment

**Inclusion Criteria:** HIV positive adults with no previous exposure to antiretroviral medications, CD4 count of 200mm³ or less within 14 days of study entry, have received a new diagnosis of TB confirmed by any clinical sample that was smear positive for acid-fast bacilli, TB treatment started less than one week from study entry, negative pregnancy test for woman of childbearing age, female candidates who are sexually active to use two reliable forms of contraception (one of which included a condom).  

**Exclusion Criteria:** Less than 18 years old, negative HIV test, CD4 counts greater than 200 mm³, non-confirmed TB, pregnant or breastfeeding, impaired hepatic function (5x ULN), unable to comprehend protocol, previously treated for TB, previous ART therapy.
### Statistical Analysis
- Power was calculated to be 80%
- Number needed per study arm based on a log-rank test = 330 patients
- Between group comparisons were performed: student t-test for continuous variables and chi-square test or Fisher’s exact test for categorical variables.
- Primary endpoint was described using Kaplan-Meier estimates and compared between groups with a log-rank test.
- The Cox proportional-hazards model was used to identify factors associated with an increased risk of death.
- Two-sided hypotheses and tests were used for all statistical inferences
- P-value ≤ 0.05 was considered statistically significant

### Results

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<tr>
<th>Primary and Secondary outcomes (Including subgroup analysis, also include both efficacy and safety parameters, if appropriate)</th>
<th><strong>Primary Outcome:</strong> Survival</th>
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<td>Rate of death in early ART arm was 8.28 per 100 persons (95% CI 6.42-10.69)</td>
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<td>Rate of death in late ART arm was 13.77 per 100 persons (95% CI 11.20-16.93)</td>
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<td>Early ART had a significantly higher rate of survival compared to late ART (p=0.004)</td>
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<td>Even when patients who were lost in follow up were considered to have died, survival remained significant higher in the early ART arm</td>
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<td>Patients with a CD4 count &lt;50 did not have an increased risk of death compared to patients with a CD4 count of 51-250 (p=0.24)</td>
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<td>Tuberculosis was the leading cause of death between both study arms</td>
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**Secondary Outcome:** TB outcome, CD4 count, viral load below detection threshold, adverse effects of medications, occurrence of tuberculosis associated IRIS, evolution of drug-resistant TB
- There were no significant differences in length of TB treatment (p=0.13) or in recurrence of TB (p=0.11) |
- There was no significant difference in the CD4 count in the study arms (p=0.22) |
- At week 50, the viral load was undetectable in 96.5% of patients with no significant difference in the two study arms (p=0.82) |
- There were no significant differences in side effects of medication (p=0.31) |
- The incidence of tuberculosis-associated IRIS was significantly increased in the early ART study arm with 3.76 per 100 person-months compared to the late ART study arm with 1.53 per 100 person-months (p<0.001) |
- There were no significant differences in evolution of drug-resistant TB (p=0.1) |

### Conclusion
- Initiating ART 2 weeks after the start of TB therapy significantly increases survival among HIV-infected adults with newly diagnosed TB and a CD4 count of 200 or lower compared with delaying the start of ART to eight weeks
- The results strongly favor early initiation of therapy despite the increased risk of IRIS
- This is of particular relevance in resource-limited settings where tuberculosis is the leading cause of death in HIV-infected patients
# Student’s Discussion & Conclusion

## Strengths
- RCT is the gold standard for testing a hypothesis
- Similar treatment groups in regards to demographics
- Appropriate follow-up clinical visits
- Tuberculosis is the leading cause of mortality in patients infected with HIV so this study has appropriate worldwide applications
- Based on data from other previously conducted trials

## Limitations
- The study has some limited use within the United States based on the choice of standard ART
- Excluded people who have had previous TB
- According to United States standards, persons with a CD4 count below 200 should have already been placed on ART

## Clinical Applications
Worldwide, TB is the leading cause of death in persons with HIV and AIDS. It is important to appropriately treat these comorbid conditions so as to extend the lives of patients. Currently, guidelines recommend starting ART 2-8 weeks after TB therapy in an HIV infected person. The benefit of this study is that it closely examined which end of the spectrum should be utilized in treating patients. This study will better help healthcare professionals and patients alike decide on appropriate treatment options, weigh risks and benefits of therapy, and make a more informed decision on when to begin therapy.

## Recommendations
I feel that though this study took place in a different country with different guideline recommendations, this study can still be applicable to the United States. While TB is not as common of a complication in Americans with HIV, it definitely affects part of the population. Therefore, using the information in the CAMELIA trial can help improve therapy as well as mortality among this patient population.

## Level of Evidence
Delfini Grade B: High quality in design, execution with non-lethal threats to validity, and sufficiently useful information to aid in clinical decision-making leading to reasonable certainty in drawing conclusion

## References