Outcomes of multidrug-resistant tuberculosis in Zambia: a cohort analysis

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Abstract

Introduction: According to WHO, there were 190,000 deaths due to multidrug-resistant tuberculosis in 2014. Drug-resistant TB (and higher degrees of resistance) continues to constitute a matter of great concern particularly in areas where the HIV pandemic is rife, such as in Southern Africa. Sub-Saharan Africa has limited surveillance systems and diagnostic capacity for MDR-TB and treatment programmes in most countries in the region is not very well established.

Methods: We conducted a retrospective cohort study of all the MDR-TB patients diagnosed at the national TB reference laboratory from across the country in a period of two years to assess outcomes and patient survival rates.

Results: The total number of patients from the census was 258. Of those, 110 (%) patients were traceable for this study. There were 67 survivor-participants (60.9%); and 43 (39.1%) were deceased. Out of the 110 patients who were traced, only 71 (64.5%) of them were started on second line treatment. There were 29 (40.8%) patients declared cured and 16.9% were still on treatment; 8.4% had treatment failure. The death rate was 20.2 per 100 person-years of follow up. HIV co-infected MDR TB patients' rate of survival was less than their HIV negative counterparts (p = 0.013). Taking ARVs was associated with a decreased risk of dying (Hazard ratio 0.12, p = 0.002). Sex, age, marital status and treatment category were not important predictors of survival in MDR TB patients.

Conclusions: More than half of the patients diagnosed with MDR-TB were lost before second line treatment was initiated, implying programmatic management of drug resistant TB (PMDT) needs strengthening.

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Introduction

The World Health Organization (WHO) estimated that in 2014 there were 1.5 million deaths due to tuberculosis (TB), including 190,000 deaths due to multidrug-resistant tuberculosis (MDR-TB), defined as TB due to a *Mycobacterium tuberculosis* strain that is resistant to at least rifampicin and isoniazid. The emergence of MDR-TB has impacted negatively on the progress so far in global TB control (WHO 2015). High mortality among HIV infected patients suffering from multi- and extensively-drug resistant tuberculosis M(X)DR-TB have raised concerns to TB Control programs in Sub Sahara Africa (Gandhi et al 2006; Shah et al 2007; Lukoye et al 2015). Although a lot of progress has been made in the recent past to understand the burden of MDR-TB in sub-Sahara Africa, data is still limited mainly due to limited surveillance systems and diagnostic capacity (Andrews et al. 2007; Berham et al. 2013; Lukoye et al 2015). The region also has high rates of HIV prevalence and consequently high TB/HIV co-infection rates (WHO 2015; Kapata et al 2011). In 2015, WHO estimated that 480,000 people developed MDR-TB but only 26% of these were notified, even fewer were started on treatment and the treatment outcomes were poor with less than half of these cases having successful outcomes (WHO 2015; Moodley & Godec 2016)

Programmatic management of drug resistant TB (PMDT), in Zambia started in 2010 (MOH 2015) Culture and drug susceptibility testing (DST) for first-line anti-TB drugs was started in 1995; therefore, MDR-TB patients have been diagnosed in the country for the past 20 years (Kapata et al. 2013). The estimated prevalence of MDR-TB in Zambia is current at 0.3 % in new patients and 1.8% in previously treated patients (Kapata et al. 2015). Since 2008, there have been three main culture and DST laboratories that diagnose M(X) DR-TB, National TB Reference Laboratory; the University Teaching Hospital in Lusaka and the Tropical Diseases Research Centre in Ndola (Kapata et al. 2013). However, only a few patients were started on second line treatment at two hospital facilities in the country.

In order to establish a baseline for measuring the impact of the programmatic management of drug resistant TB (PMDT) program, we retrospectively followed up on all the patients who were diagnosed from the three reference laboratories with the main objective to determine the outcomes of MDR-TB patients diagnosed in Zambia from 2012 to 2014 and their survival rate.

Methods

Design and population

This was a retrospective cohort study of all MDR-TB patients diagnosed across the country between 1st February 2012 and 1st February 2014, by the only TB laboratories in Zambia that performed drug susceptibility testing, i.e. the University Teaching Hospital (UTH) Laboratory in Lusaka, the Chest Diseases Laboratory (National TB Reference Laboratory), in Lusaka and the Tropical Diseases Research Centre TB laboratory in Ndola in Copper Belt Province.

A central data base was created that indicated the demographic variables of these patients; the areas and health facilities where they had come from, including their residential addresses if available. Between January 2015 and October 2015 the confirmed MDR-TB patients (according to the diagnostic register) were traced back to the areas where they had been identified as presumptive MDR-TB patients by following up on the residential details from the registers, to the health facility from where the sample was referred and then followed up to their home addresses by research assistants stationed in each of Zambia's ten provinces.

