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The impact of ART on TB case fatality stratified by CD4 count for HIV-positive TB patients in Cape Town, South Africa (2009–2011)

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Abstract

Objective—To identify determinants of TB case fatality including the impact of antiretroviral therapy (ART) at different CD4 thresholds for HIV-positive adult and adolescent TB patients.

Methods—Through a retrospective analysis of the electronic TB database, we identified the HIV status of newly registered patients 15 yrs. Multivariable Cox proportional hazard models were used to determine risk factors for TB case fatality in these patients.

Results—In 2009, 2010 and 2011, 25,841, 26,104 and 25,554 newly registered adult TB patients were treated in primary health care clinics in Cape Town, of whom 49.7%, 50.4% and 50.9% were HIV-positive. ART uptake increased over the three years from 43% to 64.9% and case fatality of the HIV-positive patients decreased from 7.0% to 5.8% ($p < 0.001$). Female gender, increasing age, retreatment TB, low CD4 counts and extrapulmonary TB (EPTB) were associated with increased case fatality while patients on ART had a substantial decrease in case fatality. The difference in case fatality between patients on ART and not on ART was most pronounced at low CD4 counts with the positive influence of ART noted up to a CD4 count threshold of 350 cells/mm³ ($p < 0.001$). Despite improvements in ART uptake, in 2011, 21% of patients with CD4 counts < 350 cells/mm³ did not start ART during TB treatment.

Conclusion—This study showed a relatively poor uptake of ART among severely immune-compromised TB patients. Patients with CD4 counts < 350 cells/mm³ were shown to clearly benefit from ART during TB treatment and ART initiation should be prioritised for this category of patients.

Keywords

Tuberculosis; HIV; CD4; Antiretroviral Therapy; mortality; case fatality

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Conflicts of Interest

The authors have no conflicts of interest.

Introduction

In sub-Saharan Africa, tuberculosis (TB) case fatality rates of 15 to 35% have been reported in HIV-positive TB patients who did not start antiretroviral therapy (ART) during TB treatment.¹ While a number of studies have shown the benefit of the early initiation of ART in co-infected TB patients with low CD4 counts,^{2–4} there is little evidence to indicate a beneficial effect of ART on TB treatment outcomes in patients with high CD4 counts. Despite this, the WHO and USA HIV treatment guidelines have advised that ART should be started in all HIV-positive TB patients regardless of WHO clinical stage or CD4 count.^{5;6} In the 2013 WHO treatment guidelines this is listed as a strong recommendation with low-quality evidence and in the 2013 USA guidelines it is listed as a strong recommendation with evidence from one or more randomized trials.^{7;8}

The references provided by both guidelines are the STRIDE, CAMELIA and SAPIt studies.^{2–4;9} While these studies provided convincing evidence of the need to start ART during TB treatment for patients with low CD4 counts, the STRIDE and CAMELIA studies enrolled patients with a CD4 count less than 250 and 200 cells/mm³ respectively while the SAPIt study enrolled patients with a CD4 count <500 cells/mm³ and showed a clear survival benefit for patients with CD4 counts <200 cells/mm³ with a trend towards lower mortality in patients with CD4 counts between 200–500 cells/mm³. These studies did not determine an upper CD4 count threshold for the beneficial effect of ART.

Prior to 2012, the South African ART treatment guidelines recommended the initiation of ART for TB/HIV co-infected patients if they had WHO stage 4 disease or met specified CD4 count criteria, initially <200 cells/mm³ in the 2004 guideline and <350 cells/mm³ in the 2010 guideline.^{10;11} In 2012 the South African ART programme adopted the WHO recommendation that all TB patients should start ART.¹²

The lowering of the threshold for ART initiation in TB patients is in line with a general international trend to start ART early in HIV disease. The 2013 WHO guidelines recommend the initiation of ART at a CD4 count <500 cells/mm³ and the 2013 USA Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents advise ART initiation irrespective of CD4 count.^{6;7} It is still unclear whether these strategies will have a beneficial effect on individual patient outcomes and while they may be easily implemented in well-resourced countries, they may be particularly challenging for low income countries with a high burden of disease. Data on ART uptake in TB/HIV co-infected patients and its impact on TB case fatality could provide insight on the potential benefit for different patient groups.

