Original article

Risk factors for mortality among HIV-positive patients with and without active tuberculosis in Dar es Salaam, Tanzania

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Background: The aim of this study was to describe risk factors for mortality and clinical characteristics of HIV-infected patients with and without tuberculosis (TB) coinfection.

Methods: A cohort of HIV-infected patients with CD4+ T-cell counts of ≤200 cells/μl was recruited, consisting of 255 HIV-infected patients without active TB and 231 patients with active TB. All received a well-supervised treatment with an efavirenz-based HAART, and those coinfected with TB received appropriate anti-TB treatment. They were followed up for 48 weeks after HAART initiation.

Results: Common presenting symptoms in HIV-only patients were fever (36.5%), headache (34.5%), skin rash (34.5%) and weight loss (32%), while in HIV–TB patients the symptoms were weight loss (58%), cough (57.6%), night sweats (44.6%) and fever (34.2%). HIV–TB patients had significantly lower body mass index, Karnofsky scores and haemoglobin levels compared to those infected with HIV only, despite similar baseline CD4+ T-cell counts. Overall, 12 (4.7%) HIV patients developed TB and 7 (3%) HIV–TB patients had worsening of their TB symptoms during the study period. Mortality was similar in the two groups, being 10.9% (16 deaths per 100 person years) and 11.3% (17 deaths per 100 person years) in HIV-only and HIV–TB patients, respectively. Overall, more males (13.1%) died compared to females (9.6%). Predictors of mortality were presence of oral candidiasis, Kaposi's sarcoma, low Karnofsky score, and low baseline white blood cell and CD4+ T-cell counts.

Conclusions: The outcomes following well-supervised treatment of HIV–TB patients are similar to those in patients with HIV alone. Predictors of mortality were those of advanced disease.

Introduction

The current prevalence of HIV/AIDS in Tanzania is estimated to be 5.7% among adults aged 15–49 years, with an estimated population of 2.3 million people living with HIV/AIDS. This places Tanzania in the 6th place among the countries with HIV infections in the world [1,2]. There are more women (6.8%) being affected as compared to men (4.7%) and the primary mechanism for HIV transmission is unprotected heterosexual intercourse, which accounts for 80% of all the new infections [3,4].

Tanzania ranks 14th in the global pandemic for tuberculosis (TB) based on annual incidence rates of all forms of TB [5]. Current data shows that approximately 52% of TB patients are coinfected with HIV, and death rates have increased among these patients, which makes it difficult for the National TB Programme to reach the World Health Organization (WHO) cure rate target of 85%. Cotreatment of these two diseases is inevitable, despite clinician's concerns on drug–drug interactions, overlapping toxicities, immune reconstitution

inflammatory syndrome and suboptimal adherence resulting from a higher pill burden [6–8].

HIV and TB act synergistically to cause an excess in morbidity and mortality [9]. To address this, Tanzania recommends HIV screening for all TB patients, regular TB screening for HIV patients, and starting all patients with a CD4+ T-cell count <200 cells/μl on HAART, although a revision of this recommendation is ongoing, which will require that HIV-positive patients are started on HAART at a CD4+ T-cell count ≤350 cells/μl. With improved access to HAART after a nationwide scale-up of free HAART in 2004, and a direct observed therapy (DOT) programme for TB, the morbidity and mortality in patients coinfected with HIV and TB is expected to decrease. Many studies show that concurrent use of HAART and anti-TB treatment significantly reduces morbidity and mortality in these patients [10–12,13].

Mortality of HIV–TB-coinfected patients has been reported to be mostly during TB treatment, ascribing the death mainly due to either TB or HIV-associated conditions other than TB [14–16,17]. A previous study in Tanzania showed a mortality rate of 30% in patients coinfected with HIV and TB in the absence of HAART, and these deaths were associated with HIV infection, low CD4+ T-cell counts, low Karnofsky scores and high viral loads [18]. Other studies also show that the majority of the deaths occur within 3 months of starting HAART, with predictors of mortality being anaemia, severe malnutrition, male sex, lower baseline CD4+ T-cell counts and a more advanced clinical stage of infection [19–22].

CD4+ T-cell counts dramatically alter the clinical presentation of TB because cell-mediated immunity is essential to host defence against mycobacterial infection. With progressive immunodeficiency, patients with pulmonary TB exhibit atypical radiological presentation and a negative sputum smear as acid fast bacilli (AFB) density falls with decreasing CD4+ T-cell count [23–25]. Furthermore it has been shown that unmasking of TB was common in the first 6 months after HAART initiation and the median time from HAART initiation to worsening of TB in patients on concurrent active anti-TB therapy was 5 weeks [26–28]. The aetiology of these reactions are presumed to occur as a consequence of HAART-related reconstitution of immunity [29,30].

