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ORIGINAL ARTICLE

Predictors of Intensive Phase Treatment Outcomes among Patients with Multi-Drug Resistant Tuberculosis in Zaria, North-Western Nigeria

Oyefabi A[1], Adelekan B[2], Adetiba E[3], Emmanuel L[3], Jimoh O[4]

[1]Department of Community Medicine, College of Medicine, Kaduna State University, Nigeria
[2]Academy for Health Development, Ife, Osun State; Ipas, Abuja. Nigeria
[3]National Tuberculosis and Leprosy Training Centre, Saye, Zaria, Kaduna State, Nigeria
[4]Department of Medical Microbiology, Ahmadu Bello University, Zaria, Kaduna State

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ABSTRACT

Background: The emergence of multidrug-resistant tuberculosis (MDR-TB) is a threat to successful TB treatment outcomes in developing nations like Nigeria. This study determined the predictors of intensive phase treatment outcomes in MDR-TB patients in Zaria, Nigeria.

Methods: This was a retrospective cross-sectional review of the records of 124 MDR-TB patients registered between September 2012 and August 2017 at the National Tuberculosis and Leprosy Training Centre, Saye, Zaria. Data were analyzed using IBM SPSS version 25.0 and the StataCorp STATA/SE 14.

Results: The median age (IQR) of the respondents was 32 (15) years. The gene Xpert test detected Mycobacterium Tuberculosis (MTB) and rifampicin resistance (RIF) in 119 (96.0%) cases. The treatment success rate was 97 (78.2%). MDR-TB and HIV co-infection rate was 17 (13.7%) while the case fatality rate was 16.1%. Bivariate analysis showed that being male (p=0.001), not currently in marital union (p=0.01) and positive smear results at 1 month (p=0.027)) were significantly associated with treatment success. Multivariate logistic regression showed that the odds for successful treatment outcome was 4 times higher for the MDR-TB patients who were employed than the unemployed (AOR= 3.98, 95% CI= 1.15-13.74). No significant relationship between MDR-TB-HIV comorbidity (AOR=1.89, 95% CI=0.44-8.19), MDR-TB susceptible to Isoniazid (AOR= 0.49, 95% CI =0.15-1.56) and successful treatment outcome.

Conclusion: Unemployment was a predictor of poor treatment outcome in this study. Cause-specific mortality due to the MDR TB was high in this setting. We advocate for optimization of access to treatment and social support system, especially for the female patients.

Correspondence to:
Dr. Adegboyega Oyefabi
Department of Community Medicine,
College of Medicine,
Kaduna State University, Nigeria.
Email: oyefabiadegboyega@yahoo.co.uk.

INTRODUCTION

The World Health Organization Global Tuberculosis report showed that an estimated 10 million people from different parts of the world developed Tuberculosis (TB) in 2017. The cause-specific death rate from this chronic infection was estimated at 1.3 million globally.[1] Nigeria harbours 4% of the global TB burden and

the country is currently regarded as the 6th most-affected TB nation in the world after India (27%), China (9%), Indonesia (8%), Philippines (6%) and Pakistan (5%).[1]

This undesirable TB morbidity is worsened by the emergence of Multidrug Resistant-TB (MDR-TB) which occurs when there is the resistance of the mycobacterium tuberculosis to at least two of the most effective first-line anti-tuberculous drugs, Rifampicin and Isoniazid.[2, 3]

When MDR-TB is not properly treated due to various health system challenges in developing countries, there can be disease progression to extensively drug-resistant TB (XDR-TB); which is MDR-TB with additional resistance to any of the fluoroquinolone and the second-line injectable Anti-TB drugs; such as Amikacin, Kanamycin or Capreomycin.[4,5] Another variant of the MDR-TB which is the total resistance to all available anti-TB drugs (TDR-TB) has been reported in some TB endemic settings.[6] The emergence and spread of MDR-TB is gradually becoming an epidemic in low-and-middle-income countries due to ignorance of the disease, treatment delays, client mismanagement and poor adherence to the treatment guidelines.[7]

A previous report in 2013 in Nigeria estimated the prevalence of MDR-TB to be 2.9% among newly detected cases and 14.5% in previously treated cases, [8] while another study conducted in 2014 showed that about 3600 MDR-TB cases occur annually among the notified pulmonary TB patients in the country with poor treatment outcome.[9] The increasing trend of this variant of TB implies that healthcare stakeholders in the MDR-TB endemic communities need to identify the specific drivers of this infection in their localities for effective prevention and control measures. The MDR-TB and its progressive variants (XDR-TB and TDR-TB) are more costly to manage, [10] have the propensity for increased transmission to community and family members,[11] present with worse cure rates [12, 13] and usually affect mostly the productive workforce population.[14-16] The prevention and management of these conditions, therefore are quintessential for the communities' and states' socioeconomic development.

