PREDICTORS OF MORTALITY AND TREATMENT SUCCESS OF MULTI- DRUG RESISTANT AND RIFAMPICIN RESISTANT TUBERCULOSIS IN ZIMBABWE: A COHORT ANALYSIS OF PATIENTS INITIATED ON TREATMENT DURING 2010 TO 2015

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Research Article

Predictors of Mortality and Treatment Success of Multi- Drug Resistant and Rifampicin Resistant Tuberculosis in Zimbabwe: a Cohort Analysis of Patients Initiated on Treatment During 2010 to 2015

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Abstract

Zimbabwe is one of the 30 countries globally with a high burden of multidrug-resistant TB or rifampicin-resistant TB (MDR/RR). The World Health Organization (WHO) recommended that patients diagnosed with MDR/RR-TB be treated with 20-24 month standardized second-line drugs (SLDs) since 2010. However factors associated with mortality and treatment success have not been systematically evaluated in Zimbabwe. To assess factors associated with Mortality and treatment success among MDR/RR-TB patients registered and treated under the National Tuberculosis programme in Zimbabwe between January 2010 and December 2015. A retrospective, secondary analysis of the routinely collected data was conducted. In Zimbabwe, TB and DRTB are notifiable diseases and the National TB Programme (NTP) maintains national case registration files on site of all patients initiated on treatment in all notification centres. Despite existing efforts to control MDR TB deaths in the country, the overall mortality rate in this study was 38.90% ; thus in every 100 TB patients approximately 39 die. The relative risk ratio estimates of MDR/RR-TB treatment failure was distributed as follows: Not recorded Culture conversion period (RRR 1.75, p=0.018; ≤ 10% missed TB treatment doses had RRR=4.75, p <0.001, >10% missed doses (RRR = 9.28, p <0.001); Comorbidity (RRR=1.44, p=0.02); patient ART status was a significant associated factor of treatment success or failure (RRR=3.92, p<0.001). Patients who were not on ART had a high risk of death by 3.92 times compared to patients who were on ART. The findings show evidence of suboptimal MDR/RR-TB treatment success rates in this largely HIV co-infected patient population mainly due to longer culture conversion period, high magnitude of >10% missed doses, poor monitoring of patients due to incomplete documentation, prevalent comorbidities, missed ART opportunities i.e. Patients who were HIV positive and not on ART were more likely to die as compared to patients who were HIV positive and on ART. Being not on ART when HIV positive was a major significant predictor of mortality. Improving ART uptake among those ART-naïve and strategies aimed at improving treatment adherence are important in improving treatment success rates. Future studies should focus on profiling management of MDR/RR-TB patients accessing care at the primary level health care facilities in this setting.

Keywords: Mortality, Predictors, Treatment Success, Rifampicin-resistant Tuberculosis, ART Monitoring, TB/HIV Co-infections

INTRODUCTION

In 2017, there were an estimated 10 million incident TB patients globally and 1.6 million deaths due to TB disease.[1]Lately, drug-resistant TB (DR-TB) has emerged as a global public health concern. DR-TB control efforts are being curtailed due to complexity of its treatment and its associated unfavourable treatment outcomes. World Health Organization (WHO) estimates were about 558,000 incident multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) patients globally in 2017, and only 29% were notified. In the same year (2017), 3.5% patients who had MDR/RR-TB were estimated to be new TB cases and 18% were previously treated TB cases.[1]

Directly observed treatment, short-course (DOTS) with 20-24 month standardized second-line drug (SLDs) regimens for treatment of MDR/RR-TB patients in low to middle income settings was recommended by WHO in 2010.[2,3] A target of achieving a 75-90% treatment success rate (i.e. cured or treatment completed) by 2015 was also set by WHO.[4] In spite of this, the 2018 global TB report shows that only 55% of patients initiated on MDR/RR-TB treatment during year 2015 had successful treatment outcomes.[1] Results of a systematic review conducted in 2017 showed a successful treatment outcome of 64% among MDR/RR-TB patients on standardized SLD regimen. However, the studies included in the review were largely from countries with low HIV coinfection and a systematic assessment of treatment outcomes in high HIV coinfection countries of sub-Saharan Africa is strongly recommended.[5]. Deafness and liver damage are usually a result of treatment of MDR/RR-TB which is not only longer and more complex but also involves use of drug regimens that are more toxic.[6,7] Though, recently WHO has recommended shorter regimens for

management of MDR/RR-TB, low-middle income countries still largely use longer standardized SLD regimens requiring patients to consume drugs for not less than eighteen months.

