Title

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High Treatment Success Rates among HIV-infected Multidrug-resistant Tuberculosis Patients after Expansion of Antiretroviral Therapy in Botswana, 2006–2013

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Abstract

Background: Few studies have examined multidrug-resistant (MDR) tuberculosis (TB) treatment outcomes among HIV-infected persons after widespread expansion of antiretroviral therapy (ART). We describe MDR-TB treatment outcomes among HIV-infected and HIV-uninfected patients in Botswana after ART expansion.

Methods: We retrospectively reviewed data from patients who started MDR-TB therapy in Botswana during 2006-2013. Multivariable regression models were used to compare treatment outcomes between HIV-infected and HIV-uninfected patients.

Results: We included 588 MDR-TB patients in the analysis, of whom, 47 (8.0%) and 9 (1.5%) were diagnosed with pre-extensively drug-resistant (XDR)-TB and XDR-TB, respectively. Of the 408 (69.4%) HIV-infected patients, 352 (86.0%) were on ART or started ART during treatment, and median baseline CD4+ T cell count was 234 cells/mm^3. Treatment success rates were 79.4% and 73.0% among HIV-uninfected and HIV-infected patients, respectively (P = 0.121). HIV-infected patients with CD4+ T cell count <100 cells/mm^3 were more likely to die during treatment compared to HIV-uninfected patients (adjusted risk ratio=1.890; 95% CI=1.098-3.254).

Conclusions: High rates of treatment success were achieved with programmatic management of MDR-TB and HIV in Botswana after widespread expansion of ART. However, a two-fold increase in mortality was observed among HIV-infected persons with baseline CD4 <100 cells/mm^3 compared with HIV-uninfected persons.

Key words: tuberculosis, treatment outcomes, HIV/AIDS, immune suppression, antiretroviral therapy

Introduction

Multidrug-resistant (MDR) tuberculosis (TB) is caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid (INH) and rifampicin (RIF), the two most important anti-TB drugs and, therefore, is more difficult and expensive to treat than drug-susceptible TB. While initiation of antiretroviral therapy (ART) during treatment for drug-susceptible TB significantly improves survival, few studies have described treatment outcomes among HIV-infected patients in MDR-TB treatment programs after widespread expansion of ART.[1–3] A recent systematic review found an overall 56.9% treatment success and 38% mortality among HIV-infected adults with MDR-TB.[4] However, most of the studies included in the review were conducted prior to widespread access to ART.[4]

The objective of the present study is to describe treatment outcomes among HIV-infected and HIV-uninfected MDR-TB patients after the expansion of the ART program in Botswana, using routinely collected MDR-TB program data. We hypothesized that high rates of treatment success can be achieved among HIV-infected MDR-TB patients, particularly among those that do not have advanced immune suppression at initial diagnosis.

Methods

Study population and program description

The study population was previously described in a paper based on an earlier version of the study database.[5] All patients enrolled in the national MDR-TB program were registered into a patient cohort database starting in 2006. For this study, we

included data from adult and adolescent patients (age ≥15 years) diagnosed with confirmed or presumed MDR-TB. Patients with unknown HIV status, those who never started treatment, and those still on treatment at the time of the analysis were excluded.

During the study period (2006 – 2013), patients diagnosed with MDR-TB in Botswana were referred to one of five specialized MDR-TB clinics across the country.[5] MDR-TB clinics were staffed by physicians, nurses, and nursing assistants trained and supervised by one of the co-authors (Dr. Modongo). At each clinic, a designated TB focal person provided comprehensive counseling to patients regarding the MDR-TB treatment and its adverse effects, infection control, and the importance of treatment adherence. The clinic physician was responsible for initiating the MDR-TB treatment, monthly monitoring of adverse effects, and monitoring of sputum results. The MDR-TB nurse provided individual follow-up of each patient, including phone calls to patients who missed their monthly consultation. Patients were initiated on a standardized regimen of amikacin, levofloxacin, ethionamide, cycloserine, and pyrazinamide, for a minimum of 18 months after culture conversion.[5] The treatment was ambulatory with the exception of the extensively drug-resistant (XDR)-TB cases, patients living with children less than five years old, and those sharing a room with other household members. These patients were treated as inpatients in the MDR-TB wards until they had culture converted. The treatment was administered daily under directly observed therapy (DOT) at the nearest clinic to the patient's residence. Audiologists and social workers also worked closely with the physician and MDR-TB nurse to provide

