Prevention of Early Mortality by Presumptive Tuberculosis Therapy Study: An Open Label, Randomized Controlled Trial

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Abstract. Early mortality after initiation of antiretroviral therapy (ART) occurs in 9–39% of patients in sub-Saharan Africa. A significant proportion of deaths are attributable to tuberculosis (TB). Low baseline CD4 T-cell count and low body mass index (BMI) are strongly associated with early mortality. We hypothesized that initiation of ART concurrent with presumptive anti-TB chemotherapy in high-risk patients would reduce mortality within the first 6 months by treating unrecognized TB. From October 2011 to December 2012, ART-naïve, smear-negative participants with a CD4 T-cell count < 50 cells/μL and BMI < 18 kg/m² were randomly assigned to undergo either empiric four-drug anti-TB treatment followed 2 weeks later by efavirenz-based ART (*N* = 23) (ART + TB) or ART only (*N* = 20). This open-label, 1:1 randomized, controlled trial took place in Uganda, Mozambique, and Gabon and was stopped prematurely by the sponsor for slow recruitment. Overall, the 43 participants had a median CD4 of 22 (interquartile range [IQR]: 9–35) cells/μL and a median BMI of 17.5 (IQR: 16.6–18.0) kg/m². The mortality was 14% (95% confidence interval [CI]: 5.3–27.9); two (10.0%) participants (ART-only group), and four (17.4%; ART + TB group). The associated hazard ratio (HR) for all-cause mortality was 1.6 (95% CI: 0.30–8.90). Despite limited enrollment, the study did not suggest that empiric TB treatment in severely immunosuppressed patients with low BMI decreased mortality and, had an HR in the opposite direction than expected. Notably, two participants in the ART + TB group died with autopsy-confirmed drug-induced hepatotoxicity. Improved TB diagnostics sensitive in immunosuppressed patients presenting late to care are urgently needed for more targeted interventions.

INTRODUCTION

In sub-Saharan Africa (SSA), there are 24.7 million people living with human immunodeficiency virus (HIV); 71% of the global total.¹ The scale-up of antiretroviral therapy (ART) in SSA has been massive, with an estimated 11.7 million HIV-infected patients on ART by the end of 2013. Early in the roll-out of life-saving ART, incidence rates of early mortality after ART in SSA ranged from 9% to 39%² and were significantly higher than in developed countries.³ Risk factors for early mortality include low CD4 T-cell count (< 50 cells/μL)^{4,5} with a combined hazard ratio (HR) across studies of 2.5 (95% confidence interval [CI]: 1.9–3.2).⁴ Low body mass index (BMI < 18 kg/m²) has also been associated with early mortality.^{6–13} Unfortunately, only 45% of HIV-infected people know their status, which contributes to the still significant proportion (30%) with a CD4 count < 100 cells/μL at presentation despite raising the CD4 threshold for initiating treatment particularly in men.^{14,15}

Tuberculosis (TB) is a common cause of ART-associated death^{16–18} among HIV-infected people in SSA, particularly in east and southern Africa.¹⁹ In populations with a high prevalence of HIV, there is a high burden of undiagnosed TB.^{12,20} ART is the most effective way to prevent TB in

adults with HIV.²¹ However, TB unmasking often occurs in patients starting ART, suggesting that early reactivation or subclinical disease exists at the time of ART initiation.^{22,23} In highly immunosuppressed patients, TB may be disseminated, smear-negative, and therefore difficult to diagnose with traditional clinical screening, including (sputum) smears.²⁴ In this trial in SSA, the primary objective was to assess the effect of presumptive anti-TB treatment on severely immunosuppressed, underweight, HIV-infected patients starting ART on 6-month mortality and to evaluate anti-TB medication-related toxicity. We hypothesized that initiation of presumptive anti-TB chemotherapy with ART would reduce mortality within the first 6 months.

METHODS

Study design and participants. This was a multicenter, open-label, 1:1 randomized, controlled trial that took place in Gabon, Mozambique, and Uganda. One group was assigned to start efavirenz (EFV)-based ART (within 2 weeks from randomization), and the other group was assigned to TB treatment at randomization, followed by ART initiation within 2 weeks. Recruitment began in October 2011 with HIV-positive men and women, 18 years of age and above, who had CD4 < 50 cells/μL and BMI < 18 kg/m². Because of very slow recruitment accrual, the CD4 threshold was changed to < 75 cells/μL, and the BMI threshold increased to < 19 kg/m² in April 2012.

The participants were recruited from inpatient and outpatient settings and prescreened by assessing age and BMI.

