Abstract: 16-1650

Urine LAM Testing in Advanced HIV-Infected Adults in a Trial of Empiric TB Therapy

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Background

The Alere Determine™ TB LAM Antigen test is a rapid, point-of-care TB diagnostic that detects urine lipoarabinomannan (LAM) in urine but its role in TB screening and treatment strategies is unclear. The sensitivity of the urine LAM test is higher in patients with low CD4 counts, making it useful in screening for TB among patients with advanced HIV disease, whose sputum AFB smears are often negative. Further study in the context of ART and TB treatment strategies is needed.

We determined:

1) the diagnostic yield of urine LAM in advanced HIV-infected adults who remained without a TB diagnosis after TB screening using routine measures during evaluation for enrollment into a trial of empiric TB therapy;
2) clinical outcomes in participants who were urine LAM + at baseline; and
3) the effect on the empiric TB trial outcomes when LAM + participants were excluded.

Methods

AIDS Clinical Trial Group (ACTG) Study 5274, Reducing Early Mortality and Morbidity by Empiric TB Treatment (REMEMBER), is an international, open-label, randomized clinical trial that demonstrated that 4-drug empiric TB therapy did not improve 24-week survival (Figure 2.A) and was associated with an increased incidence of TB during 24 weeks of follow-up compared to isoniazid preventive therapy (IPT) (Figure 3.A) in HIV-infected individuals initiating EFV-based ART with CD4 counts <50 cells/mm^3.

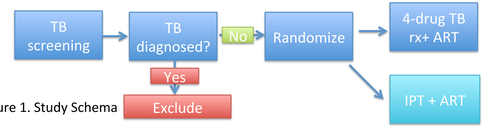


Figure 1. Study Schema

Study Design and TB Screening: Candidates were screened for TB prior to entry using a symptom screen, physical exam, locally available diagnostics, and sputum Xpert® MTB-RIF testing (implemented at screening in 398). Those without a TB diagnosis after screening were randomized 1:1 to ART+4-drug TB therapy for 24 weeks (Empiric Arm) or ART+INH for 24 weeks (IPT Arm).

Methods

Study Setting: The study was conducted at 18 sites in 10 countries, with 77% of the enrollment occurring in Sub-Saharan Africa. To be included, patients needed to be HIV-infected, ART naïve individuals age 13 and older with pre-ART CD4 counts <50 cells/mm^3. Those with probable or confirmed TB after screening were excluded.

Urine LAM testing: Retrospective testing using the Alere Determine™ TB LAM Antigen test was performed on stored, previously frozen urine obtained prior to ART initiation (baseline); tests were positive if two readers agreed.

Analysis: Kaplan Meier method was used to estimate the primary endpoint (death or unknown vital status) and TB incidence rates at week 24, and the rates were compared by the z-test. Time to confirmed or probable TB was compared by the log rank test.

Results

Overall, 850 of 1368 candidates were enrolled (Table 1). Of those screened out, 174 (34%) had suspected TB. 566 (67%) had baseline urine samples tested for LAM antigen (283 in each arm); 28 (5%) were positive (Table 2). CD4 counts were lower in those tested vs not tested (median 17 vs 21 cells/mm^3; p=0.002) .

Table 1. Baseline Characteristics by Study Arm

	Empiric (n=424)	IPT (n=426)	All (n=850)
Age (years) - median (IQR)	36 (30-42)	35 (30-42)	36 (30-42)
Male - n (%)	224 (53%)	226 (53%)	450 (53%)
CD4 count (cells/mm^3) - median (IQR)	18 (9-31)	19 (9-33)	18 (9-32)
HIV-1 RNA log10 (cp/mL) - median (IQR)	5.4 (5.0-5.7)	5.3 (4.9-5.7)	5.3 (4.9-5.7)

Table 2. Urine LAM Results at Baseline by Study Arm

LAM Result	Empiric (n=283)	IPT (n=283)	All Participants (n=566)
Negative	260 (92%)	275 (97%)	535 (94%)
Positive	21 (7%)	7 (2%)	28 (5%)
Inconclusive	2 (1%)	1 (1%)	3 (1%)

Of those urine LAM + at baseline, 1 in each arm died and 5 of 21 and 0 of 7 in the Empiric and IPT Arms, respectively, developed TB (Table 3). After exclusion, there were 21 primary endpoints (5%) in each arm (p=0.9); (Figure 2.B).