psychosocial support and hearing aids, if needed. While no monetary incentives were

provided, treatment support was provided through monthly food distribution and

transportation to the MDR-TB clinic. At completion of treatment, patients continued to

be followed up at the MDR-TB clinic to assess for relapse every quarter for two years.

Laboratory procedures

Drug susceptibility testing (DST) for first-line anti-TB drugs (INH, RIF, ethambutol

[ETH], and streptomycin [STR]) was performed using the proportional agar method on

Lowenstein-Jensen medium or the Mycobacteria Grow Indicator Tube (MGIT) 960

(Becton Dickinson Microbiology Systems, Sparks, MD).[6] DST for second-line drugs

(fluoroquinolones, ethionaminde, kanamycin, amikacin, and capreomycin) was

performed for patients who remained culture positive after six months of treatment.[7]

HIV testing was done at the clinics on an opt-out basis using rapid HIV diagnostic

tests.[8]

Measures

Treatment outcome was defined based on the 2008 World Health Organization

(WHO) guidelines.[9] Patients who were cured or completed treatment were categorized

as having achieved treatment success. Treatment failure was defined as having two or

more positive cultures during the final 12 months of treatment, having a positive culture

on any one of the final three cultures, or clinical decision to stop treatment for any

reason. Any patient whose treatment was interrupted for two or more consecutive

months was considered lost to follow-up. Death was defined as having died during treatment due to any cause.

We extracted HIV infection status and CD4+ T cell values closest to MDR-TB treatment initiation from the cohort database. CD4+ T cell counts were categorized as <100, 100 – 199, 200 – 349, and ≥350 cells/mm^3. Patients with second-line drug resistance patterns available at baseline were categorized as MDR-TB only, pre-XDR-TB (MDR-TB plus resistance to ≥1 second-line injectable drug [amikacin, capreomycin or kanamycin] or ≥1 fluoroquinolone), and XDR-TB (MDR-TB plus resistance to ≥1 second-line injectable drug and ≥1 fluoroquinolone).

Statistical analysis

Bivariate comparisons were performed using the χ^2 test or the Fisher's exact test, and continuous variables were compared using the Wilcoxon Rank Sum test. Two variables for treatment outcome were examined: 1) treatment success, defined as cure or complete (vs. death, failure, or lost to follow-up); and 2) death (vs. all other outcomes). Probabilities of treatment success and death were estimated using frequencies, and the 95% confidence intervals (95% CI) were estimated using the Score method.[10] Dose-response relationship between CD4+ T cell count categories and treatment success or death was assessed using the χ^2 test for trend.[10]

We constructed multivariable Poisson regression models with robust variance to estimate the association between HIV-related immunosuppression and treatment outcomes while controlling for confounding variables.[11–14] This method allowed us to estimate risk ratios, instead of logistic regression models, which generate odds ratio

estimates.[11–14] Separate models were constructed for treatment success and death as dependent variables. The primary independent variable was HIV-associated immune suppression, which was created by combining HIV infection status with CD4+ T cell count categories. We used this combined variable to compare the probability of outcome in each CD4+ T cell count category to that among HIV-uninfected patients. Patients with unknown CD4+ T cell counts were excluded from the bivariate and multivariable analysis. We included the following covariates into the model as potential confounders based on a pre-specified conceptual framework of the causal relationship between HIV-associated immune suppression and TB treatment outcomes: age, sex, and prior history of TB. Factors that could have been influenced by HIV associated immune suppression, including weight and other comorbidities, were not considered as confounders, because controlling for such factors could introduce bias in effect estimates.[15,16]

Ethical considerations

This study was approved by the Botswana Ministry of Health Human Research Development Committee, Centers for Disease Control and Prevention Institutional Review Board (IRB), and the University of Pennsylvania IRB. Informed consent was not obtained from participants as this study involved analysis of routine program data.

