Incidence and Predictors of Mortality and the Effect of Tuberculosis Immune Reconstitution Inflammatory Syndrome in a Cohort of TB/HIV Patients Commencing Antiretroviral Therapy

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Background: Tuberculosis-HIV (TB-HIV) coinfection remains an important cause of mortality in antiretroviral therapy (ART) programs. In a cohort of TB-HIV–coinfected patients starting ART, we examined the incidence and predictors of early mortality.

Methods: Consecutive TB-HIV–coinfected patients eligible for ART were enrolled in a cohort study at the Mulago National Tuberculosis and Leprosy Program clinic in Kampala, Uganda. Predictors of mortality were assessed using Cox proportional hazards analysis.

Results: Three hundred and two patients [median CD4 count 53 cells/μL (interquartile range, 20–134)] were enrolled. Fifty-three patients died, 36 (68%) of these died within the first 6 months of TB diagnosis. Male sex [hazard (HR): 2.19; 95% confidence interval (CI): 1.19 to 4.03; $P = 0.011$], anergy to tuberculin skin test [HR: 2.59 (1.10 to 6.12); $P = 0.030$], a positive serum cryptococcal antigen result at enrollment (HR: 4.27; 95% CI: 1.50 to 12.13; $P = 0.006$) and no ART use (HR: 4.63; 95% CI: 2. 37 to 9.03; $P < 0.001$) were independent predictors of mortality by multivariate analysis. Six (10%) patients with TB immune reconstitution inflammatory syndrome died, and in most, an alternative contributing cause of death was identified.

Conclusions: Mortality among these TB-HIV–coinfected patients was high particularly when presenting with advanced HIV disease and not starting ART, reinforcing the need for timely and joint treatment for both infections. Screening for a concomitant cryptococcal infection and antifungal treatment for patients with cryptococcal antigenemia may further improve clinical outcome.

Key Words: HIV, immune reconstitution, mortality, predictors, tuberculosis

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INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality in HIV-infected patients in sub-Saharan Africa and Asia.[1] The TB epidemic in sub Saharan Africa is fuelled by the HIV epidemic and limited resources for adequate control.[2] Increasing access to antiretroviral therapy (ART) has been associated with improved clinical outcomes in patients with TB-HIV coinfection. This is in contrast to the pre-ART era when dual TB-HIV infection was associated with rapidly progressive disease with poor outcomes.[3,4] Early mortality however persists in TB-HIV–coinfected patients with advanced HIV disease and comorbid opportunistic infections despite wide availability of ART.[5–7] The Starting Antiretroviral Therapy at 3 Points in Tuberculosis trial found a 56% reduction in mortality among patients who started ART during TB treatment versus after completion of TB treatment.[8] This further reinforces the notion that ART should not be postponed in patients with HIV-TB coinfection.[9] Recently the CAMbodia Early versus Late Initiation of ART trial demonstrated an improved survival benefit of ART initiation within 2 weeks of TB treatment compared with 8 weeks.[10] Despite WHO guidelines recommending ART start at CD4 counts <350

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The members of TB-IRIS study group are listed in Appendix I.
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cells per microliter in pulmonary tuberculosis (PTB) patients[11] and increasing evidence to start ART early, in resource-limited settings, ART initiation in TB-HIV–coinfected patients is often delayed due to limited access to ART. Concerns of drug–drug interaction, drug toxicity, the tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) and adherence to multiple therapeutic regimens remain a hindrance to early commencement of ART. Reported risk factors for mortality in TB-HIV–coinfected patients include the following: low hemoglobin and low CD4 count[12]; low body mass index (BMI) and increased age[7]; gastrointestinal TB and multidrug-resistant TB.[13] In our cohort of TB-HIV–coinfected patients commencing ART, we determined the incidence and predictors of mortality up to 2 years after start of TB treatment and the causes of mortality in patients with TB-IRIS.

