Observational Study

Medicine®

OPEN

Predictors of mortality in adults on treatment for human immunodeficiency virus-associated tuberculosis in Botswana

A retrospective cohort study

Ley Muyaya Muyaya, BSc, MD, MSc[a,b,*], Taryn Young, MD, PhD[a,c], Marian Loveday, MPhil, PhD[d]

Abstract

Mortality in patients with human immunodeficiency virus (HIV)-associated tuberculosis (TB) is high, particularly in sub-Saharan Africa. This study aimed to compare mortality and predictors of mortality in those who were antiretroviral therapy (ART) naïve to those with prior ART exposure.

This retrospective cohort study was conducted in Serowe/Palapye District, Botswana, a predominantly urban district with a large burden of HIV-associated TB with a high case fatality. Between January 1, 2013 and December 31, 2013, patients confirmed with HIV-associated TB were enrolled and followed up. Kaplan–Meier and Cox proportional hazard modeling was undertaken to identify predictors of mortality, with ART initiation included as time-updated variable.

Among the 300 patients enrolled in the study, 131 had started ART before TB diagnosis (44%). There were 45 deaths. There was no difference in mortality between ART-naïve patients and those with prior ART exposure. In the multivariate analysis, no ART use during TB treatment (hazard ratio [HR] = 5.6, 95% confidence interval [CI] = 2.9–11; $P < .001$), opportunistic infections other than TB (HR = 8.5, 95% CI = 4–18.4; $P = .013$), age ≥60 years (HR = 4.8, 95% CI = 1.8–13; $P = .002$), hemoglobin <10 g/dL (HR = 2.4, 95% CI = 1.3–4.5) and hepatotoxicity (HR = 5, 95% CI = 1.6–17; $P = .007$) were associated with increased mortality. In the subgroup analysis, among ART-naïve patients, no ART use during TB treatment (HR = 8.1, 95% CI = 3.4–19.4; $P < .001$), opportunistic infections other than TB (HR = 16, 95% CI = 6.2–42; $P < .001$), and hepatotoxicity (HR = 8.3, 95% CI = 2.6–27; $P < .001$) were associated with mortality. Among patients with prior ART exposure, opportunistic infections other than TB (HR = 6, 95% CI = 2.6–27; $P < .001$) were associated with mortality.

Mortality in patients with HIV-associated TB is still high. To reduce mortality, close clinical monitoring of patients together with initiation of ART during TB treatment is indicated.

Abbreviations: 3TC = lamivudine, ART = antiretroviral therapy, AZT = zidovudine, EFV = efavirenz, FTC = emtricitabine, HIV = human immunodeficiency virus, LPV/r = ritonavir-boosted lopinavir, NVP = nevirapine, TB = tuberculosis, TDF = tenofovir.

Keywords: deaths, human immunodeficiency virus, mycobacterium infection, outcomes, risk factors, tuberculosis

1. Introduction

Mortality in patients with human immunodeficiency virus (HIV)-associated tuberculosis (TB) is high.[1–3] Globally in 2016, there were an estimated 10.4 million cases of TB, 10% of whom were coinfected with HIV, resulting in 400,000 deaths. Sub-Saharan Africa accounts for 80% of these deaths.[1]

In Botswana, a country with a high HIV burden, TB was declared a public health emergency in 2005. By 2016, the incidence of TB was 326 per 100,000, the seventh highest in the world, and 60% of these TB cases were TB-HIV coinfected. In 2016, a mortality rate of 62 per 100,000 was reported among TB-HIV coinfected patients.[1] With universal access to antiretroviral therapy (ART), there has been a sustained decline in the number of TB cases. However, mortality in people with HIV-associated TB is almost double that of people not HIV infected.[1]

Several Southern African studies have reported on the predictors of mortality in TB-HIV coinfected patients.[4–6] However, in Botswana, the predictors of mortality in TB-HIV coinfected patients have not been documented. If we knew what the predictors of mortality in TB-HIV coinfected patients in Botswana were, this knowledge could be used to inform appropriate policy and patient care.

In this study on TB treatment among TB-HIV coinfected patients in Botswana, we compared the mortality and predictors of mortality in patients who were not on ART at the time that TB treatment was initiated (ART-naïve patients) with the mortality and predictors of mortality in patients who were on ART at the time of TB treatment initiation (prior ART exposure).

Editor: Akhilanand Chaurasia.

The dataset of this study is available upon request to the corresponding author.