Results

Patient characteristics

During 2006 – 2013, 695 patients were diagnosed with MDR-TB and entered into the MDR-TB registry. Twelve patients had multiple episodes, resulting in 708 MDR-TB cases during the period. We excluded data for 43 patients aged < 15 years, 11 patients with unknown HIV status, and 53 patients with unknown outcome status (51 patients were still on treatment, one patient did not start treatment, and the outcome for one patient was missing) (Figure 1). Of the remaining 588 patients included in this analysis, 322 (54.9%) were male and the median age was 36 years (interquartile range [IQR], 29 – 47 years) (Table 1). Most of the patients had bacteriologically confirmed pulmonary MDR-TB and a prior history of TB treatment. Among 194 patients who had available second-line DST results, 47 (24.2%) were diagnosed with pre-XDR-TB and 9 (4.6%) were diagnosed with XDR-TB.

Overall, 440 (74.8%) patients achieved treatment success and 118 (20.1%) died. Treatment outcomes for 9 patients who had initially failed MDR-TB treatment were categorized as completed (n = 1), cured (n = 5), or death (n = 4) based on their subsequent treatment outcome. Of the patients diagnosed with pre-XDR-TB, 32 (68.1%) achieved treatment success and 13 (27.7%) died. Of the patients diagnosed with XDR-TB, 5 (55.6%) achieved treatment success and 3 (33.3%) died.

Our study population included 408 (69.4%) HIV-infected patients. Of these, 208 (51.0%) patients were on ART prior to starting MDR-TB treatment and 351 (86.0%) received ART during MDR-TB treatment (Table 1). Of the 260 patients with known ART regimen, 236 (90.8%) were on first line ART regimens. The median CD4+ T cell count at baseline was 234 cells/mm^3 (IQR, 124 – 379 cells/mm^3). Among HIV-infected patients with known CD4+ T cell counts, 17.9%, 24.0%, 28.8%, and 29.2% had CD4+ T

cell counts <100, 100 – 199, 200 – 349, and ≥350 cells/mm^3, respectively. HIV-infected

MDR-TB patients were older (median age of 37 years vs. 32 years for HIV-uninfected

patients; P = 0.019) and less likely to have previous history of TB treatment (P =

0.039). None of the other characteristics we examined differed between HIV-infected

and HIV-uninfected MDR-TB patients.

HIV-associated immune suppression and treatment success

In bivariate analysis, the observed probability of treatment success was higher

among HIV-uninfected patients compared to HIV-infected patients, but this difference

was not statistically significant (79.4% vs. 73.0%; P = 0.121) (Figure 2a). Likewise, no

statistically significant differences were found when treatment success rates were

compared between HIV-infected patients in the CD4+ T cell categories (<100, 100-199,

200-349, ≥350 cells/mm^3) and HIV-uninfected patients (Table 2). However, we found

evidence of an increasing trend in the probability of treatment success with increasing

CD4+ T cell count categories (from 64.6% among <100 cells/mm^3 to 85.9% among

≥350 cells/mm^3; P_{trend} = 0.002) (Table 2; Figure 2a). In addition, we observed lower

probability of treatment success among patients who were male (70.8% vs. 80.0%

among female patients; RR = 0.885; 95% CI = 0.807 – 0.971), aged 45 – 54 years

(69.0% vs. 83.3% among patients aged 15 - 24 years; RR = 0.828; 95% CI = 0.709 –

0.966), and patients with previous history of TB treatment (74.2% vs. 92.0% among

patients with no previous history of TB treatment; RR = 0.807; 95% CI = 0.712 – 0.915)

(Table 2).