Once the patients had been traced they were assessed clinically and interviewed. Patients who did not provide informed consent or were in prison at the time of the follow-up were excluded. In cases where patients were found to have died, the consenting next of kin were interviewed.

Patient screening and interviews

Using the information from the central database, a team comprising an interviewer and an assistant data clerk travelled to the respective province to trace the patients who were recorded as diagnosed MDR-TB. This team worked in collaboration with the research assistants who were already stationed in each of the provinces.

If the patient was traced, a standardized structured questionnaire was administered by the interviewer after informed consent had been obtained. The questionnaires were designed according to different scenarios: (i) If the patient was found to be alive, symptom screening was conducted through a standard questionnaire, including history of cough, fever, night sweats, chest pain, haemoptysis, weight loss, and previous TB treatment before the recorded episode. In addition, sputum was collected and sent for microscopy, culture and

DST using MGIT or Xpert MTB/RIF. (b) If the patient was found to be deceased, a verbal autopsy questionnaire was administered to the available respondent. Where the patient had died, as much information as possible was collected from case notes and interviews with relatives through the use of the verbal autopsy tool that was adapted from the World Health Organization/ International Standard Verbal Autopsy questionnaire (WHO 1999). The verbal autopsy tool collected information pertaining to previous TB treatment before the recorded episode, history of cough, fever, chest pains, haemoptysis, weight loss, history of other diseases.

Three attempts of visits were made and if by the third visit the patient was not found or confirmed dead they were considered as lost to follow-up. Patients who were found but for whom there was no clinical information were also excluded.

Other sources of information

Other sources of information, in addition to the standardized questionnaires, included the National TB Laboratory registers, the national patient treatment cards, the national TB treatment registers, hospital record cards, growth monitoring cards and death certificates.

Data management and analysis

The information from structured questionnaires was entered using double data entry into the MS Excel database and analysed using Stata version 14. The Pearson's Chi square test or the Fisher's Exact tests were used to compare categorical variables as appropriate. Censoring for participants who were traced was on the date of the interview. Survival analysis was performed using the Kaplan Meier method, while the Log-rank test was used to compare survival rates between groups. To identify predictors of mortality among MDR TB patients, Cox proportional hazards regression was used with a backward elimination method for variables with $p<0.2$. The Akaike and the Bayesian Information criteria methods were used to compare models. A p value less than 0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Tropical Diseases Research Centre Ethics Committee, and the authority to conduct research was granted by the Ministry of Health.

Results

The cohort comprised 258 patients who were diagnosed with MDR-TB from 1st February 2012 to 1st of February 2014, from across the 10 provinces of the whole Country (Figure 1). There were 110 (42.6%) out of 258 patients whose results were received at the referring facility and we were able to trace and contact them or next of kin. The results for the other 148 (57.4%) patients could not be traced back (lost before treatment initiation).

There were 67/110 (60.9%) participants who were alive at the time of the interview. Forty-three (39.1%) were deceased and their demographic characteristics are as shown in Table 1.

The median age of the survivors was 36 years (IQR 28 – 45; range 14-82 years). The majority of the patients were male (62.8%) and more than 50% had at least a secondary education, although the majority (81.4%) were either unemployed or in informal employment. There were 39 (58.2%) patients that were HIV positive among the survivors (Table 1) and no statistically significant difference was observed between those who were alive and those deceased from univariate and multivariate analysis.

Out of the 110 patients who were traced, only 71 (64.5%) of them were started on second line treatment (Category IV); 11 of them had continued on first line treatment (10 on Category II and 1 on Category I). There were 28 (25.4%) patients whose treatment regimen was not indicated (Figure 2).

Among the 71 patients who were started on Category IV treatment 12 (16.9%) were recorded to be still on treatment at the time of interview, however, 3 out of the 12 had treatment failure and the other 9 were found to have culture conversion. There were 29 (40.8%) patients declared cured and all were alive. Nine (12.7%) patients were recorded as "lost to follow-up", however one was traced and found alive (culture positive) whereas 8 patients were found to be deceased. There were 12 (16.9%) patients whose records showed as died and were found to be deceased and so was the 1 (0.01%) patient recorded as transferred out. Among the 8 (11.3%) patients who were indicated to have stopped

treatment due to side effects, 3 of them were found to be alive and 5 had died. Further follow-up of those patients who had been started on SLD (Cat IV) revealed that 6 (8.4%) out of the 71 had failed treatment; in addition 8 of the patients who had no treatment outcome recorded had also failed on second line treatment as shown in figure 2.

Figure 3 shows the survival of MDR TB patients overall; the follow-up period was 212 person years, during which 43 MDR-TB patients died with a death rate of 20.2 per 100 person-years of follow up and more than 25% had died within one year.

The HIV co-infected MDR TB patients' rate of survival was less than their HIV negative counterparts (p = 0.013) as illustrated in figure 4. There was no difference (p = 0.35) in survival rates between patients who were on first line treatment compared to those on MDR therapy (Figure 5).

