Risk Factors for Mortality Among Patients Diagnosed With Multi-Drug Resistant Tuberculosis In Uganda- A Case-Control Study

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Abstract

Background:

The World Health Organization (WHO) End TB strategy aims to reduce mortality due to tuberculosis (TB) to less than 5% by 2035. However, mortality due to multidrug-resistant tuberculosis (MDR-TB) is particularly high and stood at 15% globally in 2018. In Uganda, MDR-TB associated mortality was 19% in the same year. We set out to examine the risk factors for mortality among a cohort of patients diagnosed with MDR-TB in Uganda.

Methods:

We conducted a case-control study nested within the national MDR-TB cohort. We defined cases as patient who died from any cause during the two years following treatment initiation. We selected two controls for each case from patients alive and on MDR-TB treatment at the time that the death occurred (incidence-density sampling) and matched the cases and controls on health facility at which they were receiving care. We performed conditional logistic regression to identify the risk factors for mortality.

Results:

Data from 198 patients (66 cases and 132 controls) started on TB from January 1 to December 31, 2016, was analyzed for this study. Majority of patients (60.6%) were male and were HIV positive (59.6%). About half (46.0%) were aged 19-34 years. On multiple regression analysis, co-infection with HIV (aOR 1.9, 95% CI [1.1-4.92] $p=0.05$); non-adherence to TB treatment (aOR 1.92, 95% CI [1.02-4.83] $p=0.04$); age over 50 years (aOR 3.04, 95% CI [1.13-8.20] $p=0.03$); and not having any education (aOR 3.61, 95% CI [1.1-10.4] $p=0.03$) were associated with MDR TB mortality.

Conclusion:

To improve MDR-TB treatment outcomes, to attention must be paid to provision of social support particularly for older persons on MDR TB treatment. Interventions that support treatment adherence and promote early detection of HIV infection should also be emphasized for all persons diagnosed with TB.

Background

Multi-drug resistant tuberculosis (MDR-TB), that is resistance to rifampicin and isoniazid, the two first line anti-tuberculous drugs, is an ongoing global public health challenge. In 2018, the World Health Organization (WHO) estimates that only about a third of the 484,000 estimated incident cases of MDR-TB were started on appropriate second line therapy¹. Among cohorts of patients on treatment, treatment outcomes have consistently been suboptimal. Overall, the proportion of MDR/RR-TB patients in the 2016 cohort who successfully completed treatment was 56%¹. The commonest reasons for non-completion of treatment were death (15%) and loss to follow-up (15%). The case fatality ratio was highest in the African

region at 18%¹. Other reasons for non-completion included failed treatment (8%) and missing treatment outcome information (6%).

Uganda is among the 30 high TB-HIV burden countries in the world. The country has an estimated TB prevalence of 253/100,000 population and about 2000 incident MDR-TB cases annually². MDR-TB case notification continues to be suboptimal and in 2019, the country notified only 534 MDR-TB cases (25% of incident TB patients)³. HIV co-infection among MDR-TB patients remains high and in 2019, 30% of the MDR-TB cohort was co-infected with HIV. Like the rest of sub-Saharan Africa, treatment outcomes are suboptimal with only about 60% of the 2016 cohort successfully completing treatment³. In this cohort, about 20% of all patients died during treatment.

Although suboptimal treatment outcomes among patients started on MDR-TB treatment are a cause of universal concern, studies examining factors associated with suboptimal outcomes are few and are mostly from clinical research studies in high resource settings^{4,5}. However, we understand that patient characteristics and modalities for provision of care in programmatic settings may be markedly different from that in clinical research settings. We therefore sought to understand the risk factors for mortality among patients diagnosed and treated with MDR-TB in a programmatic setting in a low resource setting such as Uganda.

Methods

We conducted a case-control study nested within the national MDR-TB cohort. The national MDR-TB cohort consists of all patients initiated on MDR-TB treatment at the 17 MDR-TB treatment centers countrywide. Patients are referred to these treatment centers once they are diagnosed with rifampicin resistant (RR) TB on the Xpert MTB/RIF assay. On arrival, all patients were managed according to the Uganda national guidelines for the programmatic management of drug resistant TB (PMDT)⁶. Baseline investigations are conducted including sputum culture and drug susceptibility testing, chest X-rays, HIV tests, and blood chemistry tests. Patients are then placed in a standardized MDR-TB regimen consisting of six months of Kanamycin, Levofloxacin, Cycloserine, Ethionamide, and Pyrazinamide followed by 14–16 months continuation phase of Levofloxacin, Cycloserine, Ethionamide, and Pyrazinamide.