In the multivariable model, no statistically significant differences were found in treatment success probabilities among HIV-infected patients in the CD4+ T cell count categories compared to HIV-uninfected patients after controlling for sex, age, and prior history of TB treatment (Table 2). Age was the only variable that remained independently associated with treatment success in the model (+10 years; risk ratio [RR] = 0.945; 95% CI = 0.907 – 0.985).

HIV-associated immune suppression and death

In bivariate analysis, the observed probability of death was higher among HIV-infected patients compared to HIV-uninfected patients, but this difference was not statistically significant (22.1% vs. 15.6%; P = 0.089) (Figure 2b). HIV-infected patients with CD4+ T cell counts <100 (RR = 2.009; 95% CI = 1.170 - 3.448) and 100 - 199 cells/mm^3 (RR = 1.708; 95% CI = 1.004 – 2.904) were more likely to die during treatment compared to HIV-uninfected patients (Table 3). We found evidence of a decreasing trend in the probability of death with increasing CD4+ T cell count categories (from 31.2% among <100 cells/mm^3 to 12.8% among ≥ 350 cells/mm^3; P_{trend} = 0.005) (Table 3; Figure 2b). In addition, we observed higher risk of death among patients who were male (24.5% vs. 14.7% among female patients; RR = 1.667; 95% CI = 1.178 – 2.360) and aged 45 – 54 years (29.3% vs. 14.3% among patients aged 15 - 24 years; RR = 2.052; 95% CI = 1.131 – 3.721) (Table 3).

In the multivariable model, HIV-infected patients with CD4+ T cell counts <100 cells/mm^3 had higher risk of death compared to HIV-uninfected patients (RR = 1.890; 95% CI = 1.098 – 3.254), after controlling for sex, age, and prior history of TB treatment

(Table 3). No statistically significant differences were found in risk of death between HIV-uninfected patients and HIV-infected patients in CD4+ T cell categories ≥ 100 cells/mm^3 (Table 3). Male sex (vs. female; RR = 1.630; 95% CI = 1.041 – 2.553) and older age (+10 years; RR = 1.228; 95% CI = 1.072 – 1.406) were also independently associated with death.

Discussion

We found high treatment success rates among patients managed by the national MDR-TB program in Botswana. Aspects of this program that may have contributed to high success rates include pre-initiation counseling, strict DOT, food and transport incentives, and follow-up of patients who miss their monthly consultations. In this setting, we found similar probabilities of treatment success and death between HIV-uninfected MDR-TB patients and HIV-infected MDR-TB patients in CD4+ T cell categories ≥100 cells/mm^3. Notably, the WHO goal of 75% treatment success for MDR-TB was reached for HIV-uninfected patients and HIV-infected patients with CD4+ T cell count ≥200 cells/mm^3 (Table 2; Figure 2a). However, HIV-infected MDR-TB patients with advanced immune suppression (CD4+ T cell count < 100 cells/mm^3) were more likely to die during treatment compared to HIV-uninfected patients. Thus, our data suggest that, in the ART era, high rates of treatment success can be achieved for HIV-infected MDR-TB patients who have not progressed to an advanced stage of immune suppression.

Our findings are consistent with a recent systematic review, which suggests that similar levels of treatment success can be achieved between HIV-infected and HIV-

uninfected MDR-TB patients.[4] However, the 73.0% treatment success among HIV-infected MDR-TB patients in our study is substantially higher than the 56.9% reported in that systematic review.[4] The difference in treatment success might be largely due to inclusion in the systematic review of studies done prior to ART access.[4] Our findings are similar to a recent study in Haiti that reported a 78% treatment success among HIV-infected MDR-TB patients on ART.[17] That study was limited by a small sample size (N = 110), including only 27 HIV-infected MDR-TB patients.[17] Using information from a large national cohort of MDR-TB patients, we confirm and extend the findings from the Haiti study by showing that similar levels of treatment success can be achieved among HIV-uninfected MDR-TB patients and HIV-infected MDR-TB patients with CD4+ T cell count $\geq$200 cells/mm^3, in the context of concomitant ART availability in a well-managed MDR-TB program.