Table 2 shows that taking ARVs was associated with an 88% decreased risk of dying (Hazard ratio 0.12, p = 0.002). Being HIV positive was also associated with a decreased risk of dying, after adjusting for the effect of taking ARVs and other risk factors (HR 0.10, p = 0.04). Sex, age, marital status and treatment category were not important predictors of survival in MDR TB patients.

Discussion

This article underscores the fact that most of the MDR-TB patients diagnosed in Zambia were lost to follow-up even before they were started on treatment (Figure 2). The loss to follow-up of more than half the patients diagnosed with MDR-TB within a couple of years is cause for concern. The reason for this situation can be attributed to the fact that the reference laboratories from where culture and DST are performed are centralized in Zambia and yet patients or specimens are referred from all over the country; in a country with limited resources to maintain and sustain a strong courier system for specimen referral and transportation, this poses a huge challenge (Kapata et al 2013). In a study from South Africa examining reasons for loss-to-follow up between time point of diagnosis and referral to a specialized DR-TB treatment centre, Nkosi and colleagues noted that a significant problem in the control of MDR-TB was the loss to follow-up after diagnosis and the delay in patient tracing (Nkosi et al 2013). Although there is limited literature in the region as compared to the scale of the problem, there is still need to strengthen patient flow and referral mechanisms to minimise loss of patients at this critical time. Based on WHO

recommendations, TB control programs usually report on cohorts of TB patients from those who were “enrolled for treatment” for the purposes of recording and reporting. Therefore patients lost to follow-up before starting treatment are usually not accounted for; some studies from across the globe have highlighted the high loss to follow-up among MDR-TB patients before initiation of treatment and hence have advocated for more careful cohort analysis starting from all diagnosed patients rather than only those who are started on treatment (Khaliaukin et al 2014; Khann et al 2013; Chadha et al 2011). This study underscores that need and calls for similar studies to be undertaken in other countries in the region to ascertain the magnitude of the problem. In fact one of the reasons in many countries for inadequate access to diagnosis and treatment of MDR-TB is that the network for PMDT is usually too centralized (WHO 2015).

Among the patients who were started on second line treatment during the two year cohort, 29% of them were found to have died by the time of the interviews implying that there is an urgent need for improvement in patient diagnosis, treatment, and management. This study however did not assess all the patients started on treatment in 2012 to 2014 but rather all patients started on treatment from those diagnosed during this period. It is envisaged that such cohort analysis is conducted within routine PMDT services.

There were 258 patients diagnosed during the two year period of the study which was far below the expected number of cases according to the estimated prevalence of MDR-TB in Zambia. The prevalence of 1.1 % for MDR-TB in Zambia entails the number of cases per annum is expected to be approximately 600 and thus in a two year cohort, close to 1200 patients should have been enrolled. Efforts need to be made to improve on case detection and diagnosis (Kapata et al 2013; Kapata et al 2015). New diagnostics and technologies should be scaled up and expanded to improve the status quo; the use of the Xpert MTB/RIF and technologies such as the Genotype MTBDR*plus* assay have shown to improve detection of MDR-TB in different settings and hence should be utilized (Singh et al. 2016; Metcalfe et al. 2016; Ade et al. 2016; Stagg et al. 2016; Nathavitharana et al. 2016; Nikolayevskyy et al. 2009).

Only one patient diagnosed with MDR-TB during this cohort was a child less than 15 years of age, thereby emphasizing the need to improve diagnosis in children as currently there is limited diagnostic capacity for childhood TB and MDR-TB (Hicks et al. 2014; Seddon et al.

2014). There is a need to improve diagnosis and invest in new technologies. However, the other reason could also be that there are fewer children with MDR-TB although this is unlikely given the comparative figures from the surrounding countries (WHO 2015). An autopsy study conducted by Bates and colleagues showed that childhood TB was missed in a number of patients (Bates et al 2016); including some who had rifampicin resistance (RR) and thus it is possible some of these patients could have had MDR-TB.

In this cohort there were more males diagnosed with MDR-TB than females. This is consistent with what is pertaining to the situation with drug susceptible TB (Kapata et al. 2011). The majority of the patients were also unemployed. The overall HIV/ MDR-TB co-infection rate in those who were traced was 67.4%; this is an important finding because there is limited data on MDR-TB co-infection rates in Zambia (Kapata et al 2013).

For those who were started on SLD, the cure rate was 41%; this low treatment success is not so different from what was pertaining in the region, especially in South Africa (Shean et al 2008; Brust et al 2010; Isaakidis et al 2015). Unfortunately, there are a limited number of MDR-TB cohort from Africa that have been described (Oladimeji O et al. 2014; Ahuja et al. 2012; Johnston JC et al. 2009). However, globally there were only 50% of MDR-TB patients who were successfully treated for the patients enrolled on treatment in the 2012 cohort, falling short of the 2015 target of 75% or more; implying therefore that a lot needs to be done in order to address this challenge (WHO 2015; Global plan).