For follow-up treatment, all patients are placed on daily directly observed therapy (DOT) either at the MDR-TB treatment center or at a follow-up facility (usually closer to the patient's home) which has staff trained in the delivery of MDR-TB treatment. Patients are given monthly follow-up visits at the MDR-TB treatment center where adherence to treatment is assessed and clinical, biochemical, and bacteriological improvement are measured. Clinical improvement is measured through vital measurement such as weight and blood pressure, while biochemical improvement is measured through blood chemistry tests, e.g. complete blood counts and liver and renal function tests. Finally, bacteriological improvement is measured through sputum cultures. At these monthly visits, patients are also offered social support termed “adherence enablers” to cover costs for food and transportation.

For this study, we included all patients initiated on MDR-TB treatment from January 1 to December 31, 2016. We defined cases as patients who died from any cause during the two years following MDR-TB treatment initiation. We selected two controls for each case from patients alive and on MDR-TB treatment at the time that the death occurred (incidence-density sampling) and matched the cases and controls at the health facility at which they received care.

We used a standardized case report form to abstract data from patient medical charts. We collected information about sociodemographic characteristics like sex, age, education, marital status, and occupation; clinical characteristics like HIV co-infection, TB treatment history, co-morbidity, CD4-counts at MDR-TB diagnosis and behavioral factors like adherence to MDR-TB treatment and use of recreational drugs/alcohol. We checked the data for completeness, entered it into the national health information electronic database system (DHIS II) and then exported it to Microsoft Excel, which was then imported into STATA version 14.0 for analysis.

We described patient characteristics using counts and percentages, and the differences in these characteristics between cases and controls were compared using the McNemar chi-square test. We fitted conditional logistic regression to assess risk factors for mortality among patients initiated on MDR-TB treatment. Factors which had p-value < 0.2 at bi-variable analysis were entered into a multivariable conditional logistic regression model. Variables with p-value ≤ 0.05 on multivariable regression were considered as statistically significant risk factors for MDR-TB mortality.

Results

For this study, we enrolled all 66 patients who died while on treatment along with 132 controls. Majority of patients (60.6%) were male and almost half were youth aged 19–34 years. About two thirds (59.6%) were HIV positive and half of these had advanced HIV disease (CD4 cell count < 200 cells/ul) at the start of MDR-TB treatment. More than half had previous history of TB treatment. (Table 1)

Table 1
Characteristics of participants enrolled in the study

Characteristics	Total	Cases (n = 66) n (%)	Controls (n = 132) n (%)	P-Value §
Sex				0.98
Male	120 (60.6)	40 (60.6)	80 (60.6)	
Female	78 (39.4)	26 (39.4)	52(39.4)	
Age				0.09
0–18	9 (4.6)	1 (1.52)	8 (6.1)	
19–34	91 (46.0)	32 (48.5)	59 (44.7)	
35–49	74 (37.4)	21 (31.8)	53 (40.2)	
50+	24 (12.0)	12 (18.2)	12 (9.1)	
Education				0.02
None	56 (28.3)	24 (36.4)	32 (24.2)	
Primary	78 (39.4)	28 (42.4)	50 (37.9)	
Secondary & above	64 (32.3)	14 (21.2)	50 (37.9)	
Occupation				0.51
Unskilled work	166 (83.8)	57 (86.4)	109 (82.6)	
Skilled work	32 (16.2)	9 (13.6)	23 (17.4)	
Previous history of TB				0.80
Yes	108 (55.1)	35 (53.8)	73 (55.7)	
No	88 (44.9)	30 (46.2)	58 (44.3)	
HIV Status				0.04
Positive	118 (59.6)	45 (70.3)	73 (55.3)	
Negative	78 (40.4)	19 (29.7)	59 (44.7)	
CD4 Count				0.48
< 200	28 (71.8)	11 (78.6)	17 (68.0)	

¶Missing data; Previous history of TB (cases = 1, control = 1), HIV status (cases = 2, control = 0), baseline CD4 count (cases = 31, controls = 38)