The bacteriological confirmation for the MDR-TB involves the use of the molecular test, Xpert MTB/RIF assay to detect the resistance pattern or through other rapid drug sensitivity testing (DST) to capture the sensitivity pattern of all the available anti-tuberculous drugs used for the treatment of the infection. [17, 18]

Following a confirmatory diagnosis, an MDR-TB patient in whom there is no resistance to fluoroquinolones or second-line injectable drugs is commenced on the WHO recommended shorter regimen for 9-12 months, which is different from the previously used longer regimen of 18 months.[19] This shorter regime has two treatment phases; the intensive phase and

the continuation phase. During the intensive phase, the patients are commenced on some second-line anti-tuberculosis drugs including Kanamycin (KN), Moxifloxacin (MFX), Clofazimine (CFZ), Ethionamide (ETO), Pyrazinamide (Z), Ethambutol (E) and High dose Isoniazid (H) daily for four months. The change of the therapy to the continuation phase regimen at the fifth month is usually based on sputum smear conversion and clinical response. Treatment failure occurs when the patient remains sputum smear and/or culture-positive at six months. This will require a switch to an individualized regimen. [20] The continuation phase for the shorter regimen consists of high dose moxifloxacin (MFX), clofazimine (CFZ), Ethambutol (E) and pyrazinamide (Z) for a fixed duration of five months.[20] Patients diagnosed with HIV and co-morbid drug-resistant TB are commenced on highly active antiretroviral therapy (HAART) after starting the directly observed treatment short-course (DOTs) as early as possible, within the first eight weeks, as recommended by the WHO and adopted in the Nigeria national guideline for drug-resistant tuberculosis management.[20-22] The TB HIV co-infection has been shown to complicate TB treatment by prolonging the duration and severity of the TB infection; resulting in poor treatment outcomes [23]

Previously MDR-TB patients were managed exclusively at the TB referral hospitals but the new WHO Model for MDR-TB care currently includes a combination of ambulatory rather than only hospitalization.[24,25] This management option allows for better drug adherence, adequate monitoring of adverse reactions, regular sputum smear and culture examination, and multi-disciplinary management of the patients.[26]

Literature from developing countries have attributed specific mortality due to MDR TB to be very high during the intensive phase.[27–29] Studies on the outcome of MDR TB drug treatment are very scarce in Nigeria despite being a high TB endemic nation. This study, therefore, examines the determinants of the outcome of the intensive phase management in MDR-TB patients at the National TB Reference Centre in Saye, Zaria, north-western Nigeria.

METHODOLOGY

This was a retrospective review of medical records of all the 124 MDR-TB patients who were registered between September 2012 and August 2017 at the National Tuberculosis, Buruli Ulcers and Leprosy Training Centre (NTBLTC), Saye Zaria. The NTBLTC Nigeria was established in 1991 as the Human Resource Development Unit of the National Tuberculosis, Buruli Ulcers and Leprosy Control Programme (NTBLCP) of the Federal Ministry of Health, Nigeria. It serves both as a training Centre and a referral hospital with an estimated 180 bed capacity for drug-susceptible TB, TB/HIV, MDR-TB, Leprosy and other

common dermatological cases. Twenty of the bed spaces are isolated in a separately fenced building for the management of MDR-TB patients.

The study population were all clients with the MDR-TB confirmed by Gene Xpert and Drug sensitivity testing (DST) whose record files could be retrieved from the medical record department of the facility. The plan to exclude those with incomplete records was not applicable as all the available records contained the relevant information for the study. The required data were extracted from the patients' files, collated, cleaned and entered into the computer for both descriptive and inferential analysis using the IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp) and StataCorp STATA/SE 12 (StataCorp.2011; Stata Statistical Software: Release 12, College Station, TX; StataCorp LP).