Nonetheless, the favourable outcomes could still be improved considering the fact that 17% of the patients were still on treatment at the end of the study period and thus with more efforts the treatment success rate could still be improved. For instance, Loveday et al (2015) showed in South Africa that employing a community-based approach for care was effective in increasing the treatment success rate. A study in Ethiopia showed that it was possible to improve outcome of treatment through concerted efforts from cooperating partners and national TB programs through various interventions such as: training volunteers and treatment supporters, regular monthly home visits and monitoring by trained staff, provision of food supplements, transportation and accommodation for patients, capacity building of staff, strengthening health systems and using a combination of hospital based care and ambulatory care, including management of side effects with ancillary drugs that were readily available (Meressa et al 2015). Although there are multiple challenges in

delivering appropriate MDR-TB treatment in the region and the evidence base is limited, some studies elsewhere have also shown that addressing the non-adherence issues by MDR-TB patients through improving health care worker's attitude towards patients, decentralization of services, providing sufficient and timely financial assistance and other enablers may improve treatment outcomes (Mitnick et al. 2016; Holtz et al 2006; Gler et al. 2012; Tupasi et al 2016).

There were discrepancies between the records at the health facilities and the findings in this study for some of the patients which were important to note; for instance, 11% of patients who had actually died were recorded as lost to follow-up in the treatment registers. Such findings underscore the need to ensure that the PMDT in Zambia is strengthened including the reporting and recording. Patient follow-up and tracing of lost to follow-up is cardinal to improve case holding and eventually patient outcomes.

Our study also shows that patients were more likely to die in the intensive phase of treatment than during the continuation phase. The reason for this could be that due to the fact that patients report late for treatment and it may take a long time for them to stabilize and thereby increasing their risk to die. The treatment regimen for MDR-TB during this period was, six months of an intensive phase then followed by eighteen months of the continuation phase, thereby making the whole treatment duration to be not less than twenty-four months. Although Zambia now recommends a twenty month treatment regimen, much shorter regimens as recommended by the WHO are advocated for (MOH 2015). However, intensified monitoring of patients through a strong PMDT and patient support system is cardinal to reduce mortality (WHO 2016). In addition, we strongly recommend a decentralized system of patient management, while ensuring capacity is built at all levels of care.

MDR-TB patients who were on anti-retro viral therapy were found to have better outcomes and survival rate than those who were not on ART; therefore underscoring the fact that ensuring co-infected people to be on treatment is important in order to reduce morbidity and mortality in these patients. However, HIV prevention programs should be strengthened as MDR-TB patients who are HIV negative have better survival chances.

The limitation of the study was that only MDR-TB patients were followed up and patients with rifampicin resistance (RR) were not included and neither were patients with poly-resistance included. There were no XDR-TB cases diagnosed during this period.

Conclusions: Our study shows that a lot of patients are lost to follow-up even before treatment has been instituted with more than half of the patients diagnosed with MDR-TB being lost; underscoring the fact that PMDT needs strengthening. The status quo must be challenged as a matter of urgency to improve treatment outcomes of MDR-TB patients in Zambia.