Treatment success among HIV-uninfected patients in our study was lower than the 84% – 89% treatment success reported for the short-course MDR-TB regimen recently endorsed by the WHO.[18–21] Additional research is needed to determine the effectiveness of the WHO-endorsed short-course therapy in Botswana, particularly for HIV-infected patients who comprise nearly 70% of the diagnosed MDR-TB patients.

Although Botswana's MDR-TB treatment program achieved successful outcomes and very low rates of treatment failure and loss to follow-up, mortality remained unacceptably high among HIV-infected patients with baseline CD4+ T cell counts <100 cells/mm^3. Among HIV-infected patients with known CD4+ T cell counts, nearly 20% had <100 cells/mm^3 at the time of MDR-TB treatment initiation. These findings highlight the importance of reaching all HIV-infected persons with ART as part

of comprehensive HIV care to prevent advanced immunosuppression and reduce mortality from MDR-TB and other causes. While intensified public health efforts have significantly increased ART coverage in Botswana, our study suggests that gaps in coverage continue to adversely affect HIV-related mortality.[22,23] In June 2016, Botswana launched a "test and treat" program, designed to administer ART to all patients diagnosed with HIV. Based on our findings, this new program could improve treatment outcomes for HIV-infected patients who develop MDR-TB. Additional research is needed to improve the clinical management of MDR-TB patients with advanced immunosuppression.[24]

Strengths of our study include the use of programmatic data that reflect "real-life" experience of the MDR-TB program and its patients. In addition, our sample size of nearly 600 patients, including 408 HIV-infected patients allowed us to make comparisons between HIV-uninfected patients and HIV-infected patients stratified by CD4+ T cell counts.

Our study should be interpreted with consideration of the following limitations. First, we did not collect information on the cause of death. HIV-infected persons with CD4 T cell counts <100 cells/mm^3 are at high risk of death caused by numerous etiologies other than TB, including cryptococcal meningitis and other opportunistic infections.[25] However, ascertaining the cause of death for patients with multiple comorbidities is challenging, and we used the WHO definition of defining death as death due to any cause during TB treatment.[9] Of note, we classified outcomes based on the patient's latest MDR-TB treatment episode, which partially explains the low failure rate in our study. It is also possible that more patients who died were patients

who initially failed treatment. However, given the program's strong emphasis on individual patient follow-up, such "missed" failure events are likely to be minimal. Another limitation is that the program database did not include detailed HIV-related treatment variables, including ART failure and interruption, which could have affected MDR-TB treatment outcomes.

DST for second-line drugs was not done for all MDR-TB patients. Therefore, our study could have underestimated the proportion of patients identified as having pre-XDR and XDR-TB. Similarly, we did not perform DST for pyrazinamide resistance and, as the latest national drug resistance survey did not systematically test for pyrazinamide resistance, we do not know its background prevalence.[26] During the study period, molecular diagnostics, such as Xpert MTB/RIF and line probe assays, were not routinely used. Recently, the Botswana Ministry of Health recommended replacing smear microscopy with Xpert MTB/RIF as the primary TB diagnostic tool. This policy change could lead to earlier diagnosis and more complete ascertainment of MDR-TB cases in Botswana.

Conclusions

We report treatment outcomes from a large national cohort of MDR-TB patients with access to ART in Botswana. High rates of treatment success are possible for HIV-infected MDR-TB patients with moderate to high immune function. Based on our findings, we recommend improved efforts to prevent advanced immunosuppression among HIV-infected persons and additional research to reduce mortality among MDR-TB patients with advanced HIV-associated immunosuppression.