The frequencies and the percentages of the socio-demographic and clinical profiles of the patients were computed, while bivariate analysis through chi-square test statistic was used to test the associations between patients' socio-demographic variable and MDR-TB treatment outcome.

The level of statistical significance was set at $p < 0.05$. The primary outcome variable was the MDR-TB treatment outcome, which was categorized as: Completed intensive phase; Treatment discontinued; Referred; Left against medical advice or Died.

The predictor variables identified from the patients' records were age, sex, year of treatment, place of residence, occupation, marital status and HIV comorbidity. Bivariate and multivariate logistic regression analysis were carried out against these sets of independent variables to determine the predictors of a successful outcome of MDR-TB intensive phase management.

Ethical approval (NTBLTC/ZA/HREC /001/86) for the study was obtained from the Research and Ethical Committee of the National Tuberculosis and Leprosy Training Centre, Saye, Zaria. Since this was a routinely collected programme data, informed consent from the patients was not obtained, but the safety of the clinical record and patient confidentiality was ensured.

RESULTS

A total of 124 records of MDR-TB patients were extracted from the registers. The median (IQR) age of the patients is 32 (15) years. Children less or equal to 14 years were 7 (6%). Majority of the MDR TB patients were males 87 (70.2%), more than half (53.2%) were married and mostly unemployed 75 (60.5%). The clients were from Kaduna State 37 (29.8%), other states constituted 87 (70.2%) (Table 1) The clinical profile of the MDR-TB patients shows that treatment after failure was 64 (51.6%), new patients were only 29 (23.4%), relapsed MDR 19 (15.3%), return after follow-up 7 (5.6%) and other previously treated 5 (4.0%). The

HIV/MDR comorbidity was 17 (13.7%). Most of the clients, 109 (87.9%) were treated with the longer regimen, only 15 (12.1%) were managed on the shorter regimen. About four-fifth, 97 (78.2%) completed the intensive phase and were cured, five (4.0%) discontinued treatment, two clients (1.6%) left against medical advice and 20 (16.1%) died. (Table 2)

Table 1: Socio-demographics characteristics of MDR-TB patients at the NTBLTC, Saye Zaria 2012-2017

Variables	Frequency (n=124)	Percent
Age (years)		
< 30	49	39.5
≥ 30	75	60.5
Sex		
Male	87	70.2
Female	37	29.8
Marital status		
Married	66	53.2
Not Currently Married	58	46.8
Occupation		
Unemployed	75	60.5
Employed	49	39.5
Religion		
Christianity	46	37.1
Islam	78	62.9
Ethnicity		
Hausa	53	42.7
Others	71	57.3
State of Residence		
Kaduna	37	29.8
Others	87	70.2

Table 3 shows that the Xpert MTB/RIF assay detected MTB and rifampicin resistance (RIF) in 119 (96%) cases. There were 68 (54.8%) of the clients susceptible to INH while 56 (45.2%) were resistant cases. The DST also isolated some resistant strains to Ethambutol 13(10.5%) and streptomycin 15(12%). No resistance to fluoroquinolone was reported**.**

Bivariate analysis as seen in Table 4 showed that the male sex (x2 10.9, p=0.001), not currently married (x2 =6.03, p=0.01) and positive smear results at one month after initiation of treatment

(x2=4.91, p=0.027) were associated with successful treatment outcome.

Multivariate logistic regression further showed that the odds for successful treatment outcome was about 4 times higher (AOR= 3.98, 95% CI=1.15-13.74) for the employed than for the unemployed. There was also increased odds (AOR=3.61, 95%CI =0.9-14.53) for the successful treatment outcome among those not currently married than the currently married patients. The odds were however insignificantly lower for the MDR TB cases susceptible to Isoniazid (AOR=0.49, 95%CI = 0.15-1.56) and negative smear result after 1 month on DoT (AOR=0.32. 95%CI=0.07-1.29). The HIV positive patients had insignificantly increased odds (AOR=1.89, 95%CI=0.44-8.19) for successful treatment outcome (AOR, 0.44, 95% CI= 0.09-2.15) than for the HIV negative patients. (Table 5)

Table 2: Clinical profile of the MDR-TB patients at the NTBLTC, Saye, Zaria 2012-2017

