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Empiric TB therapy versus IPT in HIV-infected persons initiating ART (ACTG 5274 48 weeks results)

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Introduction

The last decade had seen significant increase in access to antiretroviral therapy in low and middle income countries (LMIC). As a result morbidity and mortality associated with HIV have both significantly gone down. However, up to 26% of patients initiating ART in these countries die within the first year of initiating ART.

Tuberculosis is one of the leading cause of mortality in this patient population, therefore strategies to address TB-associated mortality are needed.

The A5274 REMEMBER study is an open label randomized clinical trial comparing ART + four-drug empiric TB therapy vs. ART+ isoniazid preventive therapy (IPT) in HIV-infected individuals with CD4 counts < 50 cells/mm^3.

Objectives

The 48 week objective is to evaluate the possible effects of the intervention on longer-term outcomes;

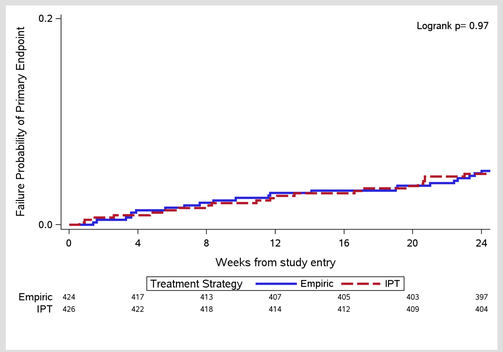
- 48-week survival
- time to death or AIDS progression
- time to confirmed or TB.
- Effect of GeneXpert testing on AIDS progression and death

Summary of the 24 Week Results?

At 24 weeks, there was no difference between arms

- In mortality
- time to death or AIDS progression
- Virologic suppression

Figure 1: **Time to Primary Endpoint by Treatment Strategy**



Methods

Screening:

Participants were Initially screened using a TB symptom screen, targeted physical exam (e.g. lymph nodes) and allowing site to perform additional evaluations as per standard of care.

Later all sites mandated to perform a single GeneXpert test for TB and collect sputum for culture. The study was stratified according to CD4 count (<25 vs. >=25 cells/mm^3) and poor prognostic factors (body mass index < 18.5, Hemoglobin < 8 g/dl, recent hospitalization).

Study setting:

Participating sites were required to have a TB incidence >100/100,000 person years and had ART programs with documented high early mortality rates (i.e., at least 5% overall at 6 months post ART initiation)
The study was conducted at 18 sites in 9 countries (6 in sub-Saharan Africa, 3 in the Americas and 1 in Asia)

Inclusion and exclusion criteria:

Inclusion criteria included:

- HIV infected but ART naïve male and female
- Age 13 years and older
- CD4 cell <50 cells/mm^3
- Karnofsky score ≥30.
- liver function tests ≤2.5x the upper limit of normal
- a creatinine clearance ≥30mL/min

Exclusion criteria included:

- Potential participants with probable or confirmed TB
- Receipt of single dose nevirapine in the preceding 2 years
- TB treatment or IPT within 96 and 48 weeks prior to study entry,
- History of or household exposure to multidrug resistant (MDR)-TB

Data analysis

Kaplan-Meier method was used to estimate the probabilities of mortality, mortality and AIDS progression, and confirmed or probable TB, which were compared with the z-test. Log rank test was used to compare all time to events between study arms. Participants whose survival status was unknown, or those who dropped out before week 48 were treated as censored at the last clinical visit. A total of 850 participants were included in the analysis.

Results

We screened 1368 potential participants and enrolled 850 (424 and 426 assigned to empiric and IPT arms respectively). Baseline characteristics were similar in both arms as shown in Table 1 below.