Competing interests: There are no potential conflicts of interest relevant to this article. All the authors reported no conflict of interest.

[a] Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, [b] Palapye District Health Management Team, Ministry of Health, Palapye, Botswana, [c] Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, [d] Health Systems Research Unit, South African Medical Research Council, Cape Town, South Africa.

[*] Correspondence: Ley Muyaya Muyaya, Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 241, Cape Town 8000, South Africa (e-mail: leymuyaya@gmail.com).

Medicine (2018) 97:16(e0486)

Received: 17 November 2017 / Received in final form: 6 March 2018 / Accepted: 28 March 2018

http://dx.doi.org/10.1097/MD.0000000000010486

2. Methods

2.1. Study design

This was a retrospective cohort study assessing the predictors of mortality in both ART-naïve patients and those with prior ART exposure during HIV-associated TB treatment.

2.2. Study setting

This retrospective cohort study was conducted in Serowe/Palapye District, Botswana, a predominantly urban district with a large burden of HIV-associated TB with a high case fatality. In accordance with country guidelines,[7] all TB patients are screened for HIV using the double rapid HIV test. The first-line TB treatment during the study period was rifampicin, pyrazinamide, ethambutol, and isoniazid during the 2 initial months ("intensive phase"), followed by rifampicin, isoniazid, and ethambutol for the next 4 months ("continuation phase"). However, in patients with central nervous system diseases or TB infection in their bones, the continuation phase was extended to 12 months.[7] All patients with HIV-associated TB were eligible for ART initiation during TB treatment.

Furthermore, the standard ART first-line regimen for TB patients was: tenofovir (TDF) + emtricitabine (FTC) or Lamivudine (3TC) + efavirenz (EFV). Nevirapine (NVP) was used in cases of EFV intolerance. The standard ART second-line regimen was zidovudine (AZT) + lamivudine (3TC) and double dosed LPV/r (ritonavir-boosted lopinavir).

While ART treatment was provided free of charge to all HIV-positive citizens of Botswana, TB treatment was free of charge regardless of citizenship. Generally, TB diagnosis (smear microscopy) was done in primary and district hospital laboratories while culture and drug sensitivity testing was done at the National Health Laboratory in Gaborone. HIV-positive patients were treated in all clinics and hospitals in the district, where the patients were seen on a daily basis as outpatients. Directly observed treatment was uniformly performed at all centers.

2.3. Study population

Between January 1, 2013 and December 31, 2013, 300 confirmed[7] HIV-infected patients ≥15 years old with a laboratory- or x-ray-confirmed diagnosis of TB and medical records available were enrolled and followed up. Medical records and TB and ART registers were reviewed at the time of TB diagnosis and 18 months later to evaluate the outcomes and to obtain all the dependent and independent variables, including information on socio-demographic factors, lifestyle factors, clinical characteristics, and laboratory profiles. ART initiation was included as time-updated variable.

Patients were categorized according to their ART status at the time of their TB diagnosis. Patients were defined as ART naïve if they were not on ART at the time of their TB diagnosis or had been on ART for <3 months prior to their TB diagnosis. Patients defined as having previous exposure to ART had been on ART for ≥3 months at the time of their TB diagnosis.

2.4. Outcomes

The primary outcome was mortality, defined as any death that occurred during TB treatment, which varied from 6 months in new TB cases, 8 months in repeat TB cases, 12 months in TB meningitis cases, and up to 18 months in bone TB cases. Major side effects were defined as any side effect that occurred during TB treatment requiring first-line TB treatment to be discontinued.[8]

2.5. Data collection and statistical analysis

We reviewed medical records to collect baseline demographic, clinical, pharmaceutical, and laboratory data. Patient response to treatment was then collected from medical records, the laboratory database and TB and ART registers. Based on the assumptions of a previous study,[9] with 80% power and a significance level of .05, an estimated sample size of 300 was enrolled in the study.

The distribution of baseline characteristics was compared using the chi-square test and Fisher exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. The Kaplan–Meier method was used to compare time to death for the overall group, namely the ART-naïve group and the group with prior ART exposure. The Logrank test was used to compare survival time between ART-naïve patients and patients with prior ART exposure. Patients who did not experience the event measured were considered censored at the date of their last visit to the clinic during the study period. To identify independent predictors of mortality, Cox proportional hazard regression was undertaken. All multivariate models used a univariate threshold of $P \leq .1$ for the variables to be considered for inclusion. Analyses were conducted using SPSS 21, IBM Corp., Armonk, New York. All results were presented in the form of hazard ratios (HR) and 95% confidence intervals (CI). The level of significance was set at .05.