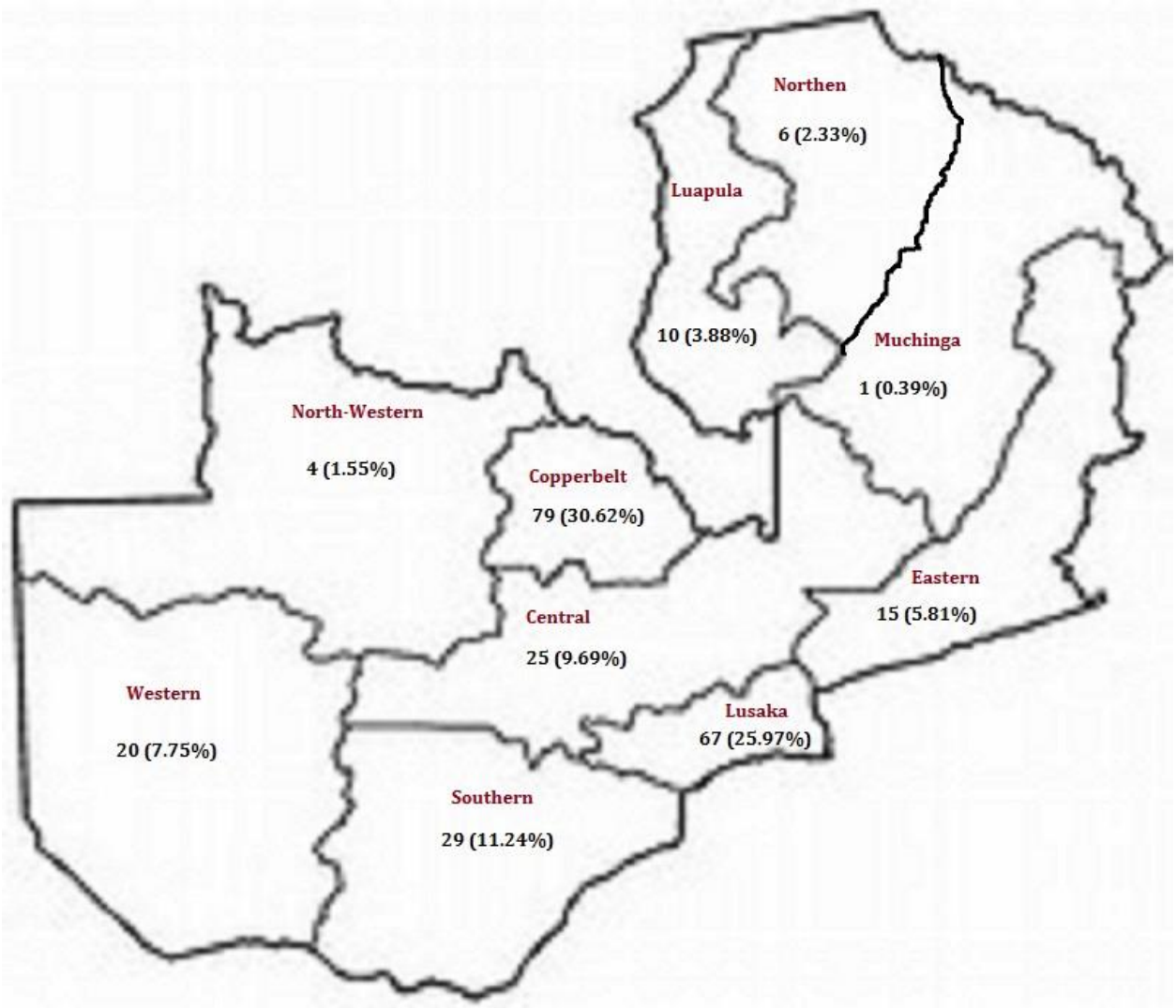
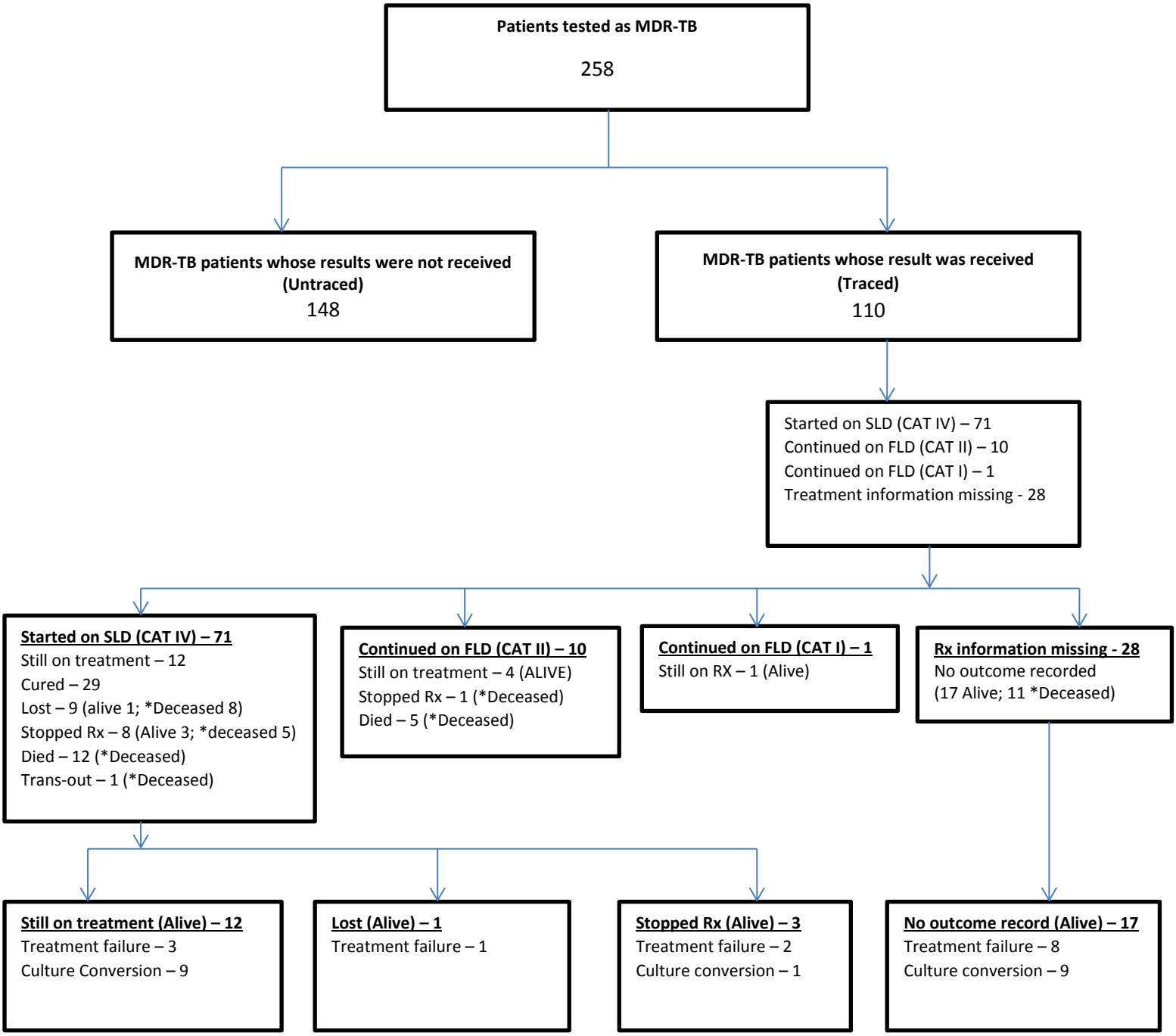