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Participants underwent formal screening with chest X-ray imaging, sputum microscopy for acid fast bacilli, and mycobacterial cultures. Participants were excluded if they were < 18 years of age, BMI ≥ 19 kg/m², had smear-positive pulmonary TB, fulfilled the diagnostic criteria for smear-negative pulmonary or extrapulmonary TB per the 2007 World Health Organization (WHO) recommendations,²⁴ had a history of previous TB treatment of more than 1 month, or a history of using antiretroviral drugs. In addition, participants were excluded who had symptomatic known or suspected underlying liver disease with transaminases > 5 times the upper limit of normal, known or suspected drug resistance to more than one first-line TB drug, cryptococcal meningitis or other severe opportunistic disease, danger signs (respiratory rate > 30 per minute, heart rate > 120 beats per minute, temperature > 39°C, or unable to ambulate), as well as those who were pregnant or breastfeeding, taking other medications incompatible with anti-TB chemotherapy or ART, unable to swallow TB medications, or unable to follow-up for regularly scheduled visits.

Eligible participants were screened with a cryptococcal antigen (CrAg) and if positive, screened for neurologic signs (e.g., headache, neck pain, behavior change, change in mental status, cranial nerve palsy) which, if present, led to exclusion and referral for further treatment of cryptococcal disease. If asymptomatic CrAg positive, then the participant was treated with fluconazole 800 mg daily for 4 weeks after which the participant was randomized. All others were randomized to either initiation of four-drug anti-TB treatment with ART (EFV-based) starting within 2 weeks of randomization, or ART (EFV-based) only (plus pyridoxine 50 mg) given within 2 weeks after randomization. Generic, fixed-dose, EFV-based ART combinations (stavudine [d4T] or zidovudine [AZT]/lamivudine [3TC]/EFV) were administered according to country-specific national guidelines. Anti-TB treatment was the internationally accepted regimen of isoniazid (INH) 5 mg/kg, rifampin (RIF) 10 mg/kg, pyrazinamide 10 mg/kg, and ethambutol 15 mg/kg with pyridoxine 50 mg orally for 8 weeks (intensive phase) followed by INH and RIF (plus pyridoxine 50 mg) for an additional 16 weeks (continuation phase) in fixed-dose combinations whenever possible based on weight. Community or family-based directly observed therapy (CB-DOTS) was taught, encouraged, and enforced where feasible. Self-reported adherence was assessed. Follow-up visits were scheduled every 2 weeks for the first 8 weeks and then monthly thereafter, with targeted medical history, physical examination with particular questions to assess drug toxicity, and visual assessment (using Snellen and Ishihara charts). Women were also assessed for pregnancy. Participants suspected to have TB during follow-up provided sputum for smear and mycobacterial culture, and underwent a repeat chest X-ray. Patients in the ART-only group were switched to ART + TB treatment upon receiving positive pretreatment or in-treatment *Mycobacterium tuberculosis* culture results.

The study took place in Uganda at Mulago National Tertiary Referral Hospital and the Infectious Diseases Institute at Makerere University in Kampala, in Mozambique at Beira Central Hospital, and Ponta Gêa Health Center, Beira, and in Gabon, at the inpatient and outpatient clinics of the Albert Schweitzer Hospital and the General Hospital in Lambaréné. Written informed consent was obtained from

each participant or his or her surrogate. The institutional review board at each participating site approved the study. The study was registered at clinicaltrials.gov (#NCT01417988).

Sample size determination. The effective sample size was 167 patients per group based on a baseline mortality (HIV-infected patient with CD4 cell count < 50 cells/ μ L and BMI < 18 kg/m²) of 30%, an effect size of 2, 20% loss-to-follow-up and pretreatment cultures becoming positive for *M. tuberculosis*, $\alpha = 0.05$, and $\beta = 0.2$. The planned analysis included three interim analyses using an alpha-sparing approach to maintain an overall $\alpha = 0.05$ at the final analysis.

Randomization. Randomization sequences were generated by block randomization stratified by country at the data analysis center in Amsterdam, the Netherlands. Block sizes varied randomly between four and eight. A single treatment allocation was provided to the site by fax, each time an eligible patient was identified. The patient, the treating physician, and the data analyst were aware of the allocated treatment group.

Statistical analysis. The primary outcome was all-cause mortality after 24 weeks of treatment with ART (26 weeks after randomization), assessed by Kaplan–Meier survival analysis with an intention-to-treat approach (all patients randomized). The survival curves of the two treatment groups were compared using a log-rank test. The magnitude of the effect of treatment group was assessed in a Cox Proportional Hazard analysis without additional covariates, given the small number of enrolled patients and outcome events (deaths). The proportional hazard assumption was assessed by plotting the Schoenfeld residuals, and assessing the presence of a non-zero slope.