In Studies conducted in various countries on MDR/RR-TB treatment outcomes, results show that factors specific to individual patients vary and are also related to TB program implementation.[8–11] Unsuccessful treatment outcomes at patient-level are usually as a result of characteristics such as HIV-coinfection, alcohol and substance use, smoking and low body mass index. Programmatic characteristics such as delay in treatment initiation, duration of treatment, type of drug sensitivity testing, individualized treatment regimens and use of directly observed therapy have also been found to be associated with adverse MDR/RR-TB treatment outcomes.[8–11]

Zimbabwe, is located in southern Africa and is among the 14 high burden countries (HBCs) with a triple burden of TB, TB/HIV and MDR-TB.[1] . In 2017 Zimbabwe had an estimated 37,000 incident TB patients and 8,300 TB-associated deaths .[1] An estimated 1,300 MDR/RR-TB patients in the country in the same year with a prevalence of 4.6% and 14% among new and previously treated TB patients respectively was reported.[1]. The National TB Programme (NTP) of Zimbabwe released the "Programmatic Management of Drug Resistant TB" guidelines in 2010 with use of standardized SLDs for twenty months.

WHO estimated that less than 40% of the MDR/RR-TB patients were diagnosed and put on treatment in Zimbabwe in 2017.[13] In the same report, among those initiated on treatment, more than 50% had unfavourable treatment outcomes.[13] There has been no systematic assessment of predictors of Mortality and treatment success of MDR/RR-TB patients treated under the Zimbabwe NTP nor has there been assessment of the individual and programmatic characteristics associated with Mortality and treatment success. Knowledge on predictors of mortality and treatment success among MDR/RR-TB patients can guide the NTP to make informed decisions on policies and strategies aimed at improving patient care for subsequent MDR/RR-TB patient cohorts. We therefore conducted a study aimed at assessing factors associated with mortality and treatment success among patients initiated on MDR/RR-TB treatment under the Zimbabwe NTP between 2010 and 2015.

RESULTS AND DISCUSSION

Demographics

The study enrolled 473 participants shown in table 1 below, these were confirmed MDR/RR-TB patients, among them 241 (51.0%) were females and 230 (48.6%) were males. The majority of patients were between 25 to 34 years, 169 (35.7%) followed by 35 to 44 years, 149 (31.5%). The median age was 34 years with an interquartile range between 29 to 42 years. Most participants were married 202 (42.7%) followed by those who were single 143 (30.2%).

Table 1. Demographic characteristics of MDR/RR-TB patients initiated on treatment during 2010 to 2015 in Zimbabwe

Characteristic (n =473	n (%)
Sex	
Male	230 (48.6)
Female	241 (51.0)
Missing	2 (<1)
Age	
<24	68 (14.4)
25-34	169 (35.7)
35-44	149 (31.5)
45-54	47 (9.9)
55+	34 (7.2)
Not recorded	6 (1.3)
Median (IQR)	34 (29 – 42)
Marital status	
Married	202 (42.7)
Single	143 (30.2)
Widowed	44 (9.3)
Divorced	25 (5.3)
Missing	59 (12.5)

IQR = interquartile range

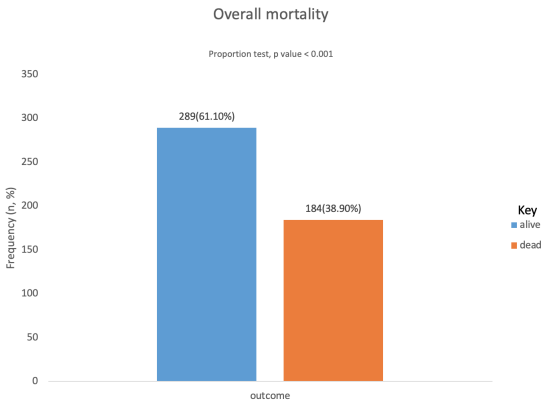

Figure 1. Overall mortality rate of MDR/RR-TB

Mortality

The overall mortality rate in this study was 38.90% (fig 1); this may imply that in every 100 MDR/RR-TB patients approximately 39 die. Further analysis across the follow up time in days during the study is shown in figure (fig 2) which show the survival of MDR/RR-TB patients along the follow up times.

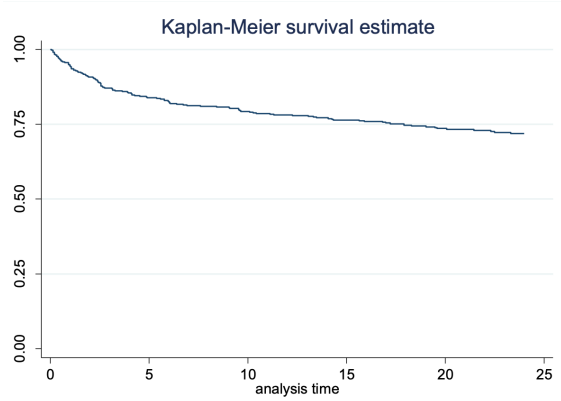

Figure 2. Cumulative survival of MDR/RR-TB patients over time in days

The Kaplan – Meier graph (figure 3) estimates survival at every time point in days, this analysis does not only show occurrence of deaths but, also in the time intervals in days the deaths occur.