In this study, we looked at trends in HIV/TB co-infection and case fatality rates in primary care TB clinics in the City of Cape Town over a three year period and ascertained the determinants of mortality in the HIV-positive patients. We also examined ART uptake and the effect of ART on TB case fatality at different CD4 thresholds to determine the potential impact of different ART initiation strategies in this patient population.

Methods

Study setting

In Cape Town, TB treatment is provided to ambulant patients in 101 community clinics run by primary health care nurses and supported by doctors. Forty of these clinics also provide antiretroviral treatment on-site with the remainder referring ART eligible patients to their nearest primary health care ART clinic.

During the period of the study, TB treatment was dispensed according to the South African National TB management guidelines with new patients receiving a treatment regimen comprised of a daily fixed dose combination tablet of rifampicin, isoniazid, pyrazinamide and ethambutol for a 2 month period, followed by rifampicin and isoniazid for 4 months. Retreatment TB patients were prescribed streptomycin 5 days a week for 2 months, rifampicin, isoniazid, pyrazinamide and ethambutol daily for 3 months, followed by rifampicin, isoniazid and ethambutol for a further 5 months.¹³

Antiretroviral treatment guidelines changed during the 3 year period with regards to both eligibility criteria and treatment regimens. Until mid-2010, adult HIV-positive patients were eligible for ART if they had a CD4 count <200 copies/mm³ or had Stage 4 disease. The recommended first line treatment regimens were d4t or AZT with 3TC and efavirenz or nevirapine.¹⁰ In 2010, the new South African ART guidelines extended the CD4 eligibility criteria to <350 cells/mm³ and recommended a first line regimen of tenofovir, 3TC and efavirenz.¹¹ Streptomycin and tenofovir were not prescribed together as both drugs are potentially nephrotoxic.¹⁴ The second line ART regimen was comprised of AZT or tenofovir depending on prior exposure during first line plus 3TC and lopinavir/ritonavir. As concomitant use of rifampicin results in lower lopinavir/ritonavir levels, patients on second line ART had the lopinavir/ritonavir boosted with extra ritonavir or the lopinavir/ritonavir dose doubled slowly over a 3 week period.^{10;11}

All TB cases were notified and the case details of patients treated in the primary care TB programme were routinely entered into a facility based paper register which was transcribed into a national electronic TB register (ETR.net) on a quarterly basis.

Population

Included in this analysis were all newly diagnosed adolescent or adult TB patients 15 yrs of age who started TB treatment at one of the primary health care TB clinics in Cape Town between 1 Jan 2009 and 31 Dec 2011. Patients who were initiated on treatment in hospital and were referred to a primary care clinic to continue their treatment were included in the analysis however, to avoid possible duplication of cases, patients who were transferred between primary care clinics were excluded. Also excluded from this study were patients with drug resistant TB.

Study design

This was a retrospective cohort study using an anonymised dataset of routine TB programme data extracted from the national electronic TB register.

Definitions

HIV-status—The HIV status of a patient was defined as positive if the patient had a positive HIV test recorded in the database or was registered as receiving ART and/or co-trimoxazole prophylaxis and/or had a recorded CD4 cell count at start of TB treatment. HIV-negative status was defined by a recorded HIV-negative test result in the database. All other patients were considered to be of unknown HIV status.

TB case definitions and outcomes—TB case definitions and treatment outcomes were recorded in the database according to the internationally recommended WHO case definitions and treatment outcomes of cure, completion, failure, death, default and transferred out.¹⁵ Patients with missing outcomes or more than one outcome were listed as outcome not determined. Case fatality was defined as death during TB treatment. Cause of death was not ascertained.