Secondary endpoints included safety and tolerability of treatment regimens (e.g., frequency of grade 3 or 4 adverse events, frequency of serious adverse events) per Division of AIDS criteria.

RESULTS

Screening and enrollment. Participants were recruited from October 2011 and enrollment was stopped by the sponsor in December 2012 due to poor study recruitment with study activities ending in June 2013, after all enrolled participants had been followed for 26 weeks. The study pre-screened 163 patients, of whom 39 were excluded for age or BMI criteria that were assessed at the routine clinic visit. Of the remaining 124 screened participants, 53 fulfilled a single exclusion criteria and 27 fulfilled at least two criteria (see Figure 1). These included diagnosis with smear-positive TB in 6.5% (8/124) and smear-negative TB in 30.6% (38/124) (Figure 1). In total, 44 participants were eligible for and consented to randomization (26 Uganda, 13 Gabon, and five Mozambique). One patient from Uganda withdrew consent at the randomization visit (and was subsequently not randomized), leaving 43 patients enrolled and randomized (Figure 1). Twenty-three patients were randomized to the ART + TB treatment group while 20 were randomized to the ART-only group. Despite using a block-randomization procedure, the groups were not of equal size. This was due to a fault in the automated message communicating the randomization result to the sites (randomization itself working without problems), resulting in the initial eight patients all receiving a message to be allocated to the ART + TB treatment group. Although corrected quickly,

FIGURE 1. Patient flow diagram.

full restoration of the 1:1 randomization sequence could only have happened at the end of the randomization process of all intended patients. Table 1 shows the baseline characteristics of the enrolled patients. There were no significant differences between the two arms. Overall, 43 participants were recruited with a median CD4 of 22 (interquartile range [IQR]: 9–35) cells/ μ L and the median BMI of 17.5 (IQR: 16.6–18.0) kg/m^2 . Thirty participants were enrolled under the revised inclusion criteria ($\text{CD4} < 75$ cells/ μ L or $\text{BMI} < 19$ kg/m^2).

All-cause mortality. Overall, 14% (6/43) (95% CI: 5.3–27.9) of the participants died; 2/20 (10.0%) in ART-only group, and 4/23 (17.4%) in ART + TB group. The Kaplan–Meier survival curve is shown in Figure 2. The associated HR for all-

cause mortality, comparing the ART + TB treatment group with the ART-only group, was 1.6 (95% CI: 0.30–8.90).

Adverse events. Among the 43 enrolled patients, 329 adverse events were reported. Most of these events were liver enzyme elevations ($N = 42$); of these, the majority were grade 1 (36/42, 85.7%) or grade 2 (4/42, 9.5%). Other frequently reported events were gastrointestinal complaints ($N = 28$), anemia ($N = 19$), leukopenia ($N = 13$), and neuropathy ($N = 16$). Ten patients reported a total of 18 serious adverse events, including death in six patients. The event descriptions for the six deaths are reported in Table 2. Two of the patients in the ART + TB treatment group died with postmortem confirmed evidence of drug-induced hepatotoxicity. In addition, one patient who was on active anti-TB

TABLE 1
Baseline characteristics of the study participants

	Total ($N = 43$)	ART only ($N = 20$)	ART + TB treatment ($N = 23$)
Sex, n (%)			
Male	18 (41.9)	8 (40)	10 (43.5)
Female	25 (58.1)	12 (60)	13 (56.5)
Age, median (IQR)	32.0 (29.0–39.0)	34.0 (29.0–40.5)	32.0 (30.0–37.0)
BMI (kg/m^2), median (IQR)	17.5 (16.6–18.0)	18.0 (17.1–18.6)	16.7 (15.9–17.8)
WHO staging, n (%)			
1	1 (2.3)	0	1 (4.3)
2	13 (30.2)	8 (40)	5 (21.7)
3	19 (44.1)	8 (40)	11 (47.8)
4	10 (23.3)	4 (20)	6 (26.1)
CD4 ⁺ (cells/ mm^3), median (IQR)	22 (9–35)	20 (8–33)	23 (13–35)
Hemoglobin (g/dL), median (IQR)	9.9 (8.5–11.5)	10.7 (8.4–12.1)	9.7 (8.6–10.4)

ART = antiretroviral therapy; BMI = body mass index; IQR = interquartile range; TB = tuberculosis; WHO = World Health Organization.