The current study is part of a larger study to describe drug–drug interactions between HIV and TB therapies. We describe risk factors of mortality and clinical characteristics in a cohort consisting of HIV-positive patients with or without TB coinfection.

Methods

Study population and setting
This study is part of a larger prospective cohort whose objective was to study the optimization of HIV and TB cotreatment based on pharmacokinetic and pharmacogenetic aspects of drug–drug interactions between rifampicin and efavirenz. The study was conducted between September 2007 and June 2010 at Muhimbili National Hospital, Infectious Disease Centre and Mwananyamala Municipal Hospital, all in Dar es Salaam, Tanzania.

The cohort included patients with diagnosed HIV infection in whom TB was excluded, referred to as 'HIV-only' as well as HIV patients coinfected with TB referred to as 'HIV-TB'. The study population included consented adults ≥18 years of age, with documented HIV infection who were naive to HAART, with a CD4+ T-cell count ≤200 cells/μl and a negative history of TB in the past 5 years. HIV was diagnosed using the algorithm set forth by the Ministry of Health and Social Welfare (Tanzania) based on the serial testing strategy recommended by WHO (two rapid tests, ELISA and western blot).

We excluded prisoners, pregnant women and those with a low haemoglobin count (≤8 g/dl). Patients were followed-up for a period of 48 weeks for HIV-only and 52 weeks for HIV-TB at regular intervals (0, 1, 2, 4, 8, 12, 16, 24, 36 and 48 weeks after HAART initiation). All patients received the usual care for HIV and TB, and any other opportunistic infections in the care and treatment centres as indicated in the guidelines. Adherence to HAART and anti-TB was assessed by self-report.

TB was defined as a definitive or presumed clinical illness consistent with TB symptoms and signs. The definitive diagnosis was made if sputum smear was AFB-positive or if histology was consistent with the presence of TB granulomas. An abnormal chest X-ray, a smear-negative sputum for AFB with persistent symptoms suggestive of TB (fever, cough, weight loss or night sweats over 2 weeks duration) despite antibiotic treatment, and in the absence of other causes of such symptoms, qualifies the patient to be started on anti-TB therapy, with the presumptive diagnosis of AFB smear-negative TB.

HIV-only patients without TB were initiated on an efavirenz (non-nucleoside reverse transcriptase inhibitor)-based regimen combined with two other nucleoside reverse transcriptase inhibitors (either zidovudine or stavudine, with lamivudine) according to the National AIDS Control Program (Tanzania) treatment guidelines. The choice of nucleoside reverse transcriptase inhibitors was determined by the attending physician.

Patients with HIV and TB coinfection were started on four anti-TB drugs (rifampicin, isoniazid, ethambutol and pyrazinamide) using the DOT regimen according to the National Tuberculosis and Leprosy Program (NTLP; Tanzania). After the first 4 weeks of anti-TB treatment, efavirenz-based HAART was added on, and

the patient continued with this combination for the remaining 1 month of the initiation phase. During the continuation phase of 4 months, the patient continued with rifampicin and isoniazid to the required TB treatment duration (6 months). The HAART regimen continued all along.

The study was approved by the Institutional Review Board of the Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania, and the Karolinska Institutet in Stockholm, Sweden.

Data collection and laboratory studies

After informed consent and appropriate pre-test counselling the demographic characteristics were ascertained. A detailed history of present and past illnesses was taken along with a general physical examination. Education on treatment and adherence counselling was provided. Clinical evaluation for any adverse event and patient progress was done at every clinical visit by the study physicians. New TB diagnosis in HIV-only patients or worsening of TB symptoms in HIV-TB patients was noted and recorded in the case report forms. A verbal autopsy questionnaire was administered by the clinician to the relatives of the deceased for reported deaths during the study period to ascertain cause of death.

The laboratory investigations were done according to the same clinical schedule in both groups. The routine laboratory testing was performed at the Central Pathology Laboratory in Muhimbili National Hospital, including complete blood count, CD4+ T-cell count, viral load assessment, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total and direct bilirubin levels. In addition hepatitis B surface antigen, hepatitis C serology and Venereal Disease Research Laboratory tests were also done.