Figure 1: Map of Zambia showing MDR-TB cases per Province (Absolute & percentage)



*There was no other treatment outcome data recorded on patients who were found to be deceased

Figure 2: Flow diagram of MDR-TB patients diagnosed in Zambia (2012-2014) and their outcomes

Legend: Rx – Treatment; CAT IV – Category IV treatment (i.e. Second Line anti TB treatment regimen); CAT I – Category I treatment (i.e. First line treatment regimen); CAT II – Category II treatment regimen (i.e. First line treatment regimen for re-treatment TB cases); FLD – First line anti-TB drugs; SLD – Second line anti-TB Drugs

Table 1: Social Demographic Characteristics of MDR-TB Patients who were traced for the 2012 - 2014 Cohort

	Traced and Alive (n 67)	**(%)**	**Traced and Deceased (n 43)**	(%)
Age Group				
0-14	1	1.5	0	0
15-24	11	16.4	6	14
25-34	23	34.3	13	30.2
35-44	18	26.9	16	37.2
>45	14	14.9	8	18.6
Sex				
Male	41	61.8	26	60.5
Female	26	38.2	17	39.5
Marital status				
Never Married	14	20.9	10	23.3
Married	33	49.2	15	34.8
Divorced/Separated	15	22.4	8	18.6
Widowed	5	7.5	10	23.3
Education status				
No education	4	6	6	13.9
Primary	24	35.8	14	32.6
Secondary	32	47.8	18	41.9
Tertiary	7	10.4	4	9.3
unknown	0	0	1	2.3
Employment status				
No employment	30	44.8	22	51.2
Informal employed	24	35.8	13	30.2
Formal employment	13	19.4	8	18.6
HIV Status				
Negative	22	32.8	4	9.3
Positive	39	58.2	33	76.7
unknown	6	9	6	14
ARVs				
No	5	7.4	4	9.3
Yes	34	50.8	28	65.1
unknown	0	0	3	7
N/A	28	41.8	8	18.6