Results

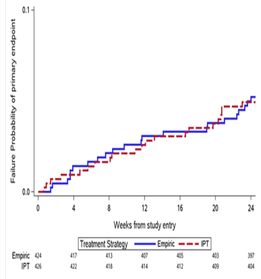


Figure 2.A: Time to primary endpoint (all randomized participants)

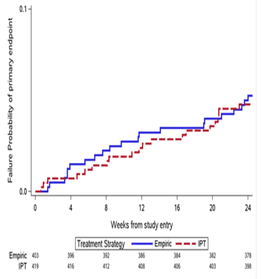


Figure 2.B: Time to primary endpoint (28 with positive baseline LAM excluded)

The incidence of TB remained higher (4.6% vs. 2.0%, p=0.04) and the time to TB remained faster in the Empiric Arm (p=0.04; Figure 3.B.; all results unchanged in competing risk analysis).

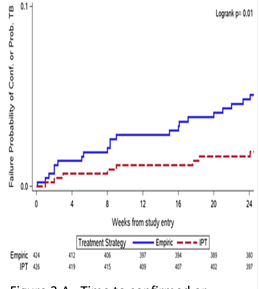


Figure 3.A: Time to confirmed or probable TB diagnosis (all randomized participants)

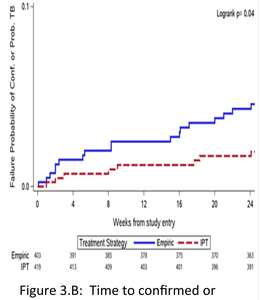


Figure 3.B: Time to confirmed or probable TB diagnosis (28 with positive baseline LAM excluded)

Results

Table 3. TB Diagnoses and Survival Status within 24 weeks by Study Arm and Baseline Urine LAM Status

	Empiric (n=281*)		IPT (n=282*)		All (n=563*)	
	LAM + (n=21)	LAM - (n=260)	LAM + (n=7)	LAM - (n=275)	LAM + (n=28)	LAM - (n=535)
TB	5 (24%)	10 (4%)	0 (0%)	5 (2%)	5 (18%)	15 (3%)
No TB	16 (76%)	250 (96%)	7 (100%)	270 (98%)	23 (82%)	520 (97%)
Death	1 (5%)	13 (5%)	1 (14%)	13 (5%)	2 (7%)	26 (5%)
Alive	20 (95%)	247 (95%)	6 (86%)	262 (95%)	26 (93%)	509 (95%)

* Three participants (2 in Empiric and 1 in IPT) with inconclusive results excluded. None developed TB, but one in Empiric died within 24 weeks.

Table 4. Urine LAM Results at Baseline by Study Arm

LAM Grade	1+	2+	3+	≥4+
Empiric (n=21 of 281)	10	3	4	4
IPT (n=7 of 282)	4	2	0	1

Conclusions

Addition of urine LAM testing yielded few positive tests among outpatients with advanced HIV who had previously been systematically screened for TB.

There was an imbalance across study arms in + pre-ART urine LAM tests. Exclusion of urine LAM+ participants did not alter the lack of an effect of empiric TB treatment on survival or the increased TB progression risk in the Empiric Arm.

Notably, a clinical diagnosis of TB was not made in 7 participants who were baseline urine LAM+ and randomized to the IPT Arm. The prognostic implication of a baseline urine LAM test in similar patient populations needs further study.

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