Statistical methods

Sample size calculation for two independent proportions via z-test (equal *n*-values) were done using Statistica version 7.1 (StatSoft Inc., Tulsa, OK, USA). A sample size of 200 was required in each arm assuming a 10% loss to follow-up or drop-outs to test the effect of rifampicin on efavirenz kinetics and treatment outcomes. The clinical assessment and laboratory results were recorded into case report forms and later entered into a Microsoft Access database. Descriptive statistics were done using SPSS (PASW) version 18 (SPSS, Inc., Chicago, IL, USA) and the statistical analyses were performed in R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria). A *P*-value <0.05 was considered statistically significant.

Absolute and relative frequencies were presented for categorical variables and mean and SD were used for the continuous variables. The χ^2 test was used to compare categorical data, while independent Student's *t*-tests and Mann–Whitney U tests were done to compare continuous data.

To avoid bias due to missing baseline characteristics, multiple imputation (*n*=10) was performed for variables with missing data using predictive mean matching. All analyses, except for the descriptive statistics, were performed on the imputed data.

Kaplan–Meier analysis was done to describe the survival characteristics of patients. Univariate and multivariate Cox proportional-hazards regressions, using the Efron method for tie handling, were used to identify predictors of mortality, where variables with *P*<0.1 in the univariate models were selected for inclusion in the multivariate model together with variables deemed to have a theoretical importance. Follow-up time was defined as time to last visit prior to loss to follow-up, exiting from the study or end of study (week 48/52), at which point censoring occurred, or last visit prior to death.

Interactions with TB as the exposure were tested for all variables included in the multivariate model. The scaled Schoenfeld residuals from the multivariable model were investigated to assess the proportional hazard assumption, whereas the Martingale residuals were visually inspected for non-linearity in the continuous variables.

In order to evaluate the effect on the results if the losses to follow-up were due to death, a sensitivity analysis was performed where patients who were lost to follow-up were assumed to have died at their last visit.

Results

This study included a total of 486 HIV-1-infected patients with a CD4+ T-cell count ≤200 cells/µl, who were eligible for HAART initiation. Of these, 255 (53%) patients were HIV-positive without TB and 231 (47%) patients were coinfected with HIV and TB (Figure 1).

There were more females (65%) with HIV-only compared to patients with HIV-TB coinfection (*P*<0.001).

There was a significant difference in the marital status and educational level between the two groups (Table 1; *P*=0.001). A larger proportion of patients with HIV-TB coinfection (40%) had a Karnofsky score of ≤80% compared to those with HIV alone (13%; *P*<0.001). Most patients were in WHO stages II and III, while only 5% were in WHO stage IV. A total of 13% of patients reported to have suffered from TB >5 years prior to enrolment in the study. Herpes zoster history and scars were found in 12% of patients. Patients with HIV-TB coinfection had a lower median body mass index of 19.4 kg/m² compared to 21.3 kg/m² among patients with HIV alone (*P*<0.001).

Table 2 shows the presenting symptoms and signs at baseline as well as the laboratory parameters. The most common presenting symptoms were weight loss (44.2%), cough (39.9%), fever (35.4%), loss of appetite (29.6%), headache (25.7%) and skin rash (25.3%). However, the proportion of those with symptoms of weight loss, cough, night sweats and fever were higher in patients coinfected with TB, in keeping with the TB symptoms ($P<0.001$). The most common clinical findings were pruritic papular eruption (18.9%), lymphadenopathy (18.7%) and oral candidiasis (15.0%). Overall 67% of patients with HIV–TB coinfection were