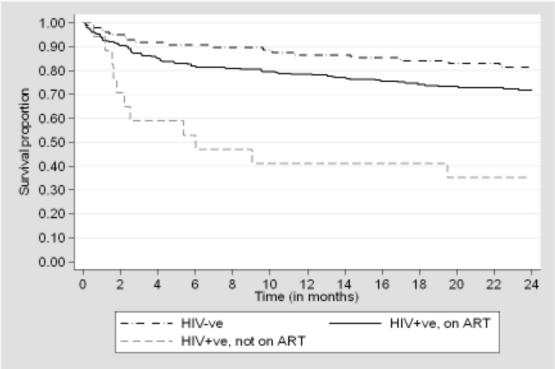

Figure 3. Kaplan-Meier Survival estimates among patients registered and commenced on MDR/RR-TB treatment in Zimbabwe stratified by HIV and ART status

The cumulative probability of MDR/RR-TB patients surviving deaths decreases over time. Further analysis using simple binomial regression modelling to test for factors associated with mortality are shown in **table 2.** These factors are shown at the level of their single effect before adjusting them with other factors in the next modelling stage, which is called multiple binomial regression modelling for risk ratios (RRR).

Table 2. Simple binomial regression modelling: showing significant factors associated with TB deaths

Outcome	RRR	Std. Err.	z	P>z	95% Conf.	Interval
Female	0.95	0.11	-0.41	0.685	0.76	1.2
Age group						
=<24	0.86	0.18	-0.75	0.454	0.57	1.29
35-44	1.06	0.15	0.4	0.69	0.8	1.41
*45-54	1.41	0.25	1.97	0.048	1	2
*55+	1.55	0.28	2.38	0.017	1.08	2.22
Not recorded	0.92	0.54	-0.14	0.892	0.29	2.91
Marriage status						
Single	1.21	0.17	1.42	0.155	0.93	1.58
Widowed	1.36	0.25	1.66	0.097	0.95	1.95
Divorced	1.14	0.3	0.49	0.623	0.68	1.91
Retreatment after						
Loss to follow	0.92	0.28	-0.27	0.786	0.5	1.69
Failure	0.92	0.13	-0.55	0.585	0.7	1.22
Relapse	0.95	0.15	-0.29	0.774	0.7	1.31
Diagnosis time						
*8-30 days	0.62	0.13	-2.3	0.022	0.41	0.93
31-90 days	0.8	0.2	-0.89	0.372	0.49	1.31
>90 days	0.8	0.2	-0.89	0.372	0.49	1.31
Not recorded	0.87	0.17	-0.7	0.482	0.59	1.28
Isoniazid therapy						
resistant	2.2	0.94	1.83	0.067	0.95	5.1
ethambutol therapy						
Resistant	0.8	0.21	-0.85	0.395	0.48	1.34
Streptomycin therapy						
Resistant	0.7	0.2	-1.26	0.206	0.4	1.22
Culture conversion period						
>6months	0.97	0.37	-0.07	0.944	0.46	2.05
*Not recorded	2.96	0.38	8.42	0	2.3	3.8
Missed TB doses						
=<10% missed	1.1	0.23	0.47	0.639	0.73	1.67
*>10% missed	2.03	0.23	6.24	0	1.62	2.53
Not recorded	1	(omitted)				
weight category						
>=50kg	1.04	0.16	0.23	0.822	0.76	1.41
HIV Status						
*HIV+ve	1.57	0.28	2.57	0.01	1.11	2.22
*HIV unknown	2.24	0.9	2.02	0.044	1.02	4.92
ART status	Ratio	Std. Err.	z	P>z	95% Conf.	Interval
*on ART	1.47	0.26	2.15	0.032	1.03	2.08
*not on ART	2.91	0.6	5.15	0	1.94	4.37
*unknown	2.24	0.9	2.02	0.044	1.02	4.92
Cotrimoxazole therapy						
*N/A	0.72	0.11	-2.1	0.036	0.53	0.98
no	1.32	0.38	0.99	0.321	0.76	2.31
Severe Adverse Events						
no	0.96	0.13	-0.31	0.756	0.73	1.26
Co-morbidity						
*Yes	1.63	0.25	3.14	0.002	1.2	2.2

The associations are shown in form of relative risk ratios (RRR) and the respective level of significance.