Clinical profile	Frequency (n=124)	Percent
Type of patient		
New	29	23.4
Relapse	19	15.3
Treatment after failure	64	51.6
Returned after loss to follow up	7	5.7
Other previously treated*	5	4.0
Comorbidities		
Yes	25	20.2
No	99	79.8
Regimen		
Longer (18 months)	109	87.9
Shorter (9-12 months)	15	12.1
HIV status		
Positive	17	13.7
Negative	107	86.3
Smear result at 2 months (n=120)		
Positive	39	32.5
Negative	81	67.5
Intensive phase Rx outcome		
Completed intensive phase	97	78.2
Treatment discontinued	5	4.0
Left against medical advice	2	1.6
Died	20	16.1

*****A patient who does not fit into other case definition, for example patient treated outside the NTBLTC network, but still smear positive for TB

Table 3: Result of laboratory gene Xpert and Drug Sensitivity Test for the MDR TB in Zaria

Gene expert	Frequency (n=124)	Percent
Rifampicin		
MTB detected RIF detected	119	96.0
MTB detected RIF not detected	5	4.0
Isoniazid (H)		
Resistance	56	45.2
Susceptible	68	54.8
Ethambutol (E)		
Resistance	13	10.5
Susceptible	111	89.5
Pyrazinamide (Z)		
Susceptible	124	100.0
Resistance	0	0.0
Streptomycin (S)		12.1
Resistance	15	87.9
Susceptible	109	
Fluoroquinolone		
Susceptible	124	100.0
Resistant	0	0.0

DISCUSSION

The majority of the people affected in this study were the young, workforce age group of the Kaduna state population. This corroborates previous reports on tuberculosis, which showed that the age group usually affected by this infection were the young adults who constitute the productive workforce of the population. [28, 29].

Most of the women with the MDR-TB in this study were mother care-givers of estimated 6% children affected with the MDR-TB in this survey.

This corroborates the earlier report that infected mother- caregivers were the major route of transmission and spread of the Childhood MDR TB. [30-32]

Table 4: Bivariate analysis of clients' socio-demographics, clinical profile and treatment outcome for MDR TB in Zaria

Variable	Successful (n=97) n (%)	Not successful (n=27) n (%)	X^2	p-value
Age				
<30	41 (83.7)	8 (16.3)		
≥30	56 (74.7)	19 (25.3)	1.41	0.24
Sex				
Male	75 (86.2)	12 (13.8)		
Female	22 (59.5)	15 (140.5)	10.9	0.001*
Occupation				
Unemployed	54 (72.0)	21 (28.0)		
Employed	42 (85.7)	7 (14.3)	3.19	0.07
Marital status				
Married	46 (69.7)	20 (30.3)		
Not currently married	51 (87.9)	7 (12.1)	6.03	0.01*
State of Residence				
Kaduna	30 (81.0)	7 (19.0)		
Other	67 (77.0)	20 (23.0)	0.25	0.615
HIV status				
Positive	11 (64.7)	6 (35.3)		
Negative	86 (80.4)	21 (19.6)	2.11	0.146
Regimen				
Shorter	14 (93.3)	1 (6.7)		0.107++
Longer	83 (76.1)	26 (23.9)		
Smear result after 1 month on DOT (n=120)				
Positive	36 (92.3)	3 (7.7)	4.91	0.027*
Negative	61 (75.3)	20 (24.7)		
Isoniazid				
Resistance	48 (85.7)	8 (14.3)		
Susceptible	49 (72.1)	19 (27.9)	3.36	0.07

++Fisher's exact test

TABLE 5: Multivariate logistic regression of the determinants of successful treatment outcome for MDR TB in Zaria

Variable	Unadjusted (95% CI). OR	p-value	Adjusted OR.	p-value
Age				
<30	1 (Ref)		1	
≥30	1.74 (0.69-4.35)	0.24	0.49 (0.11-2.23)	0.36
Sex				
Female	1 (Ref)		1	
Male	4.26 ((1.7410.43)	0.02	0.31 (0.09-1.02)	0.05
Occupation				
Unemployed	1 (Ref)		1	
Employed	0.47 (0.17-1.27)	0.15	3.98 (1.15-13.74)	**0.03***
Marital status				
Married	1 (Ref)		1	
Not currently Married	1.38 (1.07 -1.78)	0.01	3.61 (0.9-14.53)	0.07
Isoniazid				
Resistant	1 (Ref)		1	
Susceptible	2.32 (0.93-5.82)	**0.07**	0.49 (0.15-1.56)	0.22
HIV status				
negative	1 (Ref)		1	
positive	0.54 (0.18-1.64)	0.28	1.89 (0.44-8.19)	0.40
Smear result after 1 month on DoT				
Positive	1 (Ref)		1	
Negative	3.93 (1.09-14.17)	0.036	0.32 (0.07-1.29)	0.11