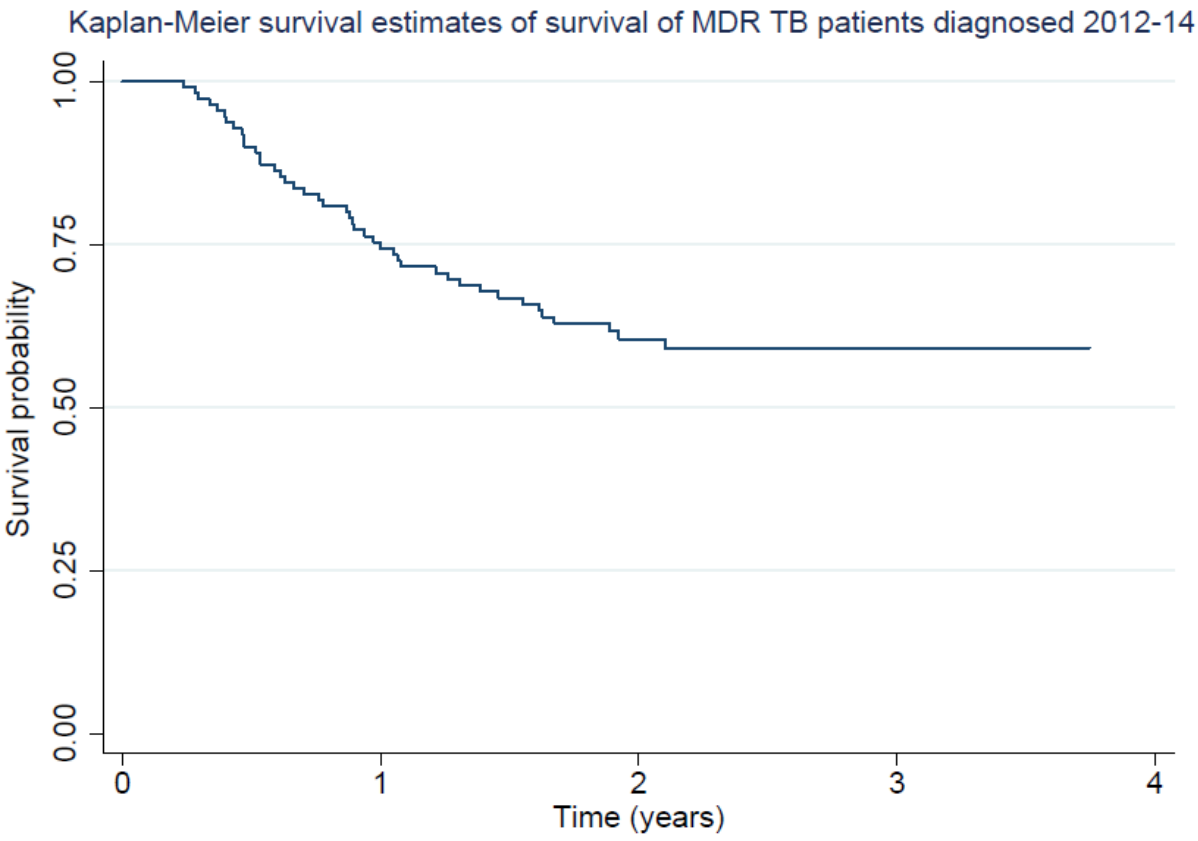


Figure 3: Kaplan-Meier survival estimates of MDR-TB patients diagnosed in 2012-2014 (Traced)

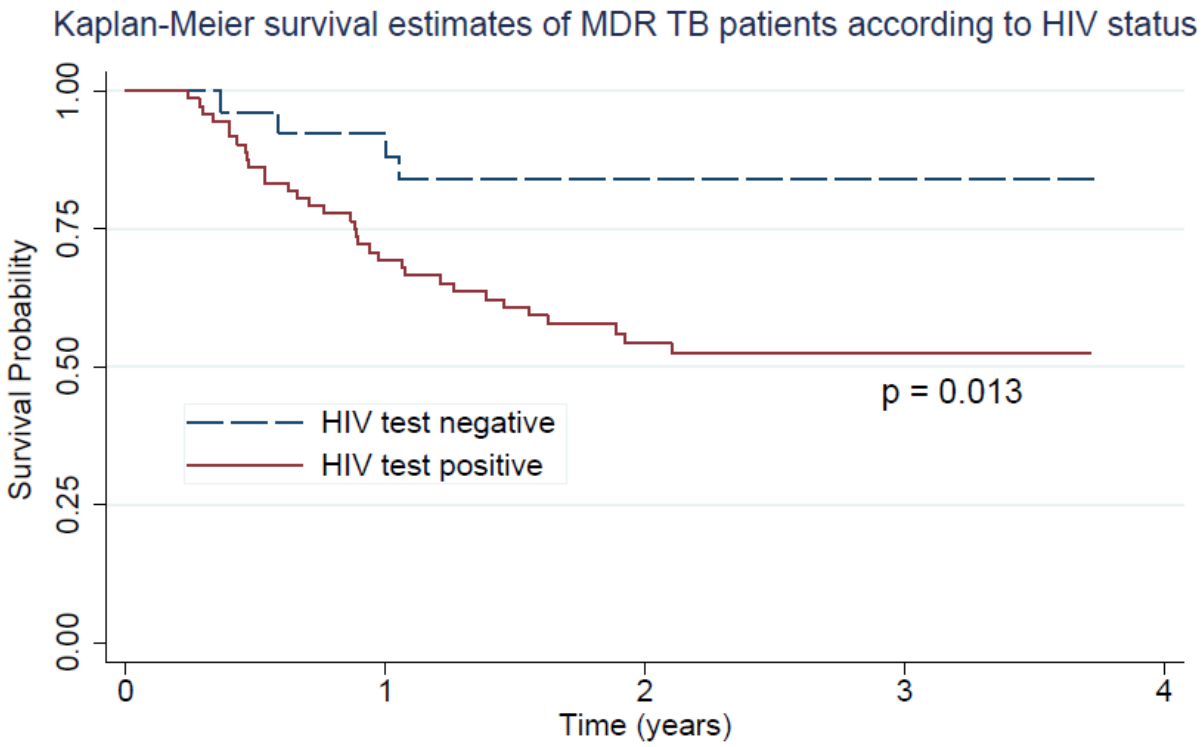


Figure 4: Kaplan-Meier survival estimates of MDR-TB patients diagnosed in 2012-2014 according to HIV status (Traced)