Table 2 show significant mortality predictors or factors associated with MDR/RR-TB deaths as listed and described below:

- age groups 45 – 54 years (RRR=1.41, p=0.048, the risk of death was increased by 1.41 times in this age compared to other age groups) and 55+ years (RRR=1.55, p=0.017, a patient in this age group had a risk of dying increased by 1.55 times compared to other age groups);
- diagnosis time duration of 8 – 30 days (RRR = 0.62, p = 0.022, a shorter diagnosis time duration between 8 to 30 days actually reduced the risk of TB deaths by 0.62 times compared to longer periods ;
- missed TB doses of >10% (RRR=2.03, p<0.001, missing TB doses of > 10% increased the risk of MDR/RR-TB deaths by 2.03 times compared to missing TB doses of ≤ 10%);
- HIV positive status (RRR = 1.57, p=0.010, the risk of dying among MDR/RR-TB infected patients is increased by 1.57 in HIV positive patients while HIV status unknown was (RRR= 2.24, p=0.044. It is more harmful to have an HIV status which is not known as the risk of dying among these patients were increased by 2.24 times when compared to those with a known HIV status;
- ART status: Among TB patients on ART, there seem to be problems with ART monitoring or adherence issues because there were significant deaths occurring among patients on ART as well (RRR=1.47, p=0.032).
- Cotrimoxazole therapy: MDR/RR-TB Patients who were not given Cotrimoxazole therapy had reduced risk of dying (RRR=0.72, p = 0.036), thus the risk of dying was reduced by 0.72 times. This may be because these patients had an HIV negative status.
- Co-morbidity: MDR/RR-TB patients with comorbid conditions had increased risk of dying (RRR=1.63, p=0.002), comorbidity increased the risk of deaths among MDR/RR-TB patients by 1.63 times.

The next table, **table 3** show adjusted RRR after adjusting for other factors included in the multivariate model, the significant factors from multiple binomial regression modelling (table 3) are listed as follows:

- Culture conversion period (Not recorded had adjusted RR (RRR) =1.75, p=0.018);
- Doses missed (≤10% missed doses had RRR=4.75, p <0.001, >10% missed doses had RRR = 9.28, p <0.001, Not recorded had RRR =3.22, p <0.001)
- Comorbidity: TB patients with comorbidities had RRR=1.44, p=0.024

Treatment Success

The most dominant duration in months for culture conversion from date DR-TB treatment started was ≤ 6 months, 259 (54.8%). Only a few samples were > 6 months, 28 (5.9%). Only 31.5% completed their treatment, among those treated only 29.6% were cured. About 8.3% were lost to follow up whilst 3.5% were not evaluated. Table 4 below show results from univariate binomial regression modelling of treatment failure, and the emerging significant factors.

Table 3. Multiple binomial regression modelling: showing RRR for possible factors of MDR/RR-TB mortality

Death	RRR	Std. Err	Z	P> z	[95% onf	Interval]
Age group						
25-34	2.85	1.78	1.69	0.092	0.84	9.66
35-44	2.63	1.67	1.52	0.129	0.76	9.12
45-54+	2.16	1.50	1.10	0.270	0.55	8.46
55+	2.82	1.81	1.61	0.107	0.80	9.95
Not recorded	1.37	1.10	0.39	0.696	0.28	6.59
Diagnosis time duration						
8-30 days	1.15	0.40	0.41	0.679	0.58	2.28
31-90 days	0.88	0.37	-0.30	0.765	0.39	2.01
>90 days	1.05	0.48	0.10	0.919	0.43	2.55
Not recorded	0.52	0.25	-1.38	0.166	0.20	1.31
***Culture conversion period**						
>6months	0.75	0.57	-0.39	0.699	0.17	3.29
Not recorded	1.75	0.42	2.36	0.018	1.10	2.79
***Doses missed**						
=<10 % missed doses	4.75	1.85	3.99	0.000	2.21	10.21
>10% missed doses	9.28	2.04	10.14	0.000	6.03	14.27
Not recorded	3.22	2.88	6.45	0.000	2.40	11.75
Hiv status						
HIV+ve	1.00	(omitted)				
Art status						
Not on ART	1.78	1.21	0.85	0.396	0.47	6.74
Cotrimoxazole therapy						
yes	1.18	0.47	0.42	0.677	0.54	2.59
***comorbidity**						
Yes	1.44	0.16	-2.25	0.024	0.22	0.90

Age group was significantly associated with treatment outcomes, older ages between 45 to 54 years (RR=1.65, p=0.029) and those aged 55+ years (RR=1.81, p=0.012) show higher risks of treatment failure respectively. Diagnosis time was associated with treatment outcome, the shorter the time from diagnosis to treatment reduces the chances of treatment failure; the period of 8 to 30 days was protective, reduced the risk of treatment failure by 0.62 times compared other time intervals. The number of people without recorded culture conversion period had a high risk of treatment failure (RR=2.96, p<0.001). The number of treatment doses missed was a predictor of treatment failure, > 10% missed doses (RR=2.03, p<0.001). Other factors important were being HIV positive (RR=1.57, p=0.01), ART status:

HIV +ve on ART (RR=1.47, p=0.032), HIV+ not on ART (RR=2.91, p<0.001), HIV status unknown (RR=2.24, p=0.044) and Comorbidity (RR=1.63, p=0.002).