*Significant values

This survey also showed that more males were infected and treated for the MDR-TB than the females, similar to studies from Malaysia and Morocco. [33, 34] The treatment outcome in this study was poorer among the female. This finding is different from most previous studies where poorer treatment outcomes were observed among the male folk [35, 36] Community surveys using a mixed-method approach and other exploratory studies need to be conducted on gender differentials and MDR-TB treatment outcome in this setting.

Most of the MDR-TB in this survey were sequel to previous TB treatment failure. Previous studies had identified poor adherence to the first-line TB drugs as a major reason for the treatment failure and subsequent progression to the MDR TB.[37, 38] This emphasized the need for TB treatment centres to practice drug adherence policy including the strict demand for reliable treatment supporters as a prerequisite for the initiation of the MDR TB therapy at the Directly Observed Therapy (DOTs) clinics. Dallo et al had reported that the poor application of the DOTs which leads to the poor adherence

to the anti-TB drugs was a major risk factor for treatment failure and subsequent progression to MDR-TB in Burkina Faso.[39]

Our study also found that unemployment was a predictor of a poorer treatment outcome for the MDR-TB. This underscores the need for the adequate assessment of the patients' socioeconomic status at the onset of treatment and provision of some form of financial incentives for the indigent patients to cater for their indirect treatment cost. [40]

We also noted the treatment outcome for the MDR-TB patients with resistance to both Rifampicin and Isoniazid did not significantly differ from Rifampicin Resistant Tuberculosis (RR-TB). Other previous studies had reported poorer treatment outcome for the MDR TB involving the two core Anti TB drugs. [41,42] The Gene Xpert test conducted in this study detected mycobacterium tuberculosis and rifampicin resistance in almost all the patients similar to a Pakistan MDR TB survey[43]. Also, the relatively few DST isolated resistance to Isoniazid, Ethambutol and Streptomycin reported were comparable to a report from a Moroccan study. [44] We have no case of resistance to fluoroquinolone nor pyrazinamide in this study, which means that there was no indication for the individualized regimen .[45] A study in China reported that MDR TB with resistance to a fluroquinolone was also a predictor of poor treatment outcomes.[46] The cure rate of 78.2% during the intensive phase in this study was lower than the WHO recommended target cure rate of 85% but slightly higher than the successful treatment outcomes of most other studies in Nigeria, which ranged from 46-62%. [47,48]

We could not establish any significant difference between HIV comorbidity and MDR TB treatment outcome in this study. This is different from a finding in a survey in South Africa where MDR-TB and HIV co-infection were less likely to have a successful treatment outcome compared to HIV negative patients.[49] The high mortality rate in this study (16%) is a thing of concern. This was higher than previous MDR-TB specific death rates in some previous studies [50, 51] though lower than the MDR-TB mortality reported in a study from South Africa**.** [52]

The limitation of this study was that of utilizing a secondary data source which contained limited variable for data analysis to determine the treatment outcome. There was also the possibility of information bias at the time of this facility-based data collection.

This study has shown that the socioeconomic status of the MDR TB patient is a major determinant of the treatment outcome. Unemployment was the risk factor which predicts poor treatment outcome. These group of patients need increased access to treatment which is essential to prevent adverse treatment outcomes such as the TB treatment failure, TB relapse, MDR-TB

and MDR-TB and HIV co-morbidity. [53] There is also a need for adequate social support systems, and TB programme with a focus on women empowerment to enhance better treatment outcomes. [54] The authors also recommend further studies to determine factors responsible for lost to follow-up or discontinuation of treatment by MDR TB patients in this setting [55]

Competing interest: The authors declare that there is no competing interest

Authors' contribution: AO is the principal investigator for the study; he contributed to the study design, data collection, and analysis as well as drafted the initial and revised manuscripts. BA contributed to the data analysis and BA, EA was involved in conceptualization and data collection, LE and OJ made critical inputs into the revision and finalization of the manuscript. All authors read and approved the final manuscript.

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