2.6. Ethics approval

Ethics approval to conduct the study was obtained from Stellenbosch University (Ethics Ref No S15/05/116), the Ministry of Health of Botswana (Ref No PPME13/18/1 PS V [357]) and the local health authorities in Serowe/Palapye District. Data routinely collected by health workers for clinical care were used in this study. To protect patient confidentiality and anonymity, the databases were de-identified and access was strictly limited. Informed consent was waived by the ethics committees as the study used data previously collected for clinical routine care and posed no additional risks to patients.

3. Results

Between January 1, 2013 and December 31, 2013, 551 TB patients were initiated on TB treatment in Serowe/Palapye District, of whom 388 (70%) were coinfected with HIV. Of these, 300 (77%) were enrolled in the study (Fig. 1).

Of the 300 patients enrolled in the study, 169 (56.3%) patients were classified as ART naïve and 131 (44%) had previously started ART. Of the 169 ART-naïve patients, 126 (74.6%) commenced ART during TB treatment (Table 1). At baseline, there were a number of significant differences between patients previously started on ART and those who were ART naïve. ART-naïve patients were younger (median 42.6 vs 38.8; $P = .004$), more frequently developed immune reconstitution inflammatory syndrome (25.4% vs 9.2%; $P < .001$), more frequently had unexplained anemia (Hb < 10 g/dL) (59% vs 27%; $P < .001$) and had lower CD4 cell counts at TB diagnosis (47.3% vs 23.7%; $P < .001$). In contrast, patients with prior ART initiation were more likely to have had a previous episode of TB (19.1% vs 5.3%; $P < .001$). In ART-naïve patients, two-thirds (109/169;

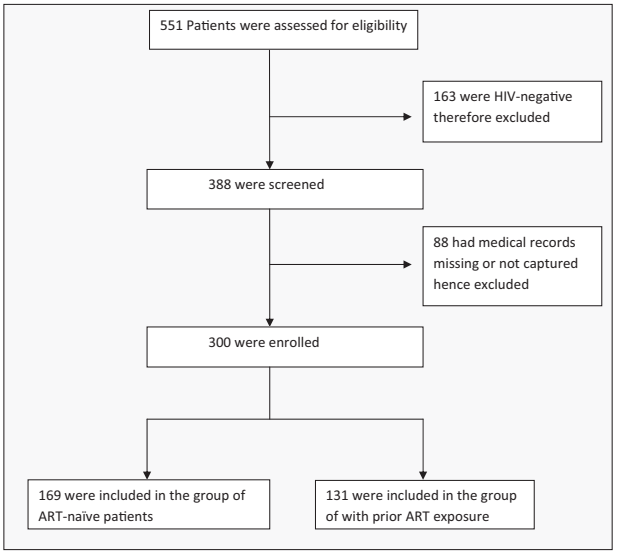

Figure 1. Flow chart of the enrolment of the study population, Serowe/Palapye district, Botswana, 2013. ART = antiretroviral therapy.

64.5%) had a CD4 cell count recorded at the time of TB diagnosis and 40% had a CD4 cell count <200 cells/μL. Of the CD4 cell counts recorded among patients previously on ART, in all but one of the patients (87/88) the CD4 cell count at ART initiation was >500 cells/μL (Table 1).

Besides TB, the other opportunistic infections reported were HIV wasting syndrome (11–3.7%), cryptococcal meningitis (2–0.67%), herpes simplex infection (1–0.33%), Kaposi sarcoma (2–0.67%), Pneumocystis jirovecii pneumonia (2–0.67%), and oral candidiasis (1–0.33%). Among patients documented to have experienced a major side effect, hepatotoxicity was reported in all but 1 patient who had Stevens Johnson syndrome.

There were 45 deaths during the study period, with 27 deaths (16%) amongst those who were ART naïve and 18 deaths (13.7%) amongst those previously started on ART. Eight patients (2.67%) defaulted on treatment, and 5 patients (1.67%) were transferred out to other facilities.

In Univariate Cox analyses (Table 2), there was no significant difference in mortality between ART-naïve patients and those with prior ART initiation ($P = .569$). Predictors of mortality were age ≥60 years ($P = .012$), loss of weight ($P = .032$), opportunistic infections other than TB ($P < .001$), no ART use during TB treatment ($P = .005$), CD4 cell counts <200 cells/μL ($P = .046$), hemoglobin <10 g/dL ($P = .007$), and major side effect ($P = .001$). In contrast, smear-positive TB ($P = .028$) was associated with a significantly lower risk of mortality.