Table 4. Univariate binomial regression modelling for risk outcomes of treatment failure

Outcome 2	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Sex						
female	0.95	0.11	-0.41	0.685	0.76	1.2
***Age group**						
25-34	1.17	0.24	0.75	0.454	0.78	1.76
35-44	1.24	0.26	1.02	0.306	0.82	1.87
*45-54+	1.65	0.38	2.18	0.029	1.05	2.6
*55+	1.81	0.43	2.5	0.012	1.14	2.88
not recorded	1.08	0.65	0.13	0.9	0.33	3.53
Marital status						
single	1.21	0.17	1.42	0.155	0.93	1.58
widowed	1.36	0.25	1.66	0.097	0.95	1.95
divorced	1.14	0.3	0.49	0.623	0.68	1.91
b1tbtyp						
Rx after LTFU	0.92	0.28	-0.27	0.786	0.5	1.69
Rx after Failure	0.92	0.13	-0.55	0.585	0.7	1.22
Rx/Relapse	0.95	0.15	-0.29	0.774	0.7	1.31
***diagtime2**						
*8-30 days	0.62	0.13	-2.3	0.022	0.41	0.93
31-90 days	0.8	0.2	-0.89	0.372	0.49	1.31
>90 days	0.8	0.2	-0.89	0.372	0.49	1.31
not recorded	0.87	0.17	-0.7	0.482	0.59	1.28
2.b14hr	2.2	0.94	1.83	0.067	0.95	5.1
2.b14e	0.8	0.21	-0.85	0.395	0.48	1.34
2.b14s	0.7	0.2	-1.26	0.206	0.4	1.22
***culturecon**						
>6months	0.97	0.37	-0.07	0.944	0.46	2.05
*not recorded	2.96	0.38	8.42	0	2.3	3.8
*dosemiss2	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
≤ 10% missed doses	1.1	0.23	0.47	0.639	0.73	1.67
*> 10% missed doses	2.03	0.23	6.24	0	1.62	2.53
not recorded	1	(empty)				
weightcat						
≥50kg	1.04	0.16	0.23	0.822	0.76	1.41
***b2hivstat2**						
*HIV+ve	1.57	0.28	2.57	0.01	1.11	2.22
*HIV unknown	2.24	0.9	2.02	0.044	1.02	4.92
***b17art**						
*not on ART	1.98	0.29	4.75	0	1.49	2.63
***hivart**						
*HIV+ve,on ART	1.47	0.26	2.15	0.032	1.03	2.08
*HIV+ not on ART	2.91	0.6	5.15	0	1.94	4.37
*HIV status unknown	2.24	0.9	2.02	0.044	1.02	4.92
***b3cotri**	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
*yes	1.38	0.21	2.1	0.036	1.02	1.87
c1sae						
no	0.96	0.13	-0.31	0.756	0.73	1.26
***como**						
*Yes	1.63	0.25	3.14	0.002	1.2	2.2

Adjusted relative risk ratio after multiple regression modelling show that patient ART status was a significant factor associated with treatment success or failure (ARR=3.92, p<0.001). Patients who were not on ART had a high risk of TB treatment failure by 3.92 times compared to patients who were on ART treatment (table 5).

Table 5. Adjusted relative risk ratio after multiple regression modelling

outcome2	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
agegroup2						
25-34	1.54	0.89	0.75	0.455	0.5	4.78
35-44	1.11	0.57	0.19	0.846	0.4	3.04
45-54+	1.12	0.89	0.14	0.888	0.24	5.28
55+	1.75	1.31	0.75	0.454	0.4	7.58
2.b14hr	2.56	1.81	1.33	0.183	0.64	10.25
2.b14s	0.48	0.18	-1.95	0.051	0.23	1
b2hivstat2						
HIV+ve	1	(omitted)				
***b17art**						
*not on ART	3.92	1.18	4.52	0	2.17	7.07
b3cotri						
no	1	(empty)				
como						
Yes	1.68	0.72	1.2	0.23	0.72	3.91
cons	0.09	0.09	-2.6	0.009	0.02	0.56