§ McNemar Chi-square P-value comparing cases and controls

Characteristics	Total	Cases (n = 66) n (%)	Controls (n = 132) n (%)	P-Value §
≥ 200	11 (28.2)	3 (21.4)	8 (32.0)	
Adherence to ART				0.99
Good	195 (98.5)	65(98.5)	130 (98.5)	
Poor	3 (1.5)	1 (1.5)	2 (1.5)	
Medical complication				
Yes	102 (51.5)	39 (59.1)	63 (47.7)	0.03
No	96 (48.5)	27 (40.9)	69 (52.3)	
Missed DR-TB doses				
Yes	126 (63.6)	38 (57.6)	88 (66.7)	0.01
No	72 (36.4)	28 (42.4)	44 (33.3)	
MDR-TB treatment site	111 (56.1)	27 (40.9)	84 (63.6)	
DOT site	87 (43.9)	39 (59.1)	48 (36.4)	0.71
¶Missing data; Previous history of TB (cases = 1, control = 1), HIV status (cases = 2, control = 0), baseline CD4 count (cases = 31, controls = 38)				
§ McNemar Chi-square P-value comparing cases and controls				

On bivariate analysis, factors with p-value < 0.2, thus qualified for multiple conditional regression, were: education level OR 3.70, 95% CI [1.5-8.0] p = 0.02; age above 50 years OR 2.51, 95% CI [0.98–6.42] p = 0.06; HIV co-infection OR 1.83, 95% CI [0.86–2.70] p = 0.07; missed doses 1.71, 95% CI[0.6–3.40] p = 0.22 and documented medical complication OR 1.82, 95% CI [0.97–3.40] p = 0.05. Male sex, type of DR TB and previous history of TB were not associated with mortality for MDR TB (Table 2).

Table 2

Conditional (fixed effects) logistic regression model of the risk factors associated with the mortality among patients of MDR TB

Characteristics	Un adjusted OR (95% CI)	P-Value	Adjusted OR (95% CI) $\ddagger$	P-Value
Age				
0–18	[1]		[1]	
19–34	0.22 [0.02–1.82]	0.16	0.18 [0.02–1.70]	0.14
35–49	0.29 [0.04–2.46]	0.26	0.28 [0.03–2.61]	0.27
50+	2.51 [0.98–6.42]	0.06	3.04 [1.13–8.20]	0.03
Education				
None	3.70 [1.5-8.0]	0.02	3.61 [1.1–10.4]	0.03
Primary	1.30 [0.58–2.6]	0.19	2.01 [0.6–4.30]	0.14
Secondary & above	[1]		[1]	
HIV status				
Negative	[1]		[1]	
Positive	1.83 [0.86–2.70]	0.07	1.9 [1.1–4.92]	0.05
Medical complication				
No	[1]			
Yes	1.82 [0.97–3.40]	0.06	2.03 [0.67–2.95]	0.09
Missed DR-TB doses				
No	[1]		[1]	
Yes	1.71 [0.6–3.40]	0.22	1.92 [1.02–4.83]	0.04
<i>OR = Odds Ratio, CI = Confidence interval. $\ddagger$ model fitted on complete records on all variables in the model (total = 190, cases = 64, controls = 126). Data was missing on HIV status on 2 cases, thus their controls were automatically dropped from the model.</i>				

At multiple conditional logistic regression analysis, risk factors for mortality included not having any education (adjusted odds ratio [aOR] 3.61, 95% CI [1.1–10.4] $p = 0.03$); missing doses (aOR 1.92, 95% CI [1.02–4.83] $p = 0.04$); age above 50 years (aOR 3.04, 95% CI [1.13–8.20] $p = 0.03$) and co-infection with HIV (aOR 1.9, 95% CI [1.1–4.92] $p = 0.05$). (Table 2).

Discussion

In this study, we sought to determine the risk factors for mortality among patients started on MDR-TB treatment under programmatic resource limited settings. We employed a case-control study nested within the 2016 national MDR-TB cohort. We found that being co-infected with HIV and being non-adherent to treatment doubled the risk of death while on MDR-TB treatment while age above 50 years tripled the risk of mortality from HIV infection. Having no education was the greatest risk factor for mortality from MDR-TB, increasing the risk of death by almost four times.