FIGURE 2. Survival analysis. Kaplan–Meier survival curves of the two treatment groups were compared by a log-rank test. ART-only group shown as a solid line and ART + TB group in the dashed line. ART = antiretroviral therapy; TB = tuberculosis.

treatment in the same group had postmortem evidence of disseminated TB at the time of death.

DISCUSSION

This trial did not reach the required sample size to answer the question of whether presumptive TB treatment of HIV-infected patients with low CD count and low BMI prevents early mortality while on ART. The results showed a HR in the opposite direction than expected. Given the consecutive enrollment of patients at multiple sites, it is unlikely that this HR is a severely biased estimate. This is the third study that has examined the effect of empiric TB treatment in severely immunosuppressed HIV-infected patients. In the REMEMBER (Reducing Early Mortality and Early Morbidity by Empiric Tuberculosis Treatment Regimens) open-label trial, HIV-infected outpatients with a CD4 < 50 cells/ μ L were individually randomized to receive either ART and preemptive TB therapy (“empiric”) or ART and INH prophylactic treatment (“IPT”).²⁵ Empiric TB therapy did not reduce mortality at 24 weeks compared with IPT, with no difference in adverse events across arms. In the TB Fast Track cluster randomized trial,²⁶ outpatients with CD4 $\leq$ 150 cells/ μ L were triaged according to an algorithm that included urine lipoarabinomannan screening, clinical symptoms, hemoglobin (< 10 g/dL), and BMI ($\leq$ 18.5 kg/m²) and, if any of the three criteria were positive, were considered at high risk for TB and empirically treated. This study also found no difference in 6-month all-cause mortality rates (intervention versus control, 19 versus 21.5 per 100 person-years) with and adjusted rate ratio of 0.87 (95% CI: 0.61–1.24). Our participants were the most ill, with all having at least one poor prognostic factor as defined in the REMEMBER trial, which had only 33% in that stratification category.

Several factors contributed to poor participant recruitment in our study. First, clinician attitudes in urban settings and thresholds for empiric TB treatment initiation in patients with low CD4 changed during the course of our clinical trial.²⁷ These treatment decisions were likely driven by data from SSA showing TB as a key cause of mortality after ART initiation^{2,4,28} and high rates of prevalent TB in patients initiating ART in a high-burden setting. In this study, 6.5% of the screened patients had smear-positive TB before ART, slightly lower than previously reported rates of prevalent TB in HIV-infected patients in SSA (15–25% in South Africa^{29,30} and 10–15% for other sub-Saharan African countries^{23,31}). However, 30.6% were diagnosed with smear-negative TB, corroborating an unusually high rate of empiric TB treatment initiation. Second, WHO prequalification and endorsement of Xpert MTB/RIF during the study further increased the rate of detection of sputum smear-negative patients at the time of ART initiation.^{32,33} New diagnostics such as urinary lipoarabinomannan (LAM)^{34–36} and Xpert MTB/RIF or Ultra³⁷ may obviate the need for empiric treatment among hospitalized patients particularly if higher sensitivity can be achieved with a combination of LAM point-of-care (POC) and Xpert rapid diagnostics. A pragmatic four-country randomized controlled trial in 2,659 hospitalized adults suspected to have TB–HIV coinfection (48% on ART with a mean CD4 of 84 (IQR: 26–208) cells/ μ L showed a statistically significant effect of LAM testing on the proportion of patients starting anti-TB treatment, 52% versus 47% ($P = 0.024$) participants, and on 8 week mortality (adjusted HR: 0.81, CI: 0.69–0.95, $P = 0.009$).³⁸

The rationale of our trial was based on available epidemiologic data in 2010; however, the context changed over the period of the study, especially in the shifting demographics of HIV patients in urban settings. With increasing availability