Discussion

This was the first nationwide study in Zimbabwe to assess predictors of mortality and treatment success among MDR/RR-TB patients in a routine programme setting. The key findings of the study which are programmatically important are listed here. After all efforts to control MDR/RR- TB deaths in the country, the overall mortality rate in this study was 38.90% ; thus in every 100 TB patients approximately 39 die, despite the current existing efforts to control deaths. After controlling for potential confounding factors, adjusting for factors included in the binomial regression multivariate model, the significant factors are listed as follows:

- The number of patients without recorded culture conversion results had a high risk of treatment failure (RR=2.96, p<0.001).
- Missing TB doses of > 10% increased the risk of MDR/RR-TB deaths by 2.03 times compared to missing TB doses of ≤ 10%);
- Co-morbidity: MDR/RR-TB patients with comorbid conditions had increased risk of dying (RRR=1.63, p=0.002), comorbidity increased the risk of deaths among MDR/RR-TB patients by 1.63 times.
- Adjusted relative risk ratio from multiple regression modelling show that patient ART status was a

significant associated factor of treatment success or failure (ARR=3.92, p<0.001). Patients who were HIV positive and not on ART had a high risk of death by 3.92 times compared to patients who were HIV positive and on ART

- The risk of death was increased by 1.41 times in Age groups 45 – 54 years (RRR=1.41, p=0.048) and 55+ years((RRR=1.55, p=0.017) compared to other age groups, a patient in this age group had a risk of dying increased by 1.55 times compared to other age groups); These results are comparable to findings from a study in South Africa by Kathryn Schnippel et-al which also noted that the aged >60yrs had an increased risk of dying. This could possibly be due to reduced immunity as a result of advanced age. The NTP of Zimbabwe and other prorammes in similar settings will therefore need to prioritise patients on care in these age groups to avert possible deaths.
- The period between diagnosis time and initiation of treatment of 8 – 30 days (RRR = 0.62, p = 0.022, was shown to reduce the risk of TB deaths by 0.62 times compared to longer periods.

The strengths of this study are well documented. This study included 473 cases of MDR/RR-TB patients under directly-observed treatment in a National TB Programme (DOTS), which Strength is notable. In addition, this reasonably big sample size allowed us to control for several variables.

Second, this study included patients from all the notifying districts in the country and data was collected for patients initiated on treatment over a five year period since the country adopted standardized SLDs, hence findings are useful for decision making in a routine programme setting. Third, the study findings were reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16]

Nevertheless, this study has some limitations. First, non-MDR/RR-TB related deaths such as accidents or other chronic diseases could have been included. However in accordance with the definition of 'Death' In TB patients, any death that occurs during the period of treatment from any cause is attributed to TB. Second, the patients who were referred back to rural primary healthcare facilities for follow-up care after MDR/RR-TB treatment initiation were not included. It is likely that some of those patients died and this may have introduced some bias as these cases were not studied. There could also have been some factors positively affecting treatment success at the rural health centres were some patients were receiving treatment and cases were not included in this study. Factors of individualised patient care may influence treatment success as there are few patients receiving care at these centres necessitating a high level of care and ultimately treatment success. Conversely, patients included in our study were more likely to be from urban areas and with better socio-economic, education levels and better access to clinical services. Thus, the current study cohort is more likely to have had positive factors influencing treatment success. Second, there were missing data on key variables which include CDST results, socioeconomic status, WHO clinical staging, CD4 cell count, nutritional status, MDR-TB drug regimens and their dosages – all which are important factors which may have informed on the predictors of mortality and treatment success. Third, data on co-morbidities was not systematically collected and reported hence, there might have been an underestimation of prevailing comorbidities like diabetes mellitus which require specific diagnostic tests.

Implications of the study findings

First, the high proportion of patients who did not have CDST results during their treatment is cause for concern as this is essential in monitoring bacteriological response to treatment. Bacteriological response to treatment will guide the clinicians on whether to continue or alter treatment. This will avert death and also improve treatment success. In this study the number of patients without recorded culture conversion results had a high risk of treatment failure (RR=2.96, p<0.001). A recent study from Zimbabwe showed leakages in receipt of sputum samples at NRLs, culture contamination among received sputum specimens leading to a reduced proportion of samples with CDST results.[26] This CDST system will require improvements including feedback of CDST results to facilities in order to inform patient management.

Second, the period between diagnosis time and initiation of treatment of 8 – 30 days was shown to reduce the risk of TB deaths by 0.62 times compared to longer periods. Failure to initiate patients on MDR/RR-TB treatment early leads to high death rates in addition to having public health ramifications.