Figure 1. Flow chart showing patient recruitment and follow-up
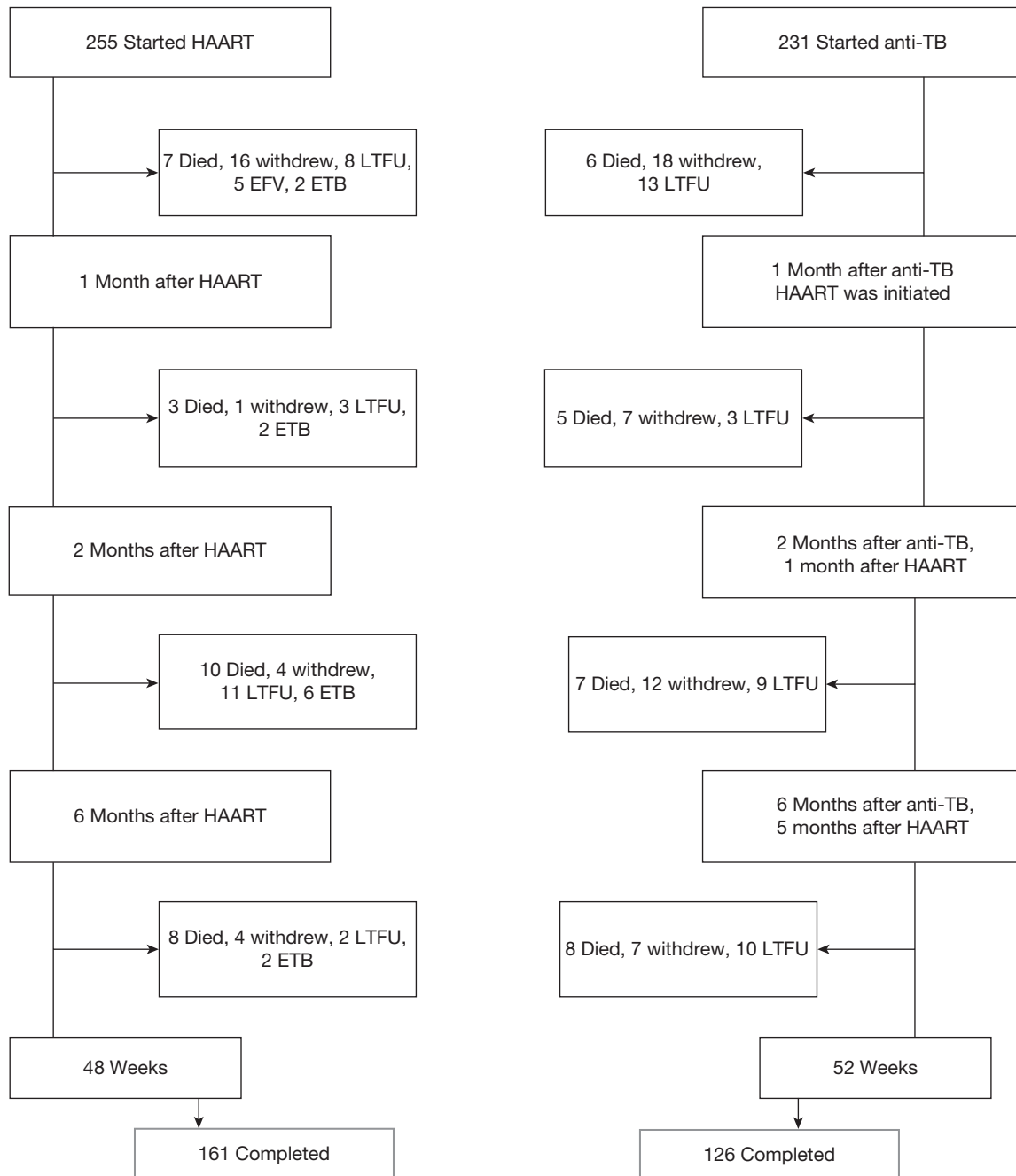
EFV, exited from the study due to efavirenz toxicity; ETB, exited from the study due to tuberculosis (TB) diagnosis; LTFU, lost to follow-up.

found to be sputum-positive for AFB and/or histology consistent with TB, with the remaining 33% being AFB-negative or having extra-pulmonary TB with atypical radiological findings (intrathoracic adenopathy, focal lower or middle lobe infiltrates and diffuse milliary or nodular infiltrates).

Hepatitis testing showed 10% of the patients were positive for hepatitis B surface antigen and 3% for hepatitis C. Patients with HIV–TB coinfection had a significantly lower mean ±SD haemoglobin levels (9.97 ±1.55 g/dl) compared to those infected with HIV alone (10.62 ±1.73 g/dl). The mean aspartate aminotransferase, alanine aminotransferase and median CD4+ T-cell counts were similar.

A combination of zidovudine, lamivudine and efavirenz was initiated in 83.1% of the patients with HIV alone, while only 49.3% of the HIV–TB-coinfected patients were initiated with the same combination. This difference was mainly due to the conjunctival pallor and a laboratory result showing low haemoglobin levels of ≤10 g/dl, in which case stavudine replaced zidovudine.

Patients were asked about their adherence to medication over the past week by researchers. Self-reported adherence to HAART was 98% over the past week for HIV-only patients, while those with HIV–TB coinfection on HAART and anti-TB therapy reported adherence of 97%.

Of the HIV-only patients who were initiated on HAART, 12 (4.7%) patients developed TB during the course of the study with a median duration to TB diagnosis being 16 weeks. Among the HIV–TB-coinfected patients, 7 (3%) developed worsening of their TB symptoms (increase in lymph node size, in some cases associated with pain and suppuration and persistent fevers). The median duration to these worsening symptoms was 12 weeks after HAART initiation, with the baseline predictors for developing these symptoms being a low baseline CD4+ T-cell count (hazard ratio =0.98, 95% CI 0.96, 0.99) and a low body mass index (hazard ratio =0.18, 95% CI 0.05, 0.61). These features were not serious and did not require any additional treatment.