METHODS

Study Setting and Population

Consecutive TB-HIV–coinfected patients, qualifying for ART initiation according to Ugandan national ART treatment guidelines (CD4 lymphocyte count <250 cells/μL),[14] were enrolled in a cohort to study TB-IRIS at the Mulago National Tuberculosis and Leprosy Programme clinic (Kampala, Uganda). Recruitment of patients was a 2-stage process: patients first provided informed consent for screening and were assessed for study inclusion/exclusion criteria. If eligible, they were consented for enrollment into the cohort study. Study eligibility criteria included the following: (1) adult (>18 yrs) living within a 20-km radius of the hospital, (2) confirmed TB-HIV infection according to WHO guidelines [sputum smear positive or negative PTB or extrapulmonary tuberculosis (EPTB)],[15] (3) starting TB treatment or having taken TB treatment for less than 2 months, and (4) eligible for ART (CD4 count <250 cells/μL). Patients with liver transaminase (alanine and/or aspartate transaminases) elevation greater than 5 times the upper limit of normal, renal failure (a serum creatinine greater than 1.2 mg/dL and suggestive clinical signs and symptoms), and severe anemia (haemoglobin <70 g/L) were excluded. At screening, an HIV test and a CD4 lymphocyte count measurement (Becton Dickinson) were performed. Relevant specimens (sputum, lymph node aspirate, pleural effusion) were examined by Ziehl Neelsen stain and Lowenstein Jensen (LJ) culture for *Mycobacterium tuberculosis*. For patients already on TB treatment, investigations were repeated for confirmation of TB diagnosis, but prior results (available from charts and TB treatment cards) were also considered. Patient characteristics (age and sex), source of patient referral (health centre or hospital), BMI, hemoglobin and tuberculin skin test (TST) (TUBERCULIN PPD RT 23 SSI, Statens Serum Institut, Copenhagen) measurement were recorded at study enrollment. A TST was considered positive when a skin induration of diameter greater than 5 mm appeared at the TST placement site within 48–72 hours of administration. A TST was repeated at months 2 and 6 after ART initiation, if the baseline or month 2 TST results were negative, respectively. A complete physical examination was performed to exclude other opportunistic infections. Testing for serum cryptococcal antigen (CrAG, Wampole Laboratories, Princeton, NJ) was done before the start of ART. TB treatment consisted of a standard fixed-dose combination with 2 months of intensive phase composing isoniazid (H), ethambutol (E), rifampicin (R), and pyrazinamide (Z) followed by either rifampicin and isoniazid for 4 months or a combination of ethambutol and isoniazid for 6 months. The first-line ART regimen was stavudine or zidovudine plus lamivudine with efavirenz. Patients with a positive serum CrAG and no abnormal neurological signs or symptoms received fluconazole 400 mg daily. All patients were offered cotrimoxazole 960 mg daily as prophylaxis, and all patients received daily pyridoxine 50 mg during TB treatment.

Patients were followed-up at 2, 4, 8, 12, and 24 weeks and every 3 months thereafter. At each visit, patients underwent a physical examination, and laboratory investigations were performed (complete blood count (CBC), aspartate and alanine transaminases; and serum creatinine). CD4 lymphocyte count testing was repeated at 6 and 12 months after the start of ART. Patients were also evaluated for response to TB treatment according to standard National TB treatment guidelines.[16] Sputum smear microscopy for acid-fast bacilli and culture on LJ media was repeated at months 2, 5, and at TB treatment completion (either month 6 or 8 depending on the TB regimen). Chest X-ray was repeated if the patients' clinical condition worsened; and/or at the completion of TB treatment. Patients who developed new or worsening symptoms were assessed for TB-IRIS using a standardized questionnaire based on the International network for the study of HIV-related IRIS criteria,[17] and examination for acid-fast bacilli and LJ culture were done on sputum or other samples (lymph node or pus aspirate) and mycobacterial blood culture to exclude alternative diagnoses. Patients who fulfilled clinical criteria for TB-IRIS but presented after 3 months of ART were classified as late onset TB-IRIS. Study participants who did not come for scheduled visits were traced using telephone contact (of the patient or a close relative or associate) or home visits for those who did not have phone contacts.

Ethical Approval

This study was approved by the Makerere University Faculty of Medicine Ethics committee, Mulago Hospital Research committee; the committee of Medical ethics from the University of Antwerp and the Institute of Tropical Medicine, Antwerp, Belgium; and the Uganda National Council of Science and Technology. Written informed consent was obtained before screening for and enrollment into the study.