Third, whilst there was a high uptake of ART among those HIV co-infected, there is need to ensure all MDR/RR-TB patients diagnosed with HIV are timely diagnosed and initiated on ART in order to lessen the risk of death. Newly diagnosed MDR/RR-TB Patients will benefit the most as they are less likely to know their HIV status upon presentation with presumptive TB hence require special focus.

Forth, there is need to ensure that patients do not have missed doses during MDR-TB treatment in order to lessen their risk of death. Continuous and consistent monitoring of missed doses can alert the health care provider to ensure the patient is counselled to enhance adherence and increase the chances of treatment success. Although adherence support by both community and health facility DOTs supporters is commendable to limit the number of missed doses, the monetary incentives then to reduce catastrophic costs was not being implemented during the study period.

Fifth, much as most patients had a known HIV status in this study, there is great need for all patients to know their HIV status as HIV status which is not known is shown in this study to increase the risk of dying by 2.24 times when compared to those with a known HIV status. It is highly likely however that these patients might have been HIV positive as the study also showed the high death rate in HIV positive ART naïve patients.

EXPERIMENTAL

Study Design

This was a retrospective cohort study using secondary data routinely collected within the Zimbabwe NTP.

General Setting

Zimbabwe has an estimated population of 17 million people and is landlocked. It shares borders with Mozambique to the east, South Africa to the South, Zambia to the North and Botswana to the South West..[1] The country is divided into ten provinces, two of which are Metropolitan provinces (Harare, the capital city and Bulawayo, the second largest city). The provinces are further sub divided into 62 Districts. The country's public healthcare referral system constitutes four levels: 1) the quaternary level constituting six central hospitals located in the two metropolitan provinces 2) the tertiary level consisting eight provincial hospitals which are the highest referral hospitals providing selected basic medical specialties for the eight rural provinces 3) the secondary level constituting at least one district and or general hospital per district and last 4) the primary care level consisting of rural and urban healthcare facilities that provide primary health care services.

Diagnosis of MDR/RR-TB:

In Zimbabwe, TB diagnosis and treatment services are provided in public healthcare facilities and are integrated with general health services. Private laboratories however complement the efforts by also providing TB diagnosis services for private patients. Prior to 2013, only previously-treated sputum positive pulmonary TB patients and MDR-TB contacts were considered as presumptive MDR-TB patients and evaluated for MDR-TB. Their sputum specimens were subjected to either phenotypic (culture and drug susceptibility testing (CDST)) or genotypic (MTB/Rif assay) testing. From 2013 onwards, Xpert MTB/Rif assay was used upfront for diagnosis of TB and rifampicin resistance in MDR-TB high risk groups (retreatment TB, chest symptomatics of MDR-TB contacts, those HIV-positive, health workers with pulmonary TB, miners with PTB and children <5 years). In all RR-TB patients, the remainder of the two collected sputum specimens is sent to one of the country's two national reference laboratories for CDST in order to assess drug susceptibility to all the first line drugs.[12]

Treatment initiation and follow-up MDR/RR-TB:

All diagnosed MDR/RR-TB patients are registered and started on treatment at either district or provincial hospitals or at polyclinics and infectious disease hospitals in metropolitan provinces. The District Medical Officer is responsible for providing oversight on the clinical management of all MDR/RR-TB patients in their respective districts.

On registration at district hospital, the patient is notified to the NTP and a patient-held DR-TB treatment card is issued. The treatment card is updated simultaneously with the health facility Directly Observed Treatment (DOT) DR-TB register at all patient follow-up visits by health facility workers. The health facility DOT DR-TB register also documents socio-demographic and clinical details of the MDR/RR-TB patients. Patient data in the health facility DOT register are also entered into the DR-TB register which is maintained and updated by DR-TB co-ordinators.

As part of pre-treatment evaluation for all patients, the laboratory investigations such as liver function tests, renal function tests and complete blood count are supposed to be done prior to initiation of treatment. The district clinical management team initiates treatment based on pre-treatment evaluation. Details of the clinical and laboratory examinations are documented in the DR-TB card and also in the clinical notes attached to the DR-TB card. During the study period, the WHO recommended standardised DOTS-

Plus regimen be used for management of MDR/RR-TB patients.[2,14] The duration of treatment was at least 20 months with a minimum of six months (and 4 months after culture conversion) in the intensive phase and 14 months of the continuation phase. Oral drugs namely levofloxacin, pyrazinamide, cycloserine and ethambutol were given both during the intensive and continuation phases. The injectable kanamycin was provided six days a week during intensive phase. Treatment dosages were dispensed based on patient weight.