During the follow-up period, a total of 54 (11.1%) patients died with a median duration to death of 13

Table 1. Socio-demographic and baseline clinical characteristics of HIV-infected patients who are HAART-naive with or without active tuberculosis on an efavirenz–based HAART

Variable	HIV-only (n=255)	HIV-TB (n=231)	P-value
Socio-demographic characteristics			
Sex	–	–	–
Female	166 (65.1)	114 (49.4)	<0.001
Male	89 (34.9)	117 (50.6)	–
Mean age (SD)	39.32 (8.97)	40.18 (9.72)	0.314
Median BMI (IQR)	21.3 (6.20)	19.4 (3.76)	<0.001
Marital status	–	–	–
Single, divorced or widowed	150 (58.8)	115 (49.8)	0.046
Married or cohabiting	105 (41.2)	116 (50.2)	–
Education status	–	–	–
Illiterate, able to read and write, or primary education	183 (71.8)	194 (84.0)	0.001
Secondary or tertiary education	72 (28.2)	37 (16.0)	–
Disease stage and status			
WHO stage	–	–	<0.001
I and II	206 (80.8)	0	–
III	38 (14.9)	217 (93.9)	–
IV	11 (4.3)	14 (6.1)	–
Karnofsky score	–	–	<0.001
90–100%	221 (86.7)	138 (59.7)	–
≤80%	34 (13.3)	93 (40.3)	–
Past medical history			
History of TB>5 years ago	34 (13.3)	28 (12.1)	0.689
History of herpes zoster	38 (14.9)	19 (8.2)	0.022
History of chronic herpes simplex	11 (4.3)	6 (2.6)	0.304
HAART initiated			
Stavudine + lamivudine + efavirenz	43 (16.9)	112 (50.7)	<0.001
Zidovudine + lamivudine + efavirenz	212 (83.1)	109 (49.3)	–

Total n=486. Data are n (%) unless indicated otherwise. BMI, body mass index; HIV-only, patients with diagnosed HIV infection in whom tuberculosis (TB) was excluded; HIV-TB, HIV-infected patients coinfected with TB.

Table 2. Baseline symptoms, signs and laboratory parameters in HAART-naive HIV patients with and without active tuberculosis on efavirenz-based HAART

Variable	HIV-only (*n*=255)	HIV-TB (*n*=231)	*P*-value
Symptoms			
Weight loss	81 (31.8)	134 (58.0)	<0.001
Cough	61 (23.9)	133 (57.6)	<0.001
Fever	93 (36.5)	79 (34.2)	0.544
Loss of appetite	68 (26.7)	76 (32.9)	0.133
Night sweats	28 (11.0)	103 (44.6)	<0.001
Headache	88 (34.5)	37 (16.0)	<0.001
Skin rash	88 (34.5)	35 (15.2)	<0.001
Dizziness	52 (20.4)	25 (10.8)	0.004
Nausea/vomiting	28 (11.0)	35 (15.2)	0.172
Chest pain	18 (7.1)	44 (19.0)	<0.001
Diarrhoea	28 (11.0)	18 (7.8)	0.231
Abdominal pain	27 (10.6)	12 (5.2)	0.029
Dyspnoea	4 (1.6)	22 (9.5)	<0.001
Genital ulcer	20 (7.8)	5 (2.2)	0.005
Signs			
PPE	54 (21.2)	38 (16.5)	0.184
Lymphadenopathy	36 (14.1)	55 (23.8)	0.006
Oral cadidiasis	46 (18.0)	27 (11.7)	0.088
Conjuctival pallor	10 (3.9)	16 (6.9)	0.142
Angular stomatitis	10 (3.9)	5 (2.2)	0.263
Kaposi's sarcoma	10 (3.9)	1 (0.4)	0.010
Laboratory parameters			
Mean haemoglobin, g/dl (SD)	10.62 (1.73)	9.97 (1.55)	<0.001
Mean neutrophil, K/µl (SD)	2.44 (2.13)	3.89 (4.33)	<0.001
Mean AST, U/l (SD)	41.65 (29.87)	40.6 (44.88)	0.800
Mean ALT, U/l (SD)	28.65 (26.9)	25.12 (26.02)	0.159
Median CD4+ T-cell count, cells/µl (IQR)	90 (118)	94.5 (123)	0.134
Viral load, log copies/ml	5.64	5.80	0.219
HBsAg-positive, %	15.5	3.5	<0.001
HCV-positive, %	4.4	1.1	0.184
VDRL-positive, %	8.7	3.9	0.160