In the overall multivariate analysis (Table 2), no ART use during TB treatment ($P < .001$), opportunistic infections other than TB ($P = .013$), age ≥60 years ($P = .002$), hemoglobin <10 g/dL ($P = .029$), and major side effect ($P = .007$) were significantly associated with higher mortality. The survival mean of the overall group from time of TB diagnosis was 14.99 months (95% CI: 13.57–16.41). The mean survival time for patients on ART during TB treatment was 15.43 months (95% CI: 13.8–17.01) while for those not on ART, the mean survival time was 9.46 months (95% CI: 7.62–11.3) with survival probability at 12 months of 0.625.

Among ART-naïve patients, 24 patients started ART within 4 weeks from the start of TB treatment and 16 patients >4 weeks from the start of TB treatment. However, there were no significant difference in survival time between the 2 groups of patients (log rank $P = .832$). The median time from ART initiation to TB diagnosis in patients previously started on ART was 37.15 months (interquartile range [IQR]: 13.93–75.97), and the median time in weeks from HIV diagnosis to ART initiation was 28.5 weeks (IQR: 4–150).

Multivariate survival analyses per subgroup were performed. The final models are shown in Table 3. Among ART-naïve patients, no ART use during TB treatment ($P < .001$), opportunistic infections other than TB ($P < .001$) and major side effect ($P < .001$) were significantly associated with higher mortality. Among patients previously started on ART, opportunistic infections other than TB ($P < .001$) were significantly associated with higher mortality (Table 3).

There was no significant difference in survival time between the 2 groups (log rank $P = .568$). The survival curve illustrates that most patients died in the first 3 months, there were few deaths after 3 months and there was no death after 6 months (Fig. 2).

Table 1

Baseline demographic and clinical characteristics of TB patients according to ART status, Serowe/Palapye district, Botswana 2013.

Variables	ART Naïve (total = 169) N (%)	Prior on ART (total = 131) N (%)	*P*-value
Age (mean [SD])	38.8 (11.3)	42.6 (11.2)	.004
Male sex	99 (58.6)	71 (54.2)	.260
Unemployed*	114 (67.5)	93 (71)	.499
Single†	144 (85.2)	112 (85.5)	.997
Smoker‡	2 (1.2)	4 (3.1)	.401
Body weight§ (mean [SD])	51.3 (10.5)	50.6 (10.2)	.665
Smear positive PTB	85 (50.3)	62 (47.3)	.579
Extrapulmonary	42 (24.8)	39 (29.8)	.395
Previous TB	9 (5.3)	25 (19.1)	<.001
Fever‖	78 (46.2)	49 (37.4)	.168
Productive cough‖	119 (70.4)	93 (71)	.860
Night sweats‖	56 (33.1)	36 (27.5)	.477
Loss of weight‖	111 (65.7)	69 (52.7)	.060
Duration of symptoms >3 months¶	21 (12.4)	23 (17.6)	.239
ART use during TB treatment	126 (74.6)	131 (100)	<.001
OI other than TB	11 (6.5)	8 (6.1)	.959
Total white blood cells# $10^3/\mu L$	6.01 (2–33)	7.43 (3–56)	.54
CD4** counts cells/μL at TB <200	80 (47.3)	31 (23.7)	<.001
CD4†† counts cells/μL at ART initiation			
<200	68 (40.2)	64 (48.9)	
200–350	23 (13.6)	18 (13.7)	
351–500	8 (4.7)	5 (3.8)	
>500	10 (5.9)	1 (0.8)	.142
Hemoglobin‡‡ <10 g/dL	59 (34.9)	26 (19.8)	<.001
Major side effect	7 (4.1)	2 (1.5)	.398
IRIS	43 (25.4)	12 (9.2)	.001

ART = antiretroviral therapy, IRIS = immune reconstitution inflammatory syndrome, SD = standard deviation, TB = tuberculosis.

Major side effect found were Hepatoxicity (8/9), and Stevens Johnson syndrome 1/9 OI: opportunistic infection. Time-updated variables: CD4 counts cells/μL at ART initiation and ART use during TB treatment.