Analysis—Descriptive analysis determined trends in annual HIV prevalence, median CD4 counts, ART uptake and TB treatment outcomes. The CD4 count distribution and case fatality rates by ART status were calculated for the three year period. Multivariable Cox proportional hazard models were used to determine risk factors for TB case fatality in the HIV-positive patients. Survival analyses with Kaplan-Meier life tables were used to assess mortality and default risks during TB treatment stratified by ART uptake and CD4 counts at start of TB treatment. Censoring occurred at dates of death, default, transfer out, failure, cure or completion within a time period of 24 weeks for new patients and 32 weeks for retreatment patients.

Ethics—Cape Town City Health Directorate approved the use of and provided an anonymised database of routinely collected TB data for this analysis. This study was approved by the University of Cape Town Research Ethics Committee.

Results

Cohort characteristics

From 1 Jan 2009 to 31 Dec 2011, 94,593 patients received TB treatment in the primary care TB clinics in the City of Cape Town. Of these, 17,094 were excluded from this analysis as they were under the age of 15 (n=12,490) or transferred in to care (n=4,604). The remaining 77,499 were patients 15yrs or older who started their TB treatment in one of the 101 primary care TB clinics.

HIV status

HIV status was determined for 96,5% of all patients treated in the three year period. Of these, 50.3% were HIV-positive, 46.2% were HIV-negative and the HIV status of 3.4% was unknown. HIV testing increased over the 3 year period with 2.0% of patients recorded as having unknown status in 2011 compared to 5.4% in 2009. There was a small increase in the proportion of HIV-positive patients over the three years with 49,7%, 50,4% and 50,9% recorded as HIV-positive in 2009, 2010 and 2011 respectively (p=0.09).

Baseline characteristics of the HIV-positive patients

The baseline characteristics of the 38,996 HIV-positive TB patients are listed by year of initiation of TB treatment in Table 1. The median age was 34 [interquartile range (IQR) 28–40] and 54% of the patients were female. There was an increase in the median CD4 count [IQR] from 152 [69–278] in 2009 to 173 [68–305] in 2011 ($p<0.001$). The majority of the patients had pulmonary TB (PTB) (75.8%) and were new TB cases (68.5%). The proportion of retreatment cases increased slightly over the three years from 30.7% in 2009 to 32.4% in 2011 ($p=0.014$). Of the PTB cases, the number of smear negative cases increased from 51.0% in 2009 to 54% in 2011 ($p=0.003$). Overall, 92.5% of patients were started on prophylactic co-trimoxazole treatment.

ART uptake

While the number of co-infected TB patients on ART at TB diagnosis increased over the three year period from 9.9% to 12.8% to 17.9% in 2009, 2010 and 2011 respectively, the majority of HIV-positive patients who started TB treatment were ART-naïve. ART uptake during TB treatment increased over the study period with 4,256 (33.1%), 6,207 (47.2%) and 6,111 (47.0%) of the HIV-positive patients starting ART during TB treatment in 2009, 2010 and 2011 respectively. Overall, 43%, 60% and 64.9% of all co-infected patients were on ART at TB diagnosis or started ART during TB treatment in 2009, 2010 and 2011.

TB treatment outcomes

Table 2 shows TB treatment outcomes by year for the HIV-positive patients. Overall, cure and completion rates were 75.7% over the 3 years. Case fatality rates declined year on year from 7% to 6.4% to 5.8% in 2009, 2010 and 2011 ($p<0.001$). There was no significant change in the default rate (8.7%) over the three years. TB treatment outcomes for the HIV-negative patients showed an overall higher cure and completion rate (82.3%) and a lower case fatality rate (3.3%) than the HIV-positive patients. There was also a decrease in case fatality for the HIV-negative patients from 3.7% to 3.3% to 2.9% in 2009, 2010 and 2011 respectively ($p=0.001$). The default rate of 8.1% was slightly lower than that of the HIV-positive patients (8.8%) over the three years. Treatment failure rates were similar for HIV-positive (2.5%) and HIV-negative patients (2.3%). Case fatality for subgroups of the TB patients are shown in Supplemental Digital Content Table 1. Case fatality for all HIV-positive patients who started ART was 5% over the three year period compared to 8% for patients who did not start ART. In a subgroup of HIV-positive, microbiologically confirmed PTB patients who comprised 31% of the HIV-positive cohort, the case fatality rate was 4.8% for the patients who started ART compared to 7.6% for patients who did not.