Total *n*=486. Data are *n* (%) unless indicated otherwise. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HIV-only, patients with diagnosed HIV infection in whom tuberculosis was excluded; HIV-TB, HIV-infected patients coinfected with tuberculosis; PPE, pruritic papular eruptions; VDRL, Venereal Disease Research Laboratory test.

weeks (17 deaths per 100 person years [py]; Figure 2). Proportionately there were more males (13.1%; 20 deaths per 100 py] who died compared to females (9.6%; 14 deaths per 100 py]. Of the 54 patients who died, 28 (16 per 100 py) had HIV-only and 26 (17 per 100 py) had HIV–TB coinfection. In the HIV-only patients, 16 (57.2%) died in the first 16 weeks, 6 (21.4%) between weeks 17–32 and 6 (21.4%) between weeks 33–48 after HAART initiation. Of the 26 HIV-TB patients who died, 6 (23%) died while still on anti-TB therapy before HAART was initiated at week 4 of treatment and 4 (15.4%) patients died during the intensive phase of TB treatment where patients used both anti-TB drugs and HAART; 8 (30.8%) patients died during the continuation phase of anti-TB treatment, and a further 8 (30.8%) died after the completion of TB treatment while continuing with HAART (Figure 1). However, in both HIV-only patients and those with HIV-TB, >50% died within the first 4 months of HAART initiation. The causes of death obtained from verbal autopsy reports and hospital records show a wide range of variation with no specific pattern seen in either HIV only or HIV-TB patients.

Multiple imputation, using predictive mean matching, was done to avoid bias due to baseline characteristics missing at random. The missing-at-random assumption was deemed to be reasonable since there was no indication that observations were missing in a systematic manner innate to the value itself. Univariate Cox proportional-hazards regressions were estimated for all variables in Tables 1 and 2 to determine baseline predictors of mortality. After univariate Cox regression analysis, variables with *P*<0.1 were put into

a multivariate model (Table 3). Multivariate analysis showed that predictors of mortality were oral cadidiasis, Kaposi's sarcoma, low Karnofsky score, and low baseline white blood cell and CD4+ T-cell counts

Violations to the proportional hazard assumption were detected for fever, chest pain, Karnofsky score and WHO stage. In order to evaluate their effect on mortality, however, these variables were included as covariates in the models, but the results should be interpreted with some care. A multivariate model stratified for fever, chest pain, Karnofsky score and WHO stage was also estimated without significant changes to the results for the other variables. The five continuous variables included in the multivariate model were assessed as having a linear relationship to the outcome.

Among 19 (5.9%) patients on initial zidovudine containing HAART, zidovudine was replaced by stavudine during the course of the study due to anaemia. Of those started on stavudine, 11 (7.1%) of the patients changed from stavudine to zidovudine due to complains of peripheral neuropathy, which occurred predominantly in patients receiving anti-TB treatment (9/112 [8%]). By the end of the study period, 25 (9.8%) of the HIV-only and 43 (18.6%) of the HIV-TB patients withdrew themselves from the study. Most patients withdrew as they were transferred to other care and treatment centres away from Dar es Salaam and, hence, could not continue participating in the study. Although withdrawn, we traced these patients by telephone calls and all were confirmed to be alive by the end of the study period. A total of 24 (9.4%) HIV-only and 36 (15.6%) HIV-TB patients were lost to follow-up. Telephone calls and home visits by home-based care workers were made to trace these patients, however their whereabouts could not be determined. A total of 161 (63%) HIV-only and 126 (54.5%) HIV-TB patients were successfully followed-up for the entire study duration. Multivariate Cox proportional hazard regression was estimated where the losses to follow-up were assumed dead; this did not, however, change the results in any significant way.

Discussion

This study describes the risk factors for mortality and clinical characteristics of HAART-naive patients initiated on treatment with the CD4+ T-cell count ≤200 cells/μl. Patients presented with clinical symptoms that have been described before [31–34]. However, patients with HIV–TB coinfection were more symptomatic and presented with features suggestive of TB, despite similar low CD4+ T-cell counts as the HIV-only patients. Many patients in the HIV–TB-coinfected group had much lower haemoglobin levels making stavudine the preferred choice in the combination rather than zidovudine because of the latter's effect on haemoglobin levels.