* Missing data for 22 patients (7.3%).
† Missing data for 21 patients (7%).
‡ Missing data for 125 patients (41.7%).
§ Missing data for 87 patients (29%).
‖ Missing data for 21 to 25 patients (7–8.3%).
¶ Missing data for 68 patients (22.7%).
# Missing data for 98 patients (32.7%). Median (minimum – maximum).
** Missing data for 57 (19%).
†† Missing data for 60 (20%).
‡‡ Missing data for 84 patients (28%).

Table 2

Predictors of death in TB patients (irrespective of ART status) in Serowe/Palapye district Botswana 2013.

Variables	Deaths total: 45 N (%)	Survivors total: 255 N (%)	Case—fatality %	Hazard ratio (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age group, y							
<35	15 (33.3)	89 (34.9)	14.4	1	–	–	–
35–59	23 (51.1)	156 (61.2)	12.8	0.89 (0.46–1.7)	.722	1.5 (0.75–3)	.245
≥60	7 (15.6)	10 (3.9)	41.2	3.15 (1.28–7.73)	.012	4.8 (1.8–13)	.002
Male sex	28 (62.2)	142 (55.7)	16.5	1.22 (0.67–2.23)	.513	–	–
Unemployed	34 (75.6)	173 (67.8)	16.4	1.2 (0.59–2.42)	.627	–	–
Smoker	3 (6.7)	3 (1.2)	50	2.53 (0.76–8.42)	.130	0.66 (0.13–3.4)	.619
Body weight <50 kg	17 (37.8)	85 (33.3)	16.7	2.1 (0.94–4.71)	.072	1.8 (0.7–4.5)	.205
Smear positive PTB	15 (33.3)	132 (51.8)	10.2	0.5 (0.27–0.93)	.028	–	–
Extrapulmonary	13 (28.9)	67 (26.3)	16.3	1.12 (0.59–2.13)	.739	–	–
Previous TB	4 (8.9)	30 (11.8)	11.8	0.74 (0.27–2.01)	.571	–	–
Fever	23 (51.1)	104 (40.8)	18.1	1.58 (0.85–2.94)	.153	–	–
Productive cough	31 (68.9)	181 (71)	14.6	0.94 (0.46–1.92)	.870	–	–
Night sweats	9 (20)	83 (32.5)	9.8	0.55 (0.26–1.16)	.116	–	–
Loss of weight	33 (73.3)	147 (57.6)	18.3	2.33 (1.07–5.04)	.032	–	–
Duration of symptoms >3 mo	7 (15.6)	37 (14.5)	15.9	3.85 (0.47–31)	.207	–	–
No ART use during TB treatment	15 (33.3)	28 (11)	34.9	2.49 (1.31–4.73)	.005	5.6 (2.9–11)	<.001
OI other than TB	12 (26.7)	7 (2.7)	63.2	7.76 (3.96–15.25)	<.001	8.5 (4–18.4)	<.001
Total white blood cells $10^3/\mu L$	–	–	–	1.03 (0.99–1.1)	.135	–	–
CD4 counts cells/μL at TB <200	21 (46.7)	90 (35.3)	18.9	2.02 (1.01–4.04)	.046	–	–
Hemoglobin <10 g/dL	22 (48.9)	63 (24.7)	25.9	2.4 (1.3–4.5)	.007	2.44 (1.3–4.6)	.029
Major side effect	5 (11.1)	4 (1.6)	55.5	4.84 (2–12.3)	.001	5 (1.6–17)	.007
IRIS	9 (20)	46 (18)	16.4	1.1 (0.53–2.27)	.808	–	–
ART naïve	27 (60)	142 (55.7)	16	1.2 (0.66–2.2)	.569	–	–
Diabetes mellitus	0	5 (2)	–	0.049 (0–2559)	.586	–	–

ART = antiretroviral therapy, CI = confidence interval, major side effect found were Hepatoxicity (8/9), and Stevens Johnson syndrome 1/9, HR = hazard ratio, IRIS = immune reconstitution inflammatory syndrome, OI = opportunistic infection. ART use during TB treatment: time-updated variable, TB = tuberculosis.

4. Discussion

Our study shows that mortality in TB-HIV coinfected patients during TB treatment in Botswana is similar in ART-naïve patients and those with prior ART exposure. In addition, we report that the predictors of mortality vary according to ART status at TB diagnosis.

In this cohort of TB-HIV coinfected patients, 44% patients were previously started on ART, a proportion that is similar to that reported in other studies.[4,9,10] Our finding supports the evidence that the incidence of TB among HIV patients on long-term ART is still higher as compared with the general population.[5,6,11] Hence, it is predictable that in areas where access to ART has been widely available for a long period, such as Botswana, a significant proportion of patients presenting with TB will not be naïve to ART.[9]

Table 3

Predictors of death in TB patients in subgroups defined according to the baseline status of ART use in Serowe/Palapye district Botswana 2013.