The risk factors elicited in this study have been found in other evaluations of TB associated mortality^{4,7-10}. HIV infection has been shown to significantly increase the risk of mortality from MDR-TB with this effect increasing with advancing disease^{7,8}. Patients with CD4 cell counts < 200 cells/mm³ are four times more likely to die from MDR-TB than those with CD4 cell counts > 200 cells/mm³⁷. In our study, patients co-infected with HIV were twice as likely to die during treatment than patients without HIV infection. Although more than half of HIV + patients enrolled in this study had a CD4 cell count < 200 cells/mm³, the increase in mortality was less than has been previously documented, probably due to the widespread use of antiretroviral therapy. All patients in this study received antiretroviral therapy within the first month of MDR-TB treatment.

The standard second line therapy for MDR-TB used in this study was a minimum of 20 months and consisted of six months of injectable medicine^{6,11}. Adherence to this regimen has been shown to be suboptimal globally with over one third of patients started on treatment being nonadherent to therapy⁸. In our study, 55% of patients were nonadherent to the TB treatment. In our context, reasons for nonadherence to this treatment regimen include long duration of injectable medicine, lack of transport to health facilities for daily DOT, and adverse drug reactions to some of the drugs used in the regimen.

Older age has been associated with increased mortality from TB due to atypical presentations, increasing co-morbidities and frequent drug related adverse events^{12,13}. In our setting, older age has also been shown to be associated with decreased access to healthcare services. The recently completed national prevalence survey found that one of the largest prevalence to notification gaps was among persons 50 years and older². Older persons are also less likely to be able to have the afford transport fares for daily DOT to the treatment initiation sites or the nearest health facility making them susceptible to suboptimal adherence to MDR TB treatment.

In our study, having no education was the strongest risk factor for mortality during MDR-TB treatment. The association between education and good health is well established^{14,15}. Globally, well-educated persons are less likely to be unemployed, more likely to have higher incomes, and more likely to have healthy lifestyles^{14,15}. In our setting, lower education levels are associated with unemployment, poorly paid work, and low social economic status¹⁶. Low social economic status has been associated with an increased likelihood of TB and HIV infection and with poorer outcomes from both diseases^{17,18}. In addition, accessing diagnosis and treatment for MDR-TB has been associated with catastrophic costs to

patients and their families^{19,20} which are likely to severely affect patients with low socioeconomic status making it difficult for them to adhere to daily DOT and refill visits.

Our study had several limitations. The use of routinely collected data resulted in missing information. However, this was minimized by triaging several data sources. The study also collected some variables from patient files which were self-reported, e.g., the alcohol use and use of recreational drugs. It is likely that some of these variables were prone to information bias as patients would have been reluctant to report undesirable behavior to their healthcare providers. Finally, the study population was chosen from a national MDR-TB cohort which had a relatively significant proportion of patients who were lost to follow-up during treatment. It is likely that a proportion of these patients could have died and that therefore the cases were underrepresented in the study. However, the national programmatic management of drug-resistant TB (PMDT) team made a team to interview relatives of patients lost to follow-up and record any known additional deaths that may have occurred. However, this was an evaluation of a national MDR-TB treatment cohort, and the findings of this study therefore reflect of the risk factors for mortality in patients managed for MDR-TB in routine care settings.

Conclusion

To improve MDR-TB treatment outcomes, to attention must be paid to provision of social support particularly for older persons on MDR TB treatment. Interventions that support treatment adherence and promote early detection of HIV infection should also be emphasized for all persons diagnosed with TB. In March 2019, the Uganda's National TB, and Leprosy Program (NTLP) changed its MDR-TB treatment regimen to the modified all oral regimen, which is a shorter, less toxic regimen that does not contain injectable medicines. In the same year, the NTLP launched an adherence enabler program to provide social support to persons diagnosed with MDR-TB. An evaluation of the effect of these two interventions would inform PMDT programs in low resource settings on their utility in improving MDR-TB mortality. Finally, the NTLP must work jointly with the National AIDS Program to promote early diagnosis of HIV infection, early return to care for those who interrupt treatment, and appropriate management of patients with advanced HIV disease.

Declarations

Ethical Statement

This study used routinely collected data from the national DR TB management information system (DRMIS) and was granted a waiver from obtaining informed consent by the Joint Clinical Research Centre (JCRC) Institutional Review Board (IRB), and by the Uganda National Council of Science and Technology (UNCST).