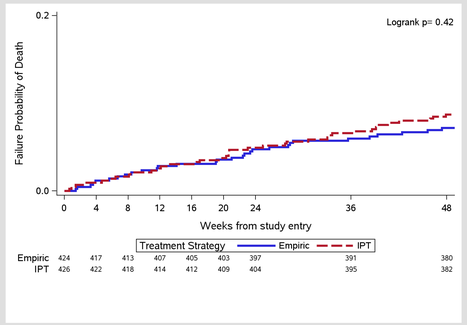
Table 1: Baseline characteristics of study participants

Characteristic		Empiric (%)	IPT (%)
Sex	Male	53%	53%
	Female	47%	47%
Race/ethnicity	Black	90%	91%
	Indian	4%	3%
	Other	6%	6%
Age, years	Median (IQR)	36 (30-42)	35 (30-42)
HIV RNA, log copies/ml	Median (IQR)	5.4 (5.0, 5.7)	5.3 (4.9, 5.7)
CD4 count cells/ mm^3	Median (IQR)	18 (9, 31)	19 (9, 33)

Mortality at 48 weeks:

There were 30 deaths (7%) in the Empiric and 37 deaths (9%) in the IPT arms respectively. The cumulative probability of death in the empiric arm was 7.2% (5.1%, 10.1%) vs 8.7% (6.4%, 11.8%) in the IPT arm giving a difference in probability of death of 1.55% (-2.11%, 5.2%; p-=0.41). There was no difference in time to death across arms (p=0.42).

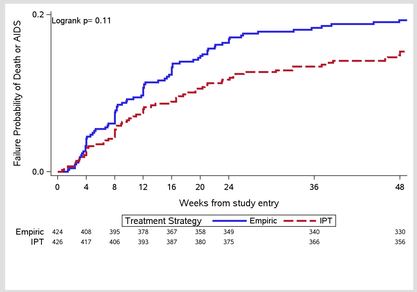
Figure 2: Time to Death by Treatment Strategy



Mortality or AIDS Progression by 48 weeks:

The probability of death or AIDS progression was not significantly different between arms [19.3% (95% CI: 15.8%, 23.4%) for the empiric arm vs. 15.3% (95% CI: 12.2%, 19.1%) for the IPT arm], absolute difference -4.0% (95% CI: -9.1%, 1.1%; p=0.13). There was no significant difference in time to AIDS progression or death between the arms (p=0.11 by log rank test).

Figure 3: Time to Death or AIDS Progression by Treatment Strategy

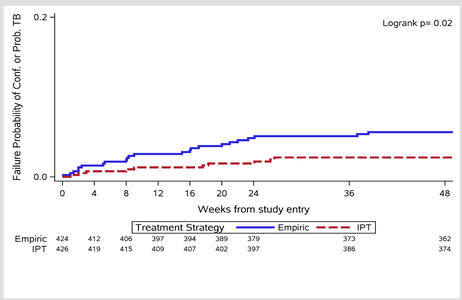


The result did not change after excluding participants that were TB positive at enrollment by GeneXpert after retrospective testing.

Confirmed or Probable TB by 48 weeks:

The rate of confirmed or probable TB at week 48 were 5.6% (95% CI: 3.8%-8.3%) for the Empiric arm, and 2.4% (95% CI: 1.3%-4.5%) for the IPT arm. The absolute difference in the event probabilities was -3.2% (95% CI:-5.9%, -0.5%; p=0.02) The time to confirmed or probable TB was more rapid in the empiric arm (p=0.02).

Figure 4: Time to Confirmed or Probable TB by Treatment Strategy



Conclusion:

The primary end point seen at 24 weeks is sustained at 48 weeks i.e. Empiric TB treatment in patients presenting for ART initiation with low CD4 cell counts below 50 cells/mL did not reduce mortality compared to IPT.
There was a significantly higher rate of AIDS progression in the Empiric arm compared with the IPT arm. This finding is surprising considering that this was a randomized clinical trial.
Use of GeneXpert or urine LAM did not significantly impact the outcome of the study
The WHO symptom TB screening if applied diligently is able to exclude many HIV/TB co-infected patients