Subgroup	Variables	HR*	95% CI	*P*
Prior ART				
	Major side effect	7.7	0.99–60	.128
	OI other than TB	6	2–18	.008
ART naïve				
	Weight at TB			
	≥50	1		
	<50	2.8	0.82–9.4	.101
	ART use during TB			
	Yes	1		
	No	8.1	3.4–19.4	<.001
	OI other than TB	16	6.2–42	<.001
	Major side effect	8.3	2.6–27	<.001

ART = antiretroviral therapy, CI = confidence interval, HR = hazard ratio, OI = opportunistic infection, TB = tuberculosis.

* Adjusted for weight at TB, ART use during TB, weight loss, smear positive, major side effect, CD4 group at TB diagnosis, opportunistic infection, age group, and hemoglobin group. Major side effect found were hepatoxicity (8/9), and Stevens Johnson syndrome 1/9. ART use during TB treatment: time-updated variable.

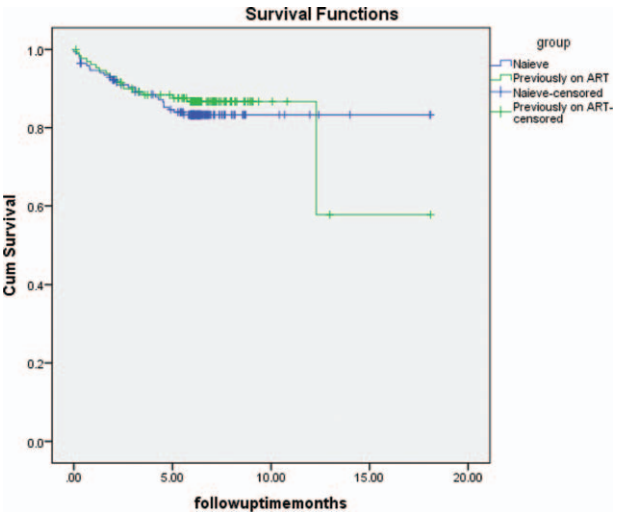

Figure 2. Kaplan–Meier survival estimates according to study subgroup. The 2 subgroups of patients were categorized based on their ART status at the time of their TB diagnosis: ART naïve: not on ART or had been on ART for <3 months prior to their TB diagnosis, previously on ART: had been on ART for ≥3 months at the time of their TB diagnosis. ART = antiretroviral therapy, TB = tuberculosis.

Lawn et al[6] have documented that the long-term risk of TB incidence in HIV-infected patients is strongly associated with CD4 cell counts <500 cells/μL; we also found that most of patients on ART presenting with TB disease had CD4 cell counts <500 cells/μL at the time of ART initiation. These findings suggest that the impact of ART on the TB disease burden will be greatly improved by ART policies that minimize the time that patients spend with CD4 cell counts <500 cells/μL.[6,12–14]

Among ART-naïve patients, only 75% were commenced on ART during TB treatment, a proportion similar to that reported by others studies[9,15] and the Botswana National TB programme.[1] This finding is probably related to poor guideline implementation and integration of TB and HIV care.[3,16,17]

The analysis of predictors of mortality in the overall study population showed that mortality was higher among patients who were not initiated on ART during TB treatment, had opportunistic infections other than TB, experienced a major side effect during TB treatment, were older and had anemia. Some of these findings are consistent with those of other studies.[4,5,9,10,18,19]

Furthermore, patients not on ART during TB treatment had a 5.6-fold increased risk of mortality (95% CI: 2.9–11) compared with patients on ART. Although the beneficial role of ART in the management of patients with TB-HIV coinfection is well documented,[18–22] the time of ART initiation during TB treatment is still controversial, especially regarding the threshold of CD4 cell counts. Recent trials have demonstrated a beneficial impact of ART initiation 2 to 4 weeks after the initiation of TB treatment in patients with advanced immunodeficiency.[23,24] Although a recent review reports improved survival if ART is initiated early in TB-HIV coinfected patients with advanced immunodeficiency, there are also reports that there is insufficient evidence to support a survival benefit conferred by early ART initiation in patients with CD4 cell counts >50 cells/μL.[25]

Furthermore, TB-HIV coinfected patients with opportunistic infection was associated with an 8.5-fold increased risk of mortality (95% CI: 4–18.4) compared with those with only TB-HIV coinfection. This finding was consistent with those of other studies.[15,19,20,26–28]

The occurrence of major side effects during TB treatment was found to be strongly associated with an increased risk of mortality (HR: 5, 95% CI: 1.6–17). Among patients documented to have experienced a major side effect, hepatotoxicity was reported in all but 1 patient who had Stevens Johnson syndrome. Previous studies have documented the association between hepatotoxicity and mortality.[29,30] This evidence highlights the importance of close monitoring of patients during TB treatment, especially during the first 2 months of TB treatment and at the time of ART initiation.