Figure 2. Kaplan–Meier analysis showing survival of HIV patients with and without active tuberculosis
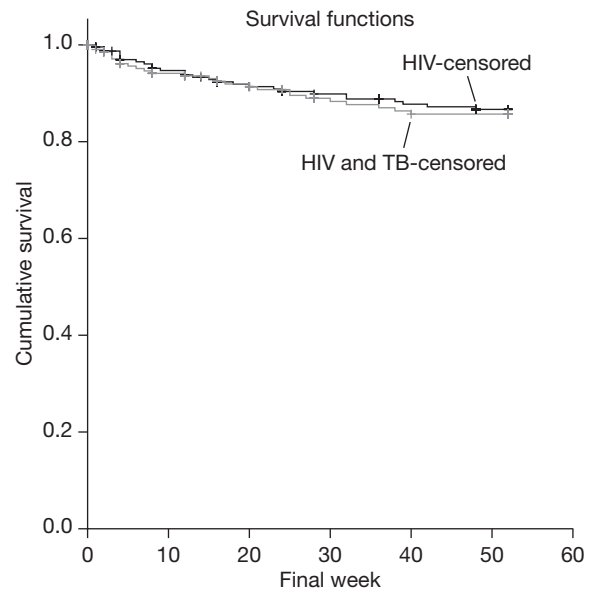
TB, tuberculosis.

During the study period, 54 (11.1%) patients died, and this compares well with other studies that had similar rates of mortality [21,22]. Of interest is that the mortality rate of patients with HIV–TB coinfection on anti-TB therapy was similar to that of patients without TB with similar median duration to death of 13 weeks. Other studies have shown that with good anti-TB therapy, mortality among HIV-infected individuals with TB need not be higher than those with HIV alone [11,13,35]. Our study showed that >50% of the patients died within 16 weeks, which is less than one-third of our patient follow-up period of 48 weeks after initiation of HAART, indicating that death occurs early during treatment [36,37]. With increasing duration of HAART use, there is improvement of patients' immune status, which may account for reduced mortality. Cox proportional-hazards regressions showed that the predictors of mortality were oral cadidiasis, Kaposi's sarcoma, low Karnofsky score, and low baseline white blood cell and CD4+ T-cell counts [38]. Verbal autopsies conducted to determine the causes of mortality showed no differences between HIV-only patients and those with HIV-TB.

TB is a common infection in developing countries with approximately one-third of the population infected with *Mycobacterium tuberculosis* (MTB) [39,40]. In HIV-negative individuals, only a small proportion of patients with MTB will develop active TB.

Table 3. Cox proportional-hazards regression for predictors of mortality in HIV-infected patients with and without active tuberculosis on an efavirenz-based HAART

Variable (reference)	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
TB (no TB)	1.083 (0.635, 1.848)	0.769	1.046 (0.367, 2.981)	0.933
Sex (male)	1.409 (0.826, 2.402)	0.208	1.270 (0.667, 2.419)	0.466
Age	1.009 (0.981, 1.037)	0.547	1.008 (0.974, 1.042)	0.643
Fever (no)	1.532 (0.893, 2.628)	0.121	1.323 (0.697, 2.508)	0.391
Cough (no)	1.086 (0.628, 1.878)	0.766	–	–
Weight loss (no)	1.901 (1.111, 3.253)	**0.019**	1.598 (0.834, 3.063)	0.157
Night sweats (no)	0.991 (0.531, 1.85)	0.978	–	–
Headache (no)	1.049 (0.571, 1.927)	0.878	–	–
Skin rash (no)	1.171 (0.653, 2.101)	0.596	–	–
Nausea/vomiting (no)	2.461 (1.268, 4.777)	**0.008**	0.938 (0.397, 2.217)	0.884
Loss of appetite (no)	1.772 (1.025, 3.062)	**0.041**	0.574 (0.279, 1.176)	0.129
Diarrhoea (no)	2.573 (1.294, 5.116)	**0.007**	1.183 (0.477, 2.929)	0.716
Dizziness (no)	1.382 (0.695, 2.747)	0.356	–	–
Chest pain (no)	2.117 (1.114, 4.022)	**0.022**	0.999 (0.442, 2.258)	0.998
Feels depressed (no)	2.914 (1.686, 5.037)	**<0.001**	2.052 (0.884, 4.762)	0.094
Insomnia (no)	1.858 (0.935, 3.693)	0.077	1.014 (0.453, 2.267)	0.972
Dyspnoea (no)	0.412 (0.057, 2.978)	0.379	–	–
Genital ulcer (no)	1.791 (0.713, 4.495)	0.215	–	–
History of PTB (no)	1.942 (1.002, 3.688)	**0.043**	1.407 (0.671, 2.948)	0.366
History of herpes zoster (no)	1.352 (0.638, 2.865)	0.431	–	–
PPE (no)	0.648 (0.293, 1.435)	0.285	–	–
Lymphadenopathy (no)	1.166 (0.601, 2.261)	0.650	–	–
Conjunctival pallor (no)	5.786 (2.724, 12.29)	**<0.001**	2.743 (0.906, 8.309)	0.074
Body mass index	0.882 (0.807, 0.964)	**0.006**	0.912 (0.825, 1.008)	0.071
Oral candidiasis (no)	2.992 (1.668, 5.367)	**<0.001**	2.552 (1.182, 5.509)	**0.017**
Chronic herpes simplex (no)	3.790 (1.622, 8.857)	**0.002**	1.875 (0.648, 5.426)	0.246
WHO stage (stage II)	–	**0.027**	–	0.501
WHO stage III	1.287 (0.722, 2.296)	0.392	0.802 (0.288, 2.233)	0.672
WHO stage IV	3.508 (1.399, 8.790)	**0.007**	0.391 (0.081, 1.898)	0.244
Kaposi's sarcoma (no)	3.229 (1.008, 10.35)	**0.048**	8.099 (1.429, 45.886)	**0.018**
Karnofsky scores (90–100%)	4.033 (2.362, 6.884)	**<0.001**	3.989 (1.916, 8.301)	**<0.001**
Haemoglobin	0.919 (0.769, 1.097)	0.35	0.949 (0.762, 1.181)	0.637
White blood cell count	1.117 (1.024, 1.218)	**0.012**	1.124 (1.005, 1.257)	**0.039**
Hepatitis C (negative)	3.580 (1.16, 11.05)	**0.026**	4.229 (0.806, 22.187)	0.088
Hepatitis B (negative)	1.288 (0.539, 3.079)	0.569	–	–
CD4$^+$ T-cell count	1.008 (0.987, 0.996)	**<0.001**	0.993 (0.988, 0.998)	**0.007**
AST	1.003 (0.997, 1.009)	0.281	–	–
ALT	0.997 (0.985, 1.009)	0.620	–	–