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Figure Legends

Figure 1. Study flowchart of multidrug-resistant tuberculosis patients in Botswana, 2006 – 2013.

Figure 2. Treatment success (A) and death (B) by HIV-infection status and baseline CD4+ T cell counts among multidrug-resistant tuberculosis patients in Botswana, 2006 – 2013.

Table 1. Characteristics of multidrug-resistant tuberculosis patients in Botswana by HIV status, 2006 – 2013.

Characteristic		All patients N = 588	HIV-uninfected N = 180	HIV-infected N = 408	*P* value**
Sex*	Female	265 (45.1%)	84 (46.7%)	181 (44.4%)	0.687
	Male	322 (54.9%)	96 (53.3%)	226 (55.5%)	
Age in years, median (IQR)		36 (29-47)	32 (24-51)	37 (31-45)	0.019
Year of treatment initiation	2006-2007	89 (15.1%)	26 (14.4%)	63 (15.4%)	0.625
	2008-2009	228 (38.8%)	75 (41.7%)	153 (37.5%)	
	2010-2011	166 (28.2%)	45 (25%)	121 (29.7%)	
	2012-2013	105 (17.9%)	34 (18.9%)	71 (17.4%)	
Prior TB	No	25 (4.3%)	10 (5.6%)	15 (3.7%)	0.039
	Yes	492 (83.7%)	157 (87.2%)	335 (82.1%)	
	Unknown	71 (12.1%)	13 (7.2%)	58 (14.2%)	
Site of Infection	Pulmonary	388 (66%)	122 (67.8%)	266 (65.2%)	0.697
	Extrapulmonary	42 (7.1%)	15 (8.3%)	27 (6.6%)	
	Unknown	158 (26.9%)	43 (23.9%)	115 (28.2%)	
Baseline weight in kg, median (IQR)		49.3 (42-56)	49 (42-56)	50 (42.7-57)	0.709
Comorbidities	Yes	71 (12.1%)	22 (12.2%)	49 (12.0%)	1.000
	No	350 (59.5%)	111 (61.7%)	239 (58.6%)	
	Unknown	167 (28.4%)	47 (26.1%)	120 (29.4%)	
Drug Resistance	Presumed MDR	109 (18.5%)	32 (17.8%)	77 (18.9%)	0.658
	MDR (no 2nd line DST done)	285 (48.5%)	93 (51.7%)	192 (47.1%)	
	Confirmed MDR only	138 (23.5%)	40 (22.2%)	98 (24.0%)	
	Pre-XDR	47 (8.0%)	14 (7.8%)	33 (8.1%)	
	XDR	9 (1.5%)	1 (0.6%)	8 (2.0%)	
Anti-TB Drug Regimen	am-lfx-eto-cs-z[¶] only	217 (36.9%)	67 (37.2%)	150 (36.8%)	0.090
	am-cfx-eto-cs-z[‡] + other	83 (14.1%)	30 (16.7%)	53 (13%)	
	am-lfx-eto-cs-z[¥] + other	65 (11.1%)	25 (13.9%)	40 (9.8%)	
	Other	48 (8.2%)	8 (4.4%)	40 (9.8%)	
	Unknown	175 (29.8%)	50 (27.8%)	125 (30.6%)	
Outcome	Completed	264 (44.9%)	90 (50%)	174 (42.6%)	0.318
	Cured	177 (30.1%)	53 (29.4%)	124 (30.4%)	
	Deceased	118 (20.1%)	28 (15.6%)	90 (22.1%)	
	Failure	5 (0.9%)	2 (1.1%)	3 (0.7%)	
	Loss to follow-up	24 (4.1%)	7 (3.9%)	17 (4.2%)	
ART administered	Yes			351 (86.0%)	
	No			24 (5.9%)	
	Unknown			33 (8.1%)	
On ART before TB treatment initiation	Yes			208 (51.0%)	
	No			79 (19.4%)	
	Unknown			121 (29.7%)	