TABLE 2
Causes of mortality

Group	Cause of death narrative
ART only	28 year-old woman (CD4 = 31 cells/mm ³ , BMI = 17 kg/m ²) was enrolled after recent discharge from the hospital where she was noted to be febrile 39°C and was treated empirically with erythromycin and metronidazole. Eight days after enrollment, she returned with generalized hypertonia with only elevated cerebrospinal fluid protein (60 mg/dL) and serum hyponatremia (119 mmol/L) and was diagnosed with presumed viral meningoencephalitis with SIADH. Two days later, she showed improvement in her hyponatremia and clinical condition, and she was started on ART. She then died 2 days later
ART only	45 year-old woman (BMI 18.7 kg/m ²) presented with diarrhea 14 days after enrollment and started on ART for which she was given loperamide. Liver function tests were normal with a CBC notable for hemoglobin 9.3 g/dL. Patient then missed her 2-month follow-up and was tracked at home and found to be exhausted and bed bound. She had discontinued her ART 4 weeks after initiation. Another home visit 3 weeks later showed a dehydrated lethargic patient with watery diarrhea and anorexia. Patient refused to be hospitalized and died at home
ART + TB	38 year-old woman admitted to hospital 2 months after enrollment and presented with severe anemia (hemoglobin 5.8 g/dL), thrombocytopenia (28,000 cells/mm ³), and leukopenia (700 cell/mm ³) in the setting of several weeks of asthenia. Despite broad spectrum antibiotics in addition to her ART and anti-TB regimen, she died on hospital day 2. Post-mortem examination showed pulmonary and disseminated tuberculosis.
ART + TB	22 year-old woman (CD4 = 23 cell/μL, BMI = 14.7 kg/m ²) with initially low WBCs (2,000 cell/mm ³), hemoglobin (7.8 g/dL) presented to a scheduled study visit 14 days after initiation of anti-TB drugs with diarrhea, anorexia and vomiting, fever 37.7°C, jaundice and tender hepatomegaly (AST = 111 U/L, ALT = 127 U/L, total bilirubin = 6.6 mg/dL), and pancytopenia. Two days after discontinuation of drugs and hydration, she improved clinically. She was found dead on hospital day 3. Drug-induced hepatotoxicity confirmed by postmortem examination with a 2,200-g deep yellow liver and bone marrow evidence of pancytopenia
ART + TB	32 year-old woman (CD4 = 14 cells/mm ³ , BMI = 16.4 kg/m ²) with hypoalbuminemia, and leukopenia (1,500 cells/mm ³) admitted to the hospital 24 days after enrollment and initiation of anti-TB meds with diarrhea and drug-induced hepatotoxicity (AST = 131 U/L, ALT = 124 U/L, bilirubin = 7.2 mg/dL). Despite discontinuation of her anti-TB medications, broad-spectrum antibiotics and intravenous fluids and improvement in her transaminases, the patient died of pancytopenia, acute renal injury (creatinine = 4.9 mg/dL), electrolyte derangement including severe hypokalemia (1.5 mmol/L), and progressive neurologic decline 30 days after admission. Postmortem examination was notable for jaundiced liver of 1,440 g, edematous colon, and consolidation of the lungs
ART + TB	32 year-old woman enrolled in the study and developed diarrhea 1 week after anti-TB meds initiated. ART initiated at week 5. Eight weeks after enrollment, she developed worsening diarrhea and leukopenia (WBC = 2.7×10^3 cells/mm ³ decreasing to 1.12×10^3 cells/mm ³ 1 week later) for which she was hospitalized, and then cough. Ultimately, she died despite intravenous fluids and antibiotics

ALT = alanine transaminase; ART = antiretroviral therapy; AST = aspartate transaminase; BMI = body mass index; CBC = complete blood count; SIADH = syndrome of inappropriate antidiuretic hormone secretion; TB = tuberculosis; WBC = white blood cell.

of ART, countries with a more mature epidemic that received external funding for HIV prevention care and treatment in the first wave of funding had a lower proportion of ART eligible patients who fulfilled the Prevention of Early Mortality by Presumptive Tuberculosis Therapy inclusion criteria, particularly low BMI. In rural areas, patients who fulfilled these inclusion criteria existed, but rural sites are challenging for clinical trial follow-up. In a recently published observational cohort study of patients initiating ART in rural Uganda that occurred in the same period, the mean BMI was relatively low at 20.6 kg/m².³¹

The proportion of patients who died (14%) was lower than previously reported for this patient population. However, the most ill patients with danger signs were eliminated through extensive screening (including cryptococcal antigen and preenrollment work up). Despite this, we reported a high risk of toxicity, particularly hepatotoxicity, in the relatively small number of participants recruited. Although the majority of these did not require intervention, two participants in the ART-TB arm died with autopsy evidence of hepatotoxicity. The risk of toxicity of presumptive TB therapy in late-stage HIV disease thus underscores the need for improved TB diagnostics in this population.

Our study was underpowered to definitively test whether empiric anti-TB treatment in severely immunosuppressed, malnourished patients can prevent early mortality. Together with the other two trials of empiric TB treatment, there is not a clear benefit to empiric TB treatment in severely immunocompromised HIV-infected patients who initiate ART and prescreening is cumbersome. Improved TB diagnos-

tics available at POC remains an urgent priority in severely immunosuppressed HIV patients who present late to care.

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