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Impact of INH adherence on TB incidence and mortality by week 96 in ACTG 5274 trial

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Background

- TB is a major cause of morbidity and mortality in low- and middle-income countries despite the use of antiretroviral therapy (ART).
- The A5274/REMEMBER trial team previously reported that a strategy of Empiric 4-drug TB therapy +ART provided no additional benefit in reducing mortality within 24 weeks after ART initiation compared to INH preventive therapy (IPT)+ART.
- We now present the 96 weeks results.

Methods

Study Participants and Design

- Multicountry open-label, randomized clinical trial.
- Participants were HIV-infected individuals with CD4<50
- Screened using a TB symptom screen, locally available diagnostics, and GeneXpert when available.
- Randomization was stratified by CD4 (<25 vs. ≥25 cells/mm3) and poor prognostic factors (BMI<18.5, HGB<8 g/dL, and recent hospitalization). Study arms were:
  - (A) efavirenz/tenofovir/emtricitabine + 4 drug empiric TB therapy x 24 weeks
  - (B) efavirenz/tenofovir/emtricitabine + INH x 24 weeks
  - Medications were provided for self-administered
- Participants transitioned to local standard of care at week 48 and were followed up by phone calls at weeks 60, 72, 84, and 96.

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 10 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
- 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 or household exposure to multidrug resistant (MDR)-TB

Methods

Adherence to study medications was assessed at weeks 1,2, 4, 8, 12, 16, 20 and 24 by self report using a validated ACTG 4 day recall questionnaire.

Data Analysis

Kaplan-Meier method was used to estimate the probabilities of mortality, 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.

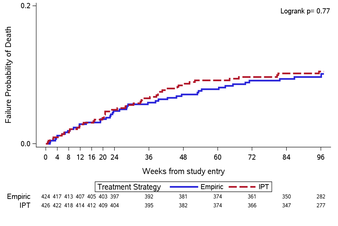
Results

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 (n=424)	IPT (n=426)
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)

Time to Death by Treatment Strategy



Mortality at 96 weeks:

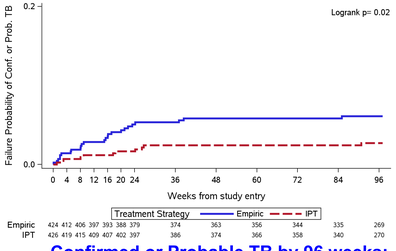
There were 41 deaths (9.7%) in the Empiric and 44 deaths (10.3%) in the IPT arms respectively. 18 of these deaths occurred after week 48. The cumulative probability of death in the empiric arm was 10.1% (7.5%, 13.6%) vs 10.5% (7.9%, 13.9%) in the IPT arm giving a difference in probability of death of 0.4% (-3.8%, 4.5%; p=0.86). There was no difference in time to death across arms (p=0.77).

Results

Modified Intention to Treat Analyses

Three modified ITT analyses were performed by excluding participants who were retrospectively identified as MTB+ at the time of study entry by Gene Xpert only (n=6), by urine LAM (n=28), and by both (n=33). Only 5 participants (3 in the Empiric arm and 2 in the IPT arm) who were identified as MTB+ by retrospective tests died within 96 weeks since randomization.

Time to Confirmed or Probable TB Diagnosis by Treatment Strategy



Confirmed or Probable TB by 96 weeks:

A total of 58 participants had 63 TB events. The rate of confirmed or probable TB at week 96 was 6.1% (95% CI: 4.2%-8.9%) for the Empiric arm, and 2.7% (95% CI: 1.5%-4.9%) for the IPT arm. The absolute difference in the event probabilities was -3.4% (95% CI:-6.2%, -0.6%; p=0.02) The time to confirmed or probable TB was more rapid in the empiric arm (p=0.02). Results remained the same for competing risk analysis.

Type of TB	Total n=63	Empiric n=39	IPT n=23
Pulmonary TB - confirmed	20	14	6
Extrapulmonary TB - confirmed	3	1	2
Pulmonary TB - probable	8	5	3
Extrapulmonary TB - probable	6	6	0
Pulmonary TB - clinical	4	1	3
Extrapulmonary TB - clinical	22	12	10

Adherence

- Adherence to IPT at weeks 2, 8, 12, and 20 was higher among participants who were alive compared to those who died.
- Adherence to IPT at weeks 1 and 8 was lower among those who developed TB by week 24 compared to those who did not.

Event		Adherence level	Hazard Ratio (95% CI)
Death	Empiric	per 10% adherence	0.77 (0.69, 0.85)
	IPT	per 10% adherence	0.80 (0.71, 0.89)
TB diagnosis	Empiric	per 10% adherence	0.94 (0.80,1.10)
	IPT	per 10% adherence	0.83 (0.70,0.98)

- Adherence to TB medications had a significant effect on deaths by weeks 24, 48, and 96 in the Empiric and the IPT arms (Cox proportional models, p<0.0001 and p<0.0035).
- The hazard of death was 23% and 20% lower per 10% increase in the proportion 100% adherence in Empiric and IPT arms, respectively.
- There was significant effect of adherence to IPT on the TB diagnoses by weeks 24, 48, and 96 weeks (Cox proportional hazards models, p<=0.0324).
- The hazard of TB diagnosis was 17% lower per 10% increase in the proportion of 100% IPT adherence.
- However adherence had no significant effect on TB diagnoses in the Empiric Arm.

Summary of Key Results

- The primary end point seen at 24 and 48 weeks is sustained at 96 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 confirmed or probable TB in the Empiric arm compared with the IPT arm.
- Adherence to both empiric and IPT was associated with improved survival.
- Adherence to IPT was associated with reduced risk of developing TB, but adherence to empiric TB therapy was not.

Conclusions

Supporting IPT+ ART initiation and adherence are critical to preventing the high TB incidence and mortality in those with advanced HIV.

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