Our study has added to the literature that reports the strong association between mortality and unexplained anemia (Hb < 10 g/dL, HR: 2.4, 95% CI: 1.3–4.5). This finding suggests that in TB-HIV coinfected patients, at the time of TB diagnosis baseline blood tests, including a full blood count should be done to exclude anemia. Other studies have also reported anemia as an HIV-related complication in HIV-infected persons.[31]

In patients previously initiated on ART, opportunistic infections other than TB were strongly associated with an increase in mortality (HR: 6, 95% CI: 2–18). This could be because of the poor adherence to ART observed in some of the patients on ART presenting with active TB disease in this study. Thus, continuous interventions are needed to improve adherence to ART to reduce the likelihood of the occurrence of opportunistic infections and to improve survival in this population.[32]

In the ART-naïve group, thus no ART use during TB treatment, the concurrence of opportunistic infection and the occurrence of a major side effect were strongly associated with increased risk of mortality (HR: 8.1, 16, and 8.3 and 95% CI: 3.4–19.4, 6.2–42, and 2.6–27, respectively). Possible reasons might be poor implementation of clinical guidelines, the challenges of the integration of TB-HIV care, inadequate clinical monitoring, and late presentation, which may limit the benefit that early ART can provide to this subgroup of patients in whom the diagnosis of HIV was mostly made at the time of TB diagnosis.[9]

The limitations of the study included the fact that it was a retrospective observational study using data from routine medical records in the public health sector. At the time, some data were missing or incomplete. For example, white blood cell differentials were not included in the multivariate analyses as so much data were missing. Further research could explore the role of white blood cell differentials, especially the neutrophil count.

Furthermore, due to the relatively low mortality by study group of interest, there could be a possibility of a Type 2 error to detect a statistically significant difference in the proportion of patients who died in the 2 groups of interest (ART naïve vs prior ART). In addition, as the sample size of this study was estimated based on a study conducted in Brazil, further research could be undertaken using a sample size estimated based of Southern Africa data with similar TB-HIV epidemiology to Botswana.

Although this study was conducted in 1 district in Botswana only, as this district is similar to other districts with regard to TB and HIV characteristics, the results can be generalized to the country as a whole.

5. Conclusion

We conclude that our study in Botswana, a setting with limited resources, demonstrates that even after a long period of universal access to ART, the rate of mortality in HIV-TB coinfected patients is still high. Our findings suggest that to reduce mortality in patients on treatment for HIV-associated TB, more careful clinical monitoring of patients together with initiation of ART during TB treatment is indicated.

Acknowledgments

The authors acknowledge and thank Tonya Esterhuizen for her help with the statistical analysis. They also thank Dr Gobusaone Morupisi, Dr Kabunda wa Kabunda, Ms Kgomotso Kebadile, Ms Giltah Goitsemodimo, Ms Baitsekgabo Majelantle, and Ms Oarabile Cynthia from the Serowe/Palapye District and facility level managers, doctors, nurses, and data capturers at the study sites for their assistance. They gratefully acknowledge the participants in the study.

Author contributions

All the authors had full access to all the data in the study. LMM as corresponding author had the final responsibility for the decision to submit the article for publication. The final version of the manuscript has been read and approved by all the authors, and the requirements for authorship have been met. Each author believes that the manuscript represents honest work.

This study was self-funded, and the article is in partial fulfilment of the requirements for an MSc in Clinical Epidemiology.

Conceptualization: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.
Data curation: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.
Formal analysis: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.
Funding acquisition: Ley Muyaya Muyaya.
Investigation: Ley Muyaya Muyaya, Marian Loveday.
Methodology: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.
Project administration: Ley Muyaya Muyaya.
Supervision: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.
Validation: Taryn Young, Marian Loveday.
Visualization: Taryn Young, Marian Loveday.
Writing – original draft: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.
Writing – review and editing: Ley Muyaya Muyaya, Taryn Young, Marian Loveday.