Study End Points and Definitions

We considered the date of TB treatment start as the baseline date for the analysis of mortality. The primary study end point was all-cause mortality during the total follow-up until the end of the study. Cause of death were determined by 2 investigators (R.C. and W.W.) after review of the study charts, hospital discharge records, and interview of next of kin in case death occurred at home.

Statistical Analysis

Data were analyzed using STATA version 11.1 (College Station, TX). Patient enrollment took place from December

17, 2007, to December 31, 2009. The maximum follow-up period was 2 years after ART start. Patients were followed-up until death, study withdrawal, loss to follow-up or administrative censoring at the end of the study (the July 31, 2010). Information about vital status and ART status of participants who had been enrolled but later transferred out of the study area was obtained by telephone. We summarized baseline characteristics of all patients as means, median, and percentages. The incidence of mortality (number of cases per 100 person-years) during the first 3 months, 3–6 months, 6–9 months, and after 9 months from the start of TB treatment were estimated using survival analysis. We used Kaplan–Meier model with log rank tests to compare survival stratified by ART use, and studied the predictors of mortality using multivariate Cox proportional hazard regression analysis. Baseline predictor variables included age, sex, BMI, CD4 lymphocyte counts, and hemoglobin at enrollment; type of TB (PTB, EPTB), TST reaction (classified as positive or negative), treatment with ART, serum CrAG, and WHO clinical stage. The effect of ART was analyzed as time-varying covariates. The final multivariable model was arrived at using backward selection with variables that were associated with mortality at univariate analysis ($P \leq 0.2$) and variables that are biologically plausible (BMI and TB category) and have been reported to be associated with increased mortality.[18–21] Nested model were tested for goodness-of-fit by the log likelihood ratio test, which was deemed significant at the $P = 0.05$ level. Scaled Schoenfeld residuals were tested to ensure the final model fulfilled Cox proportional hazards assumption.

RESULTS

Study Population

We assessed 618 suspected TB-HIV–coinfected patients for study eligibility, 239 of whom were not eligible: 68 did not have TB, 66 had higher CD4 counts than recommended for ART initiation, 33 refused study participation, 23 had severe anemia, 12 did not return for enrollment, 10 were HIV negative, and 9 lived outside the study area. Seven patients were already on ART, 4 died before enrollment, 3 patients were transferred out, 2 patients had liver disease, 1 defaulted TB treatment, and 1 was pregnant. Of the remaining 379 patients who were eligible, 77 were excluded for various reasons (Fig. 1) and 302 participants were enrolled. One patient withdrew from the study before starting TB treatment and was excluded from the analyses. Baseline characteristics of the enrolled patients are shown in Table 1. Two hundred and thirty (76%) patients were diagnosed with PTB only, 58 (19%) EPTB only, and 14 (5%) with both PTB and EPTB. Seven participants (2.3%) were positive for serum CrAG.

Patients were followed up for a median of 393 days [interquartile range (IQR): 206–576 days]. Two hundred and seventeen patients (72%) completed study follow-up and 131 (43%) had at least 12 months of follow-up; 53 patients (17%) died, 12 (4%) declined further study participation, and 20 (7%) were lost to follow-up. Two hundred and fifty-eight participants started ART. The median (IQR) time to starting ART was similar for patients who survived, 46 days (IQR: 29–65 days), and those who died, 42 days (IQR: 29–58 days) (Table 2).

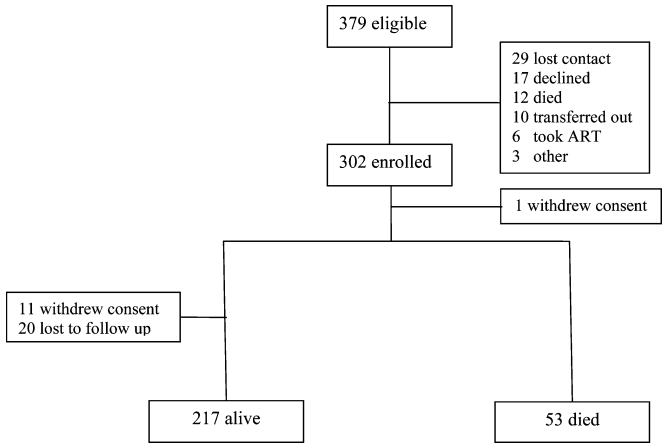

FIGURE 1. Patients with TB–HIV coinfection eligible for ART.