CD4 count distribution

Absolute CD4 counts were available for 95.3% ($n=37,163$) of the HIV-positive patients who started TB treatment. Of note is that 33% ($n=12,251$) of the patients were severely immune-compromised with CD4 counts less than 100 cells/mm³ and over 82% ($n=30,492$) had CD4 counts less than 350 cells/mm³ making them eligible for ART based on the 2010 South African National Antiretroviral Guidelines.¹¹ Figure 1a shows uptake of ART by CD4 categories. Over the three year period, 35.4% ($n=10,807$) of the patients with CD4 counts

<350 cells/mm³ did not start ART. Poor uptake of ART was also noted at low CD4 counts with 31.9% (n=2,006) of 6,290 patients with a CD4 <50 cells/mm³ not starting ART. Despite improvements in ART uptake over the three years, in 2011, 21% of patients with CD4 counts <350 cells/mm³ still did not start ART during TB treatment.

Case fatality by CD4 count

Figure 1b shows case fatality rates by CD4 count categories for patients on ART at TB diagnosis (Dx), patients who started ART during TB treatment (Rx) and patients who did not start ART during TB treatment. While the difference in case fatality between patients on ART and not on ART is most pronounced at low CD4 counts, the positive influence of ART is apparent for all patients with CD4 counts less than 350 cells/mm³. Of note is the low case fatality rate for patients with CD4 counts from 350–499 cells/mm³ who were not on ART. At 3.2% (95% CI: 2.5–3.8%), this is no different to the HIV-negative patients who had a case fatality rate of 3.3% (95% CI: 3.2 – 3.5%) over the three year period. It is also not significantly different to the HIV-positive patients who started ART however this should be interpreted with caution as patients with CD4 counts above 350 cells/mm³ were only eligible for ART in this time period if they had a Stage 4 disease. Patients with CD4 count <350 cells/mm³ had a 2.4 increased odds of case fatality compared to those patients with CD4 counts >350 cells/mm³ (OR: 2.4; 95% CI: 2.0–2.7%).

Risk factors for case fatality during TB treatment

In multivariate analysis using Cox proportional hazard models (Table 3), increasing age, female gender, retreatment and extra-pulmonary TB (EPTB) were associated with a higher risk of death during TB treatment. CD4 counts at start of TB treatment were most strongly associated with TB case fatality up to a threshold of 350 cells/mm³. The risk of death for patients with CD4 counts between 200–349 cells/mm³ was 1.87 (95% CI: 1.46–2.42) compared to patients with CD4 counts ≥ 500 cells/mm³ (p<0.001). Although there was a small increase in case fatality for patients with CD4 counts between 350–499 cells/mm³ (Hazard Ratio (HR): 1.19; 95% CI: 0.89–1.58) when compared to patients with CD4 counts ≥ 500 cells/mm³, this was not statistically significant (p=0.24).

The risk of death was reduced in patients receiving ART. This reduction was greatest in patients who started ART during TB treatment (HR: 0.42; CI: 0.39–0.47) but was also reduced by almost half in patients who were on ART at TB diagnosis (HR: 0.53; 95% CI: 0.39–0.47) when compared to patients who did not start ART (p<0.001).