References

[1] World Health Organization. Global Tuberculosis Report 2017. Geneva, Switzerland: World Health Organization. Available at: http://www.who.int/tb/publications/global_report/en/. Accessed November 1, 2017.
[2] Mukadi YD, Dermot M, Anthony H. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS 2001;15:143–52.
[3] Gupta RK, Lucas SB, Fielding KL, et al. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015;29:1987–2002.
[4] Pepper DJ, Marais S, Wilkinson RJ, et al. Clinical deterioration during antituberculosis treatment in Africa: incidence, causes and risk factors. BMC Infect Dis 2010;10:83.
[5] Komati S, Shaw PA, Stubbs N, et al. Tuberculosis risk factors and mortality for HIV-infected persons receiving antiretroviral therapy in South Africa. AIDS 2010;24:1849–55.
[6] Lawn SD, Myer L, Edwards D, et al. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS 2009;23:1717–25.
[7] Botswana National ARV Therapy Programme. National HIV&AIDS Treatment Guidelines, 2012. Gaborone, Botswana: Ministry of Health; 2012.
[8] World Health Organization. Treatment of Tuberculosis Guidelines. 4th ed. Geneva, Switzerland; 2010. Available at: http://www.who.int/tb/publications/2010/9789241547833/en/. Accessed March 2, 2015.
[9] Schmaltz CA, Santoro-Lopes G, Lourenço MC, et al. Factors impacting early mortality in tuberculosis/HIV patients: differences between subjects naive to and previously started on HAART. PLoS One 2012;7:e45704.
[10] Taarnhøj GA, Engsig FN, Ravn P, et al. Incidence, risk factors and mortality of tuberculosis in Danish HIV patients 1995–2007. BMC Pulm Med 2011;11:26.
[11] Gupta A, Wood R, Kaplan R, et al. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. PLoS One 2012;7:e34156.
[12] Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med 2012;9:e1001270.
[13] Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493–505.
[14] Severe P, Jean Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med 2010;363:257–65.
[15] Ismail I, Awang B. Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. PLoS One 2013;8:e73250.
[16] Lawn SD, Wood R. Timing of antiretroviral therapy for HIV-1-associated tuberculosis. N Engl J Med 2012;366:474author reply 475–6.
[17] Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011;365:1492–501.
[18] Worodria W, Massinga-Loembe M, Mazakpwe D, et al. Incidence and predictors of mortality and the effect of tuberculosis immune reconstitution inflammatory syndrome in a cohort of TB/HIV patients commencing antiretroviral therapy. J Acquir Immune Defic Syndr 2011;58:32–7.
[19] Català L, Orcau A, García de Olalla P, et al. Survival of a large cohort of HIV-infected tuberculosis patients in the era of highly active antiretroviral treatment. Int J Tuberc Lung Dis 2011;15:263–9.
[20] Girardi E, Palmieri F, Angeletti C, et al. Impact of previous ART and of ART initiation on outcome of HIV-associated tuberculosis. Clin Dev Immunol 2012;2012:8.
[21] Loveday M, Wallengren K, Brust J, et al. Community-based care vs. centralised hospitalisation for MDR-TB patients KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis 2015;19:163–71.
[22] Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. J Acquir Immune Defic Syndr 2009;50:148–52.
[23] Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010;362:697–706.
[24] Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011;365:1471–81.
[25] Uthman OA, Okwundu C, Gbenga K, et al. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis. Ann Intern Med 2015;163:32–9.
[26] Podlekareva DN, Panteleev AM, Grint D, et al. Short-and long-term mortality and causes of death in HIV/tuberculosis patients in Europe. Eur Respir J 2014;43:166–77.
[27] Moore D, Liechty C, Ekwaru P, et al. Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. AIDS 2007;21:713–9.
[28] Wong EB, Omar T, Setlhako GJ, et al. Causes of death on antiretroviral therapy: a post-mortem study from South Africa. PLoS One 2012;7:e47542.
[29] Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003;167:1472–7.
[30] Sharma SK. Antituberculosis drugs and hepatotoxicity. Infect Genet Evol 2004;4:167–70.
[31] Volberding PA, Levine AM, Dieterich D, et al. Anemia in HIV infection: clinical impact and evidence-based management strategies. Clin Infect Dis 2004;38:1454–63.
[32] Wood E, Hogg RS, Yip B, et al. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 × 109 cells/L. Ann Intern Med 2003;139:810–6.