All Cause and Cause-Specific Mortality

The total study follow-up duration was 330.9 person-years. The overall mortality rate was 16.0 per 100 person-years of follow-up. Mortality rates were 33.9 [95% confidence interval (CI) 22.7 to 50.5] per 100 person-years during the first 3 months, 19.0 (95% CI: 10.8 to 33.4) per 100 person-years between 3 and 6 months, 17.0 (95% CI: 8.8 to 32.7) per 100 person-years from 6 to 9 months, and 5.6 (95% CI: 2.8 to 11.1) per 100 person-years of observation after 9 months, respectively. Twenty-three (43%) deaths occurred in the first 3 months [12 of 23 (52%) before starting ART], and 36 (68%) deaths occurred within the first 6 months.

A contributing cause of death was identified in 33 (62%) patients, the details of which are summarized in Table 3. A postmortem was only done in the patient with a clinical diagnosis of renal failure and demonstrated disseminated TB involving the lungs, liver, spleen, and kidneys.

Fifty-three (20.5%) patients of the 258 who started ART developed paradoxical IRIS according to the International network for the study of HIV-related IRIS definition[17]; an

TABLE 1. Baseline Characteristics of HIV–TB-Coinfected Patients Eligible for ART

Characteristic	Number of Participants, n = 302
Mean age (yrs), (SD)	34.4 (8.5)
Females, (%)	135 (45)
Body Mass Index (kg/m^2), (IQR)*	18.7 (17.1–20.3)
Mean hemoglobin (g/L), (SD)	93 (22)
Median CD4 count (cells/μL), (IQR)	53 (20–134)
Hospitalized, (%)	74 (25)
Extrapulmonary TB, (%)	72 (24)
TST result negative, (%)†	222 (74)
WHO clinical stage IV, (%)	77 (26)

*Nine patients had missing values for body mass index.
†Two patients had missing values for TST; 78 (26%) patients had a positive TST result.

TABLE 2. Time to the Start of ART by Vital Status

Time to the Start of ART (Days)	Number (%) of Participants Who Survived, Total = 228	Number (%) of Participants Who Died, Total = 30
Less than or equal to 30	70 (31)	10 (33)
31–60	92 (40)	13 (43)
Greater than 60	66 (29)	7 (24)

additional 8 patients had late-onset TB-IRIS. Six (10%) patients diagnosed with TB-IRIS died. In 5 of them, there was a contributing cause of death unrelated to TB-IRIS such as gastroenteritis (1), pneumonia (1), intestinal obstruction (1), advanced TB disease (1), and respiratory failure (1). Two other patients died of Kaposi sarcoma-IRIS.

Predictors of Mortality

Survival of patients was significantly better when ART was used (log rank test, $P = 0.001$; Fig. 2). In univariate analysis, predictors of mortality included male sex, being hospitalized, a negative TST, a positive serum CrAG at enrollment, and not starting ART (Table 4). In multivariable analysis, male sex (HR: 2.19; 95% CI: 1.19 to 4.03; $P = 0.011$), a negative TST (HR: 2.59; 1.10 to 6.12; $P = 0.030$), a positive serum CrAG at enrollment (HR: 4.27; 95% CI: 1.50 to 12.13; $P = 0.006$), and not starting ART (HR: 4.63; 95% CI: 2.37 to 9.03; $P \leq 0.001$) remained statistically significant (Table 4).

A total of 7 patients with a median CD4 lymphocyte count of 15 cells per microliter (IQR: 3–37) had a positive serum CrAG at enrollment. All started fluconazole 400 mg daily and 4 were able to start ART. Four of the patients who had a positive serum CrAG died: 1 from cryptococcal meningitis, 1 from gastroenteritis with severe dehydration, 1 from intestinal obstruction, and 1 from progressive TB disease. The patient who developed cryptococcal meningitis was on fluconazole but not yet on ART. Of the remaining 3 patients, 2 completed follow-up, and 1 was lost to follow-up after requesting transfer to another clinic.

