

Treatment outcome of among DR-TB Patients in Nigeria: A 5 Year Review

Jacob A Dunga^{1*}, Yakubu Adamu², Datonye Alasia³, Samuel Ogiri⁴, Jafiada J Musa¹, Babawale Victor A⁵, Anthony A Mshelia⁶, Lawanson Adebola⁵, Aderonke Agbaji⁷, Vivian Ibeziako⁷ and Olusoji Ige⁸

¹Abubakar Tafawa Balewa University Bauchi, Nigeria

²US DOD Walter Reed Project, Abuja, Nigeria

³University of Port Harcourt Teaching Hospital, Nigeria

⁴World Health Organization, Abuja, Nigeria

⁵National Tuberculosis and Leprosy Control Programme, Nigeria

⁶Federal Neuropsychiatric Hospital Maiduguri, Nigeria

⁷Institute of Human Virology, Nigeria

⁸University College Hospital Ibadan, Nigeria

***Corresponding Author:** Jacob A Dunga, Abubakar Tafawa Balewa University, Bauchi, Nigeria.

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Abstract

Background: Drug Resistant Tuberculosis (DR-TB) is a critical threat to public health and Programmatic Management of DR-TB (PMDT) programs in various countries, as it is associated with high mortality and failure rates. Treating patients with DR-TB poses a serious challenge to the Government in terms of human and monetary resources as well as to the patients in terms of prolonged exposure to the second line drugs (SLD) and its antecedent adverse reactions (catastrophic cost). In Nigeria DR-TB treatment was commenced in 2010 with a lot of success and draw-backs. This study looked at the outcome of this intervention as it's relate to treatment completed, cured, lost to follow up (LTFU), failed treatment, died and treatment success. Adverse drug Reaction (ADR) associated morbidity, mortality as it influences the outcomes was also considered.

Methods: This study was a retrospective study from all DR-TB cases were identified from the National e-Tb manager data base from July 2010 to December 2014.

Results: A total of 973 data of patient treated for DR-TB were studied with a median age of 34.6ys. There were 62%, males and 38% females. About 89% were Tb retreatment cases and 11% were new cases. About 56.6% have completed their treatment with 26% cases declared cured. There were 4% of cases loss to follow up (LTFU) and 12% of patients died during treatment. About 1.1% failed treatment and were diagnosed pre-XDR-TB. No case of XDR was notified. The total success rate was 83%. About 28% (P = 0.0001) had comorbidity and 47.6 (P = 0.0001) of the patients had ADRs. There was an increase in mortality (34.2%) in 2013 and 2014 with 34% cases of ADRs and 11% cases comorbidity, suggesting a linear relationship.

Conclusion: This study shows that the treatment success rate in patients among DR-TB was about the national target, there is a decline in LTFU and mortality within the reporting period. Comorbidity and ADR are associated with poor clinical outcome; there is need to incorporate active drug safety management (aDSM) and specialist review and management for co morbidities as part of the management protocol.

Keywords: DRT-TB; Treatment; Outcome; Nigeria

Abbreviations

ADR: Adverse Drug Reaction; aDSM: Active Drug Safety Monitoring and Management; DR-TB: Drug Resistant Tuberculosis; DOT-Plus: Direct Observation Therapy Plus; DST: Drug Sensitivity Test; LPA: Line Probe Assay; LTFU: Loss to Follow Up; MDR-TB: Multi Drug Resistant Tuberculosis; SLD: Second Line Drugs; Pre XDR-TB: Pre Extensively Drug Resistant Tuberculosis; XDR: Extensively Drug Resistant Tuberculosis; Xpert MTB/RIF assay: Expert *Mycobacterium Tuberculosis* Rifampicin Assay

Introduction

Drug Resistant Tuberculosis (DR-TB) is a critical threat to public health and Programmatic Management of DR-TB (PMDT) programs in various countries is associated with high mortality and failure rates. Treating patients with Drug-resistant tuberculosis (DR-TB) poses a serious challenge to the Government in terms of human and monetary resources as well as to the patients in terms of prolonged exposure to the second line drugs (SLD) and its antecedent adverse reactions (catastrophic cost) [1]. In Nigeria DR-TB treatment was commenced in 2010 with a lot of success and draw-backs. The National TB case detection and treatment success rates in 2013 (Global TB Report, 2013) stand at 40% and 83% respectively falling short of the National targets of 70% and 85% [1,2]. This study aims to look at the outcome of this intervention as it's relate to treatment completed, cured, lost to follow up (LTFU), failed treatment, died and treatment success. Adverse drug Reaction associated morbidity, mortality and potential factors as it influences the outcomes.

Despite increased awareness, improved diagnostic facilities, and global control efforts, tuberculosis (TB) remains one of the deadliest infectious diseases in Nigeria and the rest of the world. TB control has become challenging because of HIV co-infection and the emergence of multidrug-resistant TB (MDR-TB) [2,3]. Extensive drug-resistant TB (XDR-TB) has also arisen as a threat to public health [3].