Consent for publication

Not Applicable

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests

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Authors' contributions

EK, KM and SZM conceived the study; EK, HN and SZM collected the data; JM, KM, TK and FT analyzed and interpreted the data; EK, SZM, NSK, AN, EB, SD and DBL reviewed contributed to the drafting and critical review of the manuscript. All authors contributed to the final review of the manuscript.

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References

1. World Health Organization. Global Tuberculosis Report 2019. 2019. 278 p.
2. Uganda Ministry of Health. The Republic of Uganda The Uganda National Tuberculosis Prevalence Survey, 2014–2015 Survey Report. 2015.
3. Uganda Ministry of Health. NTLP Annual Report. 2019.
4. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis*. 2009;9(3):153–61.
5. Pradipta IS, Van 'T, Bovenind-Vrubleuskaya N, Akkerman OW, Alffenaar JWC, Hak E. Treatment outcomes of drug-resistant tuberculosis in the Netherlands, 2005–2015. *Antimicrob Resist Infect Control*. 2019;8(1):1–12.
6. Ministry of Health U. Ministry of Health Uganda National Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis National Tuberculosis and Leprosy Program. 2016.
7. Gandhi NR, Andrews JR, Brust JCM, Montreuil R, Weissman D, Heo M, Friedland AM, Shah G. N. Risk Factors for Mortality among MDR- and XDR-TB Patients in a High HIV-Prevalence Setting. *Int J Tuberc Lung Dis*. 2012 January ; 16(1): 90–97. doi:10.5588/ijtld.11.0153. High HIV-Prevalence Setting NR. *Int J Tuberc Lung Dis* 2012 January; 16(1) 90–97. 2012;16(1):90–7.

8. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: A systematic review and meta-analysis of published studies. *Infect Dis Poverty*. 2017;6(1):1–8.
9. Takarinda KC, Sandy C, Masuka N, Hazangwe P, Choto RC, Mutasa-Apollo T, et al. Factors Associated with Mortality among Patients on TB Treatment in the Southern Region of Zimbabwe, 2013. *Tuberc Res Treat*. 2017;2017(January):1–11.
10. Bajehson M, Musa BM, Gidado M, Nsa B, Sani U, Habibu AT, et al. Determinants of mortality among patients with drug-resistant tuberculosis in northern Nigeria. *PLoS One*. 2019;14(11):1–10.
11. Mitnick CD, Rodriguez CA, Hatton ML, Brigden G, Cobelens F, Grobusch MP, et al. Programmatic Management of Drug-Resistant Tuberculosis: An Updated Research Agenda. *PLoS One*. 2016;11(5):1–16.
12. Negin J, Abimbola S, Marais BJ. Tuberculosis among older adults - time to take notice. *Int J Infect Dis*. 2015;32:135–7.
13. Loveday M, Mzobe YN, Pillay Y, Barron P. Figures of the dead: A decade of tuberculosis mortality registrations in South Africa. *S Afr Med J*. 2019;109(10):728–32.
14. Ross CE, Wu C. The Links Between Education and Health. *Am Sociol Rev*. 2009;60(5):719–45.
15. Lleras-Muney DMC and A. Education and health: evaluating theories and evidence. 2006 Jul 3. *Natl Bur Econ Res*. 2006;July(3):805–11.
16. UDHS. Uganda Demographic and Health Survey Key Indicators Report 2016. RoU. 2017.
17. Wu J, Dalal K. Tuberculosis in Asia and the pacific: the role of socioeconomic status and health system development. *Int J Prev Med*. 2012;3(1):8.
18. Cantwell MF, McKenna MT, McCray E, Onorato IM. Tuberculosis and race/ethnicity in the United States impact of socioeconomic status. *Pneumologie*. 1998;52(11):626.
19. Uganda Ministry of Health. Direct and Indirect costs due to Tuberculosis and proportion of Tuberculosis-affected households experiencing catastrophic costs due to TB in Uganda. 2019.
20. Walcott RL, Ingels JB, Corso PS, Zalwango S, Whalen CC, Sekandi JN. There's no such thing as a free TB diagnosis: Catastrophic TB costs in Urban Uganda. *Glob Public Health*. 2020;1–12.