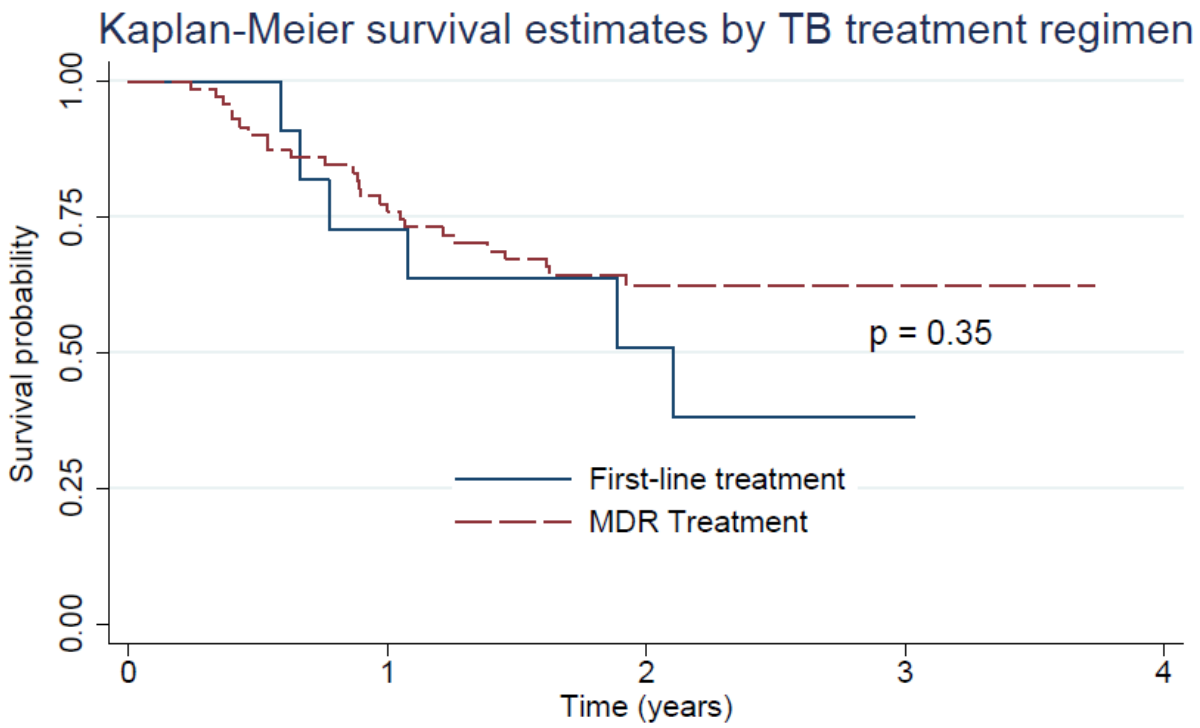


Figure 5: Kaplan-Meier survival estimates of MDR-TB patients diagnosed in 2012-2014 according to TB treatment regimen (Traced)

Table 2: Predictors of survivor of MDR TB patients diagnosed between 2012 and 2014 in Zambia

		Crude Hazard Ratios (HR)*		Adjusted Hazard ratios*	
Variable	Number N=110	HR (95% CI)	P-value	HR	P-value
Sex					
Male	43	Ref	-	Ref	-
Female	67	0.99	0.98	1.53	0.58
Age group (years)					
24 and below	18	Ref	-	Ref	-
25-34	36	1.07	0.89	2.76	0.28
35-44	34	1.53	0.37	0.54	0.57
45 and older	22	1.08	0.89	0.64	0.72
Level of education					
No	11	Ref	-	Ref	-
Primary	38	0.48	0.12	3.39	0.07
Secondary	50	0.48	0.10	4.43	**0.03**
Tertiary	11	0.45	0.20	5.19	0.13
Marital status					
Never	24	Ref	-	Ref	-
Married	48	0.64	0.27	2.15	0.53
Divorced	23	0.72	0.48	1.72	0.63
Widowed	15	2.03	0.11	2.27	0.45
Employment status					
No	55	Ref	-	Ref	-
Self	33	0.80	0.53	0.98	0.97
Informal	4	0.49	0.49	1.66	0.73
Formal	21	0.80	0.59	0.28	0.09
HIV status					
Negative	26	Ref	-	Ref	-
Positive	72	3.45	0.02	0.10	**0.04**
Took ARVs before death					
No	4	Ref	-	Ref	-
Yes	28	0.24	0.01	0.12	**0.002**
N/A	75	0.01	<0.001	<0.001	<0.001
Treatment category					
First line	11	Ref	-	Ref	-
Second line	71	0.65	0.35	1.17	0.87
Phase of Treatment					
Continuation	33	Ref	0.02	Ref	-
Intensive	34	2.55	0.02	0.56	0.24
N/A	43	0.31		0.00	-

* Crude and adjusted hazard ratios using Cox Regression analysis

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