Survival analysis

Figure 2 shows Kaplan-Meier plots of survival and retention in care for the HIV-positive patients. Survival for the HIV-positive patients by CD4 count categories shows significant differences in mortality by CD4 strata in patients with CD4 counts below 350 cells/mm³ (logrank test: p<0.001). However, there was no difference in mortality by CD4 count strata in patients with CD4 counts above 350 cells/mm³ (p=0.69). The survival analysis by ART status was restricted to patients with CD4 count >350 cells/mm³, and shows improved survival in HIV-positive patients receiving ART (p<0.001). Patients on ART were also

significantly less likely to default TB treatment than patients who did not start ART ($p<0.001$). Default rates however were not associated with CD4 count ($p=0.21$).

Discussion

This was a large, well monitored cohort of HIV/TB co-infected patients, with HIV status determined for 96.5% of the patients, CD4 counts available for over 95.3% and TB treatment outcomes ascertained for 97.5% of the HIV-positive patients.

At 50.3% percent, the HIV co-infection rate was high; most patients were not on ART and the median CD4 count at time of TB diagnosis was low, indicating that the primary care TB service remains an important entry point into antiretroviral treatment. While there was an increase in ART uptake during the 3 year period and a concomitant decrease in case fatality among the HIV-positive patients, over a third of patients with CD4 counts <350 cells/mm³ did not start ART.

The effect of ART on case fatality was most pronounced at low CD4 counts but was apparent at all CD4 count categories below 350 cells/mm³. While it is difficult to interpret the influence of ART on case fatality above CD4 counts of 350 cells/mm³ as these patients would only have started ART if they had Stage 4 disease or other co-morbidities, the case fatality rate of 2.5% in patients with CD4 counts above 500 cells/mm³ who did not start ART was lower than the case fatality rate of HIV-negative patients (3.3%) and suggests little potential for an additional beneficial effect of ART during TB treatment for this group of patients.

Poor ART uptake and high case fatality rates for HIV-positive patients have been reported in other studies in sub-Saharan Africa. An integrated TB/HIV clinic in Kenya reported an ART uptake of 70% for co-infected TB patients with 13% of patients dying before starting ART and 6% dying while on ART.¹⁶ In Malawi, ART uptake was 38% in a cohort of smear positive PTB patients with a reported case fatality of 3% for patients on ART and 7% for patients not on ART¹⁷ and in Zimbabwe, ART uptake was 42% in a cohort of 2655 HIV-positive patients with 14% of patients dying while on ART.^{17;18}

While ART uptake in our study compares favourably with these cohorts, that over a third of co-infected TB patients did not access ART confirms that poor ART uptake among TB patients remains an urgent problem. The overall case fatality rate of 6.4% for HIV-positive patients in our cohort was better than many other studies, however this needs to be interpreted with caution as the treatment location for this study was the primary health care TB service and it therefore favoured ambulant patients and did not include patients who received in-patient treatment. It also excluded patients with drug resistant TB. These patients were likely to be sicker and have higher case fatality rates. This analysis may therefore be an underestimate of overall TB case fatality in Cape Town.

While the trend in case fatality on and off ART provides clear evidence of the influence of ART on TB case fatality for different CD4 count categories, this was an observational cohort analysis and the case fatality data may have been subject to both survival bias and bias by indication. Early mortality during TB treatment could result in survival bias which

could inflate the case fatality rates of patients who did not start ART while bias by indication would result from a clinician's propensity to start the sicker patients on ART and could result in increased case fatality on ART. There were insufficient variables in the routine data for us to adjust the analysis for either of these potential biases.

A further limitation of the study was that the programme registered a relatively high default rate. True outcomes for these patients could not be determined and the default rate may have concealed a higher case fatality rate. However in contrast to the case fatality analysis, in the default analysis there was no association between default and CD4 count categories for the HIV-positive patients indicating that default was unlikely to be due to unascertained mortality during TB treatment.

As many of the TB clinics did not provide ART, the recording of ART data occurred through patient history for some patients and may not have been as rigorously captured as the TB data. ART data also did not include ART start dates, so while the positive influence of ART on mortality was clearly shown in the multivariate analysis, the influence of the timing of the start of ART could not be determined.