Baseline CD4+ T cell count, cells/mm3, median (IQR)[1]		234 (124-379)
Baseline CD4+ T cell categories, cells/mm3	<100	48 (11.8%)
	100 - 199	64 (15.7%)
	200 - 349	77 (18.9%)
	≥350	78 (19.1%)
	Unknown	141 (34.6%)
ART regimen***	First line	236 (57.8%)
	Second line	24 (5.9%)
	Not on ART	24 (5.9%)
	Unknown	124 (30.4%)

*Sex unknown for one patient

**Based on the X^2 –test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables

[1]CD4+ T cell counts were unknown for 141 patients

[¶] Amikacin-Levofloxacin-ethionamide-cycloserine-pyrazinamide only

[‡] Amikacin-Ciprofloxacin-ethionamide-cycloserine-pyrazinamide + other second-line drugs

[¥] Amikacin-Levofloxacin-ethionamide-cycloserine-pyrazinamide + other second-line drugs

***First line ART regimens were primarily: Tenofovir-Emtricitabine-Nevirapine, Zidovudine-Lamivudine-Efaviranz, Tenofovir-Emtricitabine-Efaviranz, or Zidovudine-Lamivudine-Nevirapine

IQR = interquartile range; ART = antiretroviral therapy; TB = tuberculosis

Table 2. Bivariate and multivariable analysis of the association between HIV-associated immune suppression and treatment success among multidrug-resistant tuberculosis patients in Botswana, 2006 – 2013.

Variable	Percent with treatment success (n/N)	Bivariate analysis Risk ratio (95% confidence intervals)	Multivariable model Risk ratio (95% confidence intervals)
Sex			
Female	80.0% (212/265)	1.00	1.00
Male	70.8% (228/322)	0.885 (0.807-0.971)	0.934 (0.847 - 1.031)
Age in years			
15 - 24	83.3% (70/84)	1.00	
25 - 34	77.1% (121/157)	0.925 (0.814-1.051)	
35 – 44	76.0% (127/167)	0.913 (0.803-1.037)	
45 – 54	69.0% (80/116)	0.828 (0.709-0.966)	
≥55	67.9% (36/53)	0.815 (0.662-1.004)	
Age (+10 year)			0.945 (0.907 - 0.985)
Prior TB			
No	92.0% (23/25)	1.00	1.00
Yes	74.2% (418/563)	0.807 (0.712-0.915)	0.895 (0.772 - 1.037)
CD4+ T cell count, cells/mm^3*			
HIV-uninfected	79.4% (143/180)	1.00	1.00
<100	64.6% (31/48)	0.813 (0.651-1.015)	0.835 (0.667 - 1.046)
100 – 199	70.3% (45/64)	0.885 (0.742-1.055)	0.958 (0.810 - 1.133)
200 – 349	80.5% (62/77)	1.014 (0.888-1.157)	1.021 (0.896 - 1.164)
≥350	85.9% (67/78)	1.081 (0.962-1.215)	1.077 (0.963 - 1.205)

*Patients with unknown CD4+ T cell counts (n = 141) were excluded from the analysis.

Table 3. Bivariate and multivariable analysis of the association between HIV-associated immune suppression and death among multidrug-resistant tuberculosis patients in Botswana, 2006 – 2013.