TABLE 3. Contributing Causes of Death in 33 Patients With TB and HIV Coinfection in Whom a Cause of Death was Identified

Contributing Cause of Death	Number (%)
Gastroenteritis	7 (21.2)
Severe anaemia	4 (12.1)
Kaposi's sarcoma*	6 (18.2)
Tuberculous meningitis	3 (9.1)
Pneumonia	2 (6.1)
Respiratory failure	2 (6.1)
Cryptococcal meningitis	1 (3.0)
Cerebral infarct	1 (3.0)
Headache of undetermined origin	1 (3.0)
Pulmonary embolism	1 (3.0)
Intestinal obstruction	1 (3.0)
Peritonitis	1 (3.0)
Hepatic failure	1 (3.0)
Renal failure	1 (3.0)
Cor pulmonale associated with advanced TB	1 (3.0)

*Two of the patients with Kaposi sarcoma had Kaposi sarcoma immune reconstitution.

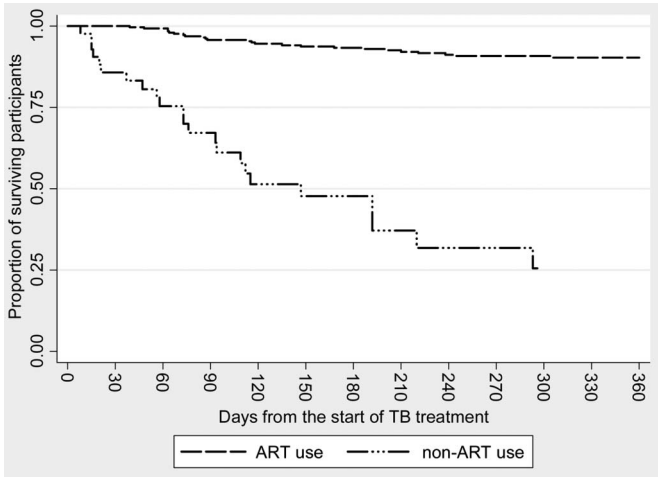

FIGURE 2. Kaplan–Meier curve showing survival of 302 patients with HIV–TB coinfection with or without ART use.

DISCUSSION

In this cohort of HIV-TB–coinfected patients eligible for ART, we documented high rates of early mortality. Two-thirds of the deaths occurred within the first 6 months after TB diagnosis. This is similar to what has been reported previously.[6,7,22]

No ART use was the main risk factor for increased mortality. Several retrospective studies and clinical trials have reported the benefit of ART in reducing HIV-associated mortality.[13,23,24] This led to the revision of the World Health Organization guidelines for initiation of ART in all TB-HIV–coinfected patients regardless of their CD4 lymphocyte count.[25] Unfortunately, in Africa, still many patients present late for TB treatment, with advanced immune deficiency and without prior knowledge of their HIV status. This is illustrated in our cohort where the median nadir CD4 lymphocyte count was 53 cells per microliter. This low CD4 count may also reflect delayed referral for ART by the physicians in charge of TB treatment. In most hospitalized patients, ART could only be started after discharge and referral to the TB/HIV clinic. Many patients consequently deteriorate although on TB treatment because they miss an early opportunity for concurrent HIV care. In primary care clinics in Kampala, there is a low uptake of HIV testing among patients diagnosed with TB except where an "opt-out" approach is used.[26] In our clinic, an "opt-out" approach was used, and all patients with TB were routinely offered HIV testing, and previous studies in this and other hospitals indicate HIV testing acceptance rates of 95%–98%.[27,28]

Male participants were almost 3 times more likely to die than females. In a community-based surveillance study, Zwang et al[3] found higher PTB-HIV death rates in males

TABLE 4. Predictors of Mortality in TB/HIV Patients Eligible for ART: Cox Proportions Hazards Analysis