Despite these limitations, this study has provided insight into HIV testing and HIV prevalence rates, the CD4 count distribution and case fatality in a very large TB treatment programme. Because of the comprehensive CD4 data, our study was able to stratify patients both by ART status and CD4 count categories. This provided excellent data on case fatality for patients on and off ART at various CD4 count categories.

This study showed a relatively poor uptake of ART among severely immune-compromised TB patients and a marked survival benefit of ART at low CD4 counts. Patients with CD4 counts <350 cells/mm³ were shown to clearly benefit from ART during TB treatment and ART initiation should be prioritised for this category of patients. While this study did not show a decrease in TB case fatality in patients starting ART with CD4 counts >350 cells/mm³, the duration of the study was restricted to the period of TB treatment and our findings do not preclude a potential long term survival benefit of starting all patients on ART during TB treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was done in collaboration with Cape Town City Health Directorate, who provided access to the data they routinely collect to monitor the primary care TB treatment programme.

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Figure 1.

ART uptake and TB case fatality stratified by CD4 count for HIV-positive patients with baseline CD4 counts over the 3 year period (n=37,163) (a) ART uptake stratified by CD4 count (b) TB case fatality stratified by CD4 count and ART status. TB=Tuberculosis; Dx=Diagnosis; Rx=Treatment

Figure 2.

Kaplan-Meier plots showing survival and retention in care for the HIV-positive patients. (a) Survival by ART status for HIV-positive patients with CD4 <350 cells/mm³. (b) Survival by CD4 count for HIV-positive patients. (c) Retention in care by ART status for HIV-positive patients. (d) Retention in care by CD4 count for HIV-positive patients.

Table 1

Baseline characteristics of the HIV-positive TB patients 15 years in the primary health care TB programme of the City of Cape Town from 1 Jan 2009 to 31 Dec 2011.

Year	2009	2010	2011	All
All patients, n	25,841	26,104	25,554	77,499
HIV-positive patients, n (%)	12,848 (49.7)	13,151 (50.4)	12,997 (50.9)	38,996 (50.3)
Age, years, median [IQR]	34 [28–40]	34 [28–40]	34 [29–41]	34 [28–40]
Gender				
Female n (%)	6,874 (53.5)	7,189 (54.7)	6,978 (53.7)	21,041 (54.0)
Median CD4 count [IQR]	152 [69–278]	159 [73–284]	173 [68–305]	161 [74–290]
CD4 count categories n (%)				
0–49	2,119 (16.5)	2,163 (16.5)	2,008 (15.5)	6,290 (16.1)
50–99	2,006 (15.6)	2,080 (15.8)	1,875 (14.4)	5,961 (15.3)
100–199	3,186 (24.8)	3,337 (25.4)	3,190 (24.5)	9,713 (24.9)
200–349	2,586 (20.1)	2,884 (21.9)	3,058 (23.5)	8,528 (21.9)
350–499	1,153 (9.0)	1,363 (10.4)	1,489 (11.5)	4,005 (10.3)
500	800 (6.2)	854 (6.5)	1,012 (7.8)	2,666 (6.8)
Not done	998 (7.8)	470 (3.6)	365 (2.8)	1,833 (4.7)
Classification n (%)				
PTB	9,692 (75.4)	9,907 (75.3)	9,951 (76.6)	29,550 (75.8)
EPTB	2,864 (20.9)	2,813 (21.4)	2,664 (20.5)	8,161 (20.9)
Both PTB/EPTB	472 (3.7)	431 (3.3)	382 (2.9)	1,285 (3.3)
Category n (%)				
New	8,901 (69.3)	9,018 (68.6)	8,786 (67.6)	26,705 (68.5)
Retreatment	3,947 (30.7)	4,133 (31.4)	4,211 (32.4)	12,291 (31.5)
PTB and both PTB/EPTB n (%)				
Smear positive	4,331 (42.6)	4,309 (41.7)	4,155 (40.2)	12,795 (41.5)
Smear negative	5,187 (51.0)	5,371 (51.9)	5,554 (53.8)	16,112 (52.3)
No smear	646 (6.4)	658 (6.4)	624 (6.0)	1,928 (6.3)
On ART at start of TB Rx n (%)	1,274 (9.9)	1,683 (12.8)	2,320 (17.9)	5,277 (13.5)
Co-trimoxazole n (%)				
Yes	11,443 (89.1)	12,436 (94.6)	12,144 (93.6)	36,023 (92.5)
No	353 (2.7)	410 (3.1)	549 (4.2)	1,312 (3.4)
Unknown	1,041 (8.1)	298 (2.3)	283 (2.2)	1,622 (4.2)