Variable	Percent of patients who died (n/N)	Bivariate analysis Risk ratio (95% confidence intervals)	Multivariable model Risk ratio (95% confidence intervals)
Sex			
Female	14.7% (39/265)	1.00	1.00
Male	24.5% (79/322)	1.667 (1.178-2.360)	1.630 (1.041 - 2.553)
Age in years			
15 - 24	14.3% (12/84)	1.00	
25 - 34	15.9% (25/157)	1.115 (0.591-2.104)	
35 - 44	17.4% (29/167)	1.216 (0.654-2.259)	
45 - 54	29.3% (34/116)	2.052 (1.131-3.721)	
≥55	26.4% (14/53)	1.849 (0.927-3.687)	
Age (+10 year)			1.228 (1.072 - 1.406)
Prior TB			
No	4% (1/25)	1.00	1.00
Yes	20.8% (117/563)	5.195 (0.756-35.691)	3.558 (0.493 - 25.664)
CD4+ T cell count*			
HIV-uninfected	15.6% (28/180)	1.00	1.00
<100	31.2% (15/48)	2.009 (1.170-3.448)	1.890 (1.098 - 3.254)
100 - 199	26.6% (17/64)	1.708 (1.004-2.904)	1.338 (0.756 - 2.370)
200 - 349	16.9% (13/77)	1.085 (0.595-1.98)	1.137 (0.634 - 2.036)
≥350	12.8% (10/78)	0.824 (0.421-1.613)	0.886 (0.441 - 1.781)

*Patients with unknown CD4+ T cell counts (n = 141) were excluded from the analysis.

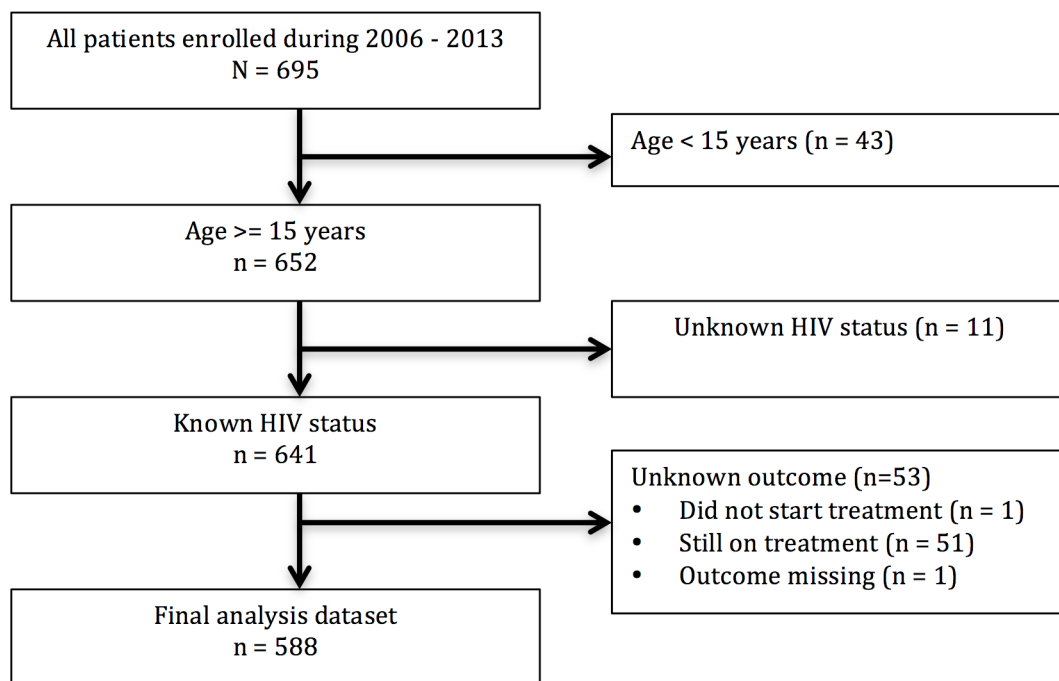Figure 1. Study flowchart of multidrug-resistant tuberculosis patients in Botswana, 2006 – 2013.

Figure 2. Treatment success (A) and death (B) by HIV-infection status and baseline

CD4+ T cell counts among multidrug-resistant tuberculosis patients in Botswana, 2006

– 2013.