After treatment initiation, patients are monitored for two weeks at facilities where treatment is initiated before considering if the patient is stable and tolerating the regimen. Those considered "Stable" were patients who were able to ingest medication, did not show signs of adverse drug reaction and had all the laboratory investigations within normal limit. Based on clinical severity and distance of travel from the patient's residence (>10 kms), they are either admitted and monitored or asked to visit the district hospital daily. After two weeks, based on proximity to a health facility, patients either continue DOTS-Plus in district hospitals or they are referred to primary health facilities nearest to their residence. Patients are followed-up as per PMDT guidelines and the programmatic treatment outcomes are ascertained by the medical officer (**Supplementary Table-1**). If a patient developed side-effects due to kanamycin, their dosage was reduced however currently they are switched to capreomycin. [12]

Patients are also offered provider-initiated HIV testing services in the MDR-TB pre-treatment phase and those found to be HIV positive are assessed for initiation on antiretroviral therapy (ART) and cotrimoxazole preventive therapy (CPT). As per the national guidelines in use during the study period, they were initiated on a fixed-dose combination once-daily pill of Tenofovir v+ Lamuvidine (or Emtricitabine) + Efavirenz (TDF+3TC (or FTC)+EFV) as the preferred first-line ART regimen among adult PLHIV and abacavir+lamuvidine+efavirenz (or Lopinavir/r) (ABC + 3TC + EFV (or Lop/r)) as the preferred first-line ART regimen in children living with HIV.[15]

Study Population

All MDR/RR-TB patients initiated on treatment between 2010 and 2015 under the Zimbabwe NTP and continued their treatment at either district hospitals or urban polyclinics were included in the study. Those patients who were referred back to primary health facilities for DOTS-Plus treatment were excluded due to resource and time constraints in travelling to all primary healthcare facilities to collect their socio-demographic and clinical details.

Data Variables, sources of data and data collection

Patient demographic and clinical data were extracted from the health facility DOT register, individual patient clinical notes and the district DR-TB register using a structured proforma. Data extraction was done by District TB coordinators of the respective districts following training by the principal investigator. A data extraction manual was also shared by the principal investigator which indicated the source of variables and explaining standard procedure to be followed while extracting each variable. District Environmental Health Officers (DEHOs) of the respective districts also crosschecked the source registers and validated 10% of the extracted data. Data was extracted during August to December, 2018.

Operational Definitions:

Percentage of missed doses: percentage of the number of days with missed doses divided by the total number of days a patient was on treatment up until date of outcome.

Duration from diagnosis to treatment initiation: The number of days between the diagnosis date of rifampicin resistance to date of initiating standardised SLDs for management of MDR/RR-TB.

Severe Adverse Events (SAEs): All the adverse events as listed in PMDT guidelines of Zimbabwe (12).

Other comorbidities: All the self-reported comorbidities other than HIV recorded during the initiation of treatment.

Data entry and analysis

Data were double entered and validated using EpiData entry software (EpiData Association, Odense, Denmark). Data were analysed using EpiData analysis (version 2.2.2.182, EpiData Association, Odense, Denmark) and Stata (version 12.0 STATA Corp., College, TX, USA).

Categorical variables such as MDR/RR-TB deaths were summarized using numbers and percentages whilst medians (interquartile range (IQR)) were calculated for skewed continuous data such as age and weight at treatment initiation. The primary outcome was "Death" whilst 'cured' and 'treatment completed'

comprised 'treatment success'.

Unadjusted and multivariate-adjusted relative risks were calculated to obtain factors associated with "death" using univariate and multivariate generalized linear model with a log-link and binomial distribution or alternatively a poisson distribution with robust error variances, if the model failed to converge. Potential factors with a $p \leq 0.25$ were included in the multivariate-adjusted regression model. A □value< 0.05 was considered statistically significant.

Ethics Approval

Ethics approval was granted by the Medical Research Council of Zimbabwe (MRCZ). Permission to access data was granted from the Ministry of Health and Child Care. No patient consent was required as this was already granted by the Ministry of health and child care on behalf of the patients since this was a retrospective study.

CONCLUSION

In conclusion, our findings presence a broader view of factors associated with mortality and treatment success in a routine TB programme which factors will add more knowledge and understanding on the part of programme managers and implementers on how to improve programme performance. Factors such as high magnitude of >10% missed doses , poor monitoring of patients due to incomplete documentation, prevalent comorbidities, missed ART opportunities i.e. Patients who had an unknown HIV status but could have been HIV positive had a higher risk of death, Improving ART uptake among those ART-naïve and strategies aimed at improving treatment adherence are important in improving treatment success rates and avert death. Future studies should focus on profiling management of MDR/RR-TB patients accessing care at the primary level health care facilities in this setting. On the other hand being not ART when HIV positive was a major significant predictor of mortality.

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