TB=tuberculosis; IQR=interquartile range; PTB=pulmonary tuberculosis; EPTB=extra-pulmonary tuberculosis

Table 2

TB treatment outcomes by year for the HIV-positive TB patients 15 years in the primary health care TB programme of the City of Cape Town from 1 Jan 2009 to 31 Dec 2011.

Year	2009	2010	2011	All
Patients on TB treatment, n	12,848	13,151	12,997	38,996
Treatment Outcome n (%)				
Cured	3,119 (24.3)	3,130 (23.8)	3,019 (23.2)	9,268 (23.8)
Completed	6,379 (49.7)	6,920 (52.6)	6,940 (53.4)	20,239 (51.9)
Failed	350 (2.7)	341 (2.6)	265 (2.0)	956 (2.5)
Died	900 (7.0)	844 (6.4)	752 (5.8)	2,496 (6.4)
Defaulted	1,095 (8.5)	1,151 (8.7)	1,158 (8.9)	3,404 (8.7)
Moved Out	56 (0.4)	58 (0.4)	82 (0.6)	196 (0.5)
Transferred Out	541 (4.2)	503 (3.8)	434 (3.3)	1,478 (3.8)
Not Determined	408 (3.2)	204 (1.6)	347 (2.7)	959 (2.5)

Table 3

Bivariate and multivariate Cox proportional hazard analyses of risk of death during TB treatment for HIV-positive patients (n=36,176)

	Bivariate		Multivariate	
Patient characteristic	HR (95% CI)	p-value	HR (95% CI)	p-value
Study year	0.91 (0.86–0.95)	<0.001	1.04 (0.98–1.09)	0.188
Age	1.03 (1.03–1.03)	<0.001	1.03 (1.03–1.04)	<0.001
Female Gender	0.90 (0.83–0.97)	0.006	1.16 (1.06–1.26)	0.001
New TB	1		1	
Retreatment TB	1.25 (1.15–1.36)	<0.001	1.34 (1.23–1.48)	<0.001
PTB	1		1	
EPTB	1.11 (0.01–1.22)	0.029	1.12 (1.02–1.24)	0.022
PTB+EPTB	1.31 (1.08–1.60)	0.007	1.18 (0.96–1.45)	0.114
CD4 categories				
0–49	4.34 (3.41–5.51)	<0.001	6.71 (5.26–8.56)	<0.001
50–99	2.93 (2.29–3.74)	<0.001	4.38 (3.41–5.61)	<0.001
100–199	2.06 (1.61–2.62)	<0.001	3.04 (2.38–3.89)	<0.001
200–349	1.42 (1.11–1.83)	0.006	1.87 (1.46–2.42)	<0.001
350–499	1.12 (0.84–1.49)	0.446	1.19 (0.89–1.58)	0.24
500	1		1	
Not on ART	1		1	
On ART at TB diagnosis	0.67 (0.59–0.76)	<0.001	0.53 (0.46–0.60)	<0.001
Started ART during TB Rx	0.58 (0.53–0.63)	<0.001	0.42 (0.39–0.47)	<0.001

HR=Hazard Ratio; CI=confidence interval; TB=tuberculosis; PTB=pulmonary tuberculosis; EPTB=extra-pulmonary tuberculosis; ART=antiretroviral therapy; Rx=treatment