P-values <0.05 are shown in bold. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; PPE, pruritic papular eruptions; PTB, pulmonary tuberculosis.

By contrast, among HIV patients with MTB coinfection, the incidence of active TB is approximately 0.9% per year with a life expectancy of 50% [41,42]. It is well-known that patients with advanced HIV disease with active TB may have atypical presentation of TB. Improvement of immune status associated with HAART brings about unmasking of TB symptoms [26,27]. In this study, 4.7% of the HIV-only patients developed active TB after HAART initiation. These were classified as HAART-related TB, with similar prevalence's to those reported in other studies [43–46].

Among HIV-TB patients on anti-TB who were started on HAART, 3% of patients developed exaggerated features of TB, which we defined as TB immune reconstitution inflammatory syndrome [29,30]. These features were in the form of increased fever episodes and enlargement of lymph nodes.

Patients self-reported adherence to medication was found to be high in our study. This may be due to persistent counselling given to patients on adherence during each clinic visit, and the encouragement to have treatment assistants. This has been reported previously

in our study [47]. Despite good counselling, 12% of patients were lost to follow-up. This proportion was higher, however not statistically significant, in patients with HIV–TB coinfection compared to those with HIV-only. Many patients usually register themselves as residents of Dar es Salaam in order to access better care and treatment. However, after initiation of treatment and improvement, they tend to go back to regions of origin where they continue with their treatment.

Other important findings in the study include the gender differences between the two patient groups. In the HIV-only group, there were more females compared to males. This is similar to other studies, which showed that most patients who attended HIV clinics are predominantly females. This is attributed to the different health seeking behaviours between males and females [48,49]. A near equal proportion of males to females among patients with TB coinfection can be explained by the fact that active TB is more common among males compared to females [50]. The prerequisite for the Tanzanian NTLP is that all patients with TB have to receive DOT; hence, this forces males to attend TB clinics.

Conclusion

Mortality is still considerable in those patients who are started on HAART with a CD4+ T-cell count of <200 cells/μl, with mortality occurring early in the treatment duration. HIV-related TB is high among patients attending HAART clinics. Predictors of mortality among HIV patients included oral candidiasis, Kaposi's sarcoma, low Karnofsky scores, and low baseline white blood cell and low baseline CD4+ T-cell counts. There was no significant difference in mortality between HIV-only patients started on HAART and HIV-TB patients started on rifampicin-based anti-TB therapy and HAART. From this, we would recommend to reduce national in-programme delays in initiating HAART for HIV patients with and without TB before development of advanced HIV disease to reduce morbidity and mortality.

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Disclosure statement

The authors declare no competing interests.

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