Characteristic	Univariate HR, (95% CI)	*P*	Adjusted HR, (95% CI)	*P*
Age				
≥40 versus, yrs	1.24 (0.72 to 2.14)	0.438	—	—
<40 years	1		—	—
Sex				
Males	1.84 (1.02 to 3.31)	0.043	2.19 (1.19 to 4.03)	0.011
Females	1		1	
BMI (kg/m^2)*				
<18.5	1.12 (0.65 to 1.93)	0.685	—	—
≥18.5	1		—	—
Recruitment site				
In-patient	2.10 (1.19 to 3.70)	0.010	—	—
Outpatient	1		—	—
Hemoglobin (g/L)				
<100	1.52 (0.83 to 2.77)	0.173	—	—
≥100	1		—	—
CD4 counts (cells/μL)				
<50	1.70 (0.97 to 2.95)	0.062	—	—
≥50	1		—	—
TB category				
EPTB	0.92 (0.48 to 1.75)	0.792	—	—
PTB	1		—	—
Tuberculin skin test				
Negative	2.84 (1.21 to 6.67)	0.016	2.59 (1.10 to 6.12)	0.030
Positive	1		1	
ART†				
No ART use	5.39 (2.80 to 10.38)	<0.001	4.63 (2.37 to 9.03)	<0.001
ART use	1		1	
TB-IRIS†				
Developed TB-IRIS	0.61 (0.26 to 1.44)	0.257	—	—
No TB-IRIS	1		—	—
Serum CrAG*				
Positive	4.40 (1.58 to 12.22)	0.005	4.27 (1.50 to 12.13)	0.006
Negative	1		1	

*Two hundred ninety-three patients had complete BMI results and 288 patients had complete serum CrAG results.

†Time-varying covariates.

‡Adjusted for age, BMI, recruitment site, hemoglobin, CD4 lymphocyte count, TB category.

and in older age groups. A study by Cornell et al[29] in a South African ART program found that male patients presented late and with advanced disease compared with women. This was associated with higher early mortality. Thus higher mortality in males coinfected with TB-HIV may likely be attributed to differences in health-seeking behavior, although biological differences cannot be ruled out.

In our study among patients who started ART, 10% of the patients who developed TB-IRIS died, and in most cases, there were other non-IRIS–related contributing causes of death. This is consistent with previous reports that indicate life-threatening TB-IRIS is uncommon.[8,10,30–32] A systematic review by Muller et al[33] concerning the incidence and outcome of IRIS which included information on 54 cohorts, of which 23 had data available on deaths, reported a mortality of only 3% in patients with TB-IRIS.

Cryptococcal antigenemia was associated with a 4-fold increase in the risk of dying. This is consistent with the 7-fold increase in the risk of early mortality reported in a rural Ugandan cohort of patients with HIV infection and asymptomatic cryptococcal antigenemia commencing ART.[34] In another Ugandan urban cohort of patients where serum CrAG was systematically measured before ART, fluconazole treatment in patients with a positive serum CrAG and a CD4 lymphocyte count ≤100 cells per microliter was reported as being cost-effective.[35] The cost to test and treat to prevent 1 death from cryptococcal meningitis was $299.[35]

Some risk factors for mortality such as low CD4 lymphocyte count,[7,20] low BMI,[18,36] low hemoglobin level,[37] and EPTB[20] were not identified in our study. This may have been because most of our study participants had a low CD4 lymphocyte count, a low BMI, and because patients with very low hemoglobin were excluded from the study. Anergy to TST was associated with a 2-fold increase in mortality, which is consistent with previous reports[38,39] and likely a reflection of the advanced CD4 T-cell depletion.[40]

Our study had some limitations. First, 20% of eligible patients with TB-HIV coinfections were not enrolled. Of patients enrolled, 20 (7%) were lost to follow-up; some of whom may have died. Second, in most patients, the cause of death was unknown because postmortem examination was done in only 1 patient.

In conclusion, despite the availability of ART, many of our TB-HIV–infected patients presented with advanced HIV disease. High mortality occurs as patients wait to access ART. Male gender and cryptococcal antigenemia were recognized as additional independent risk factors for early death. Early initiation of ART in patients coinfected with TB-HIV, routine screening for cryptococcal antigenemia in patients with a CD4 count < 250 cells per microliter, and antifungal treatment for those identified to be positive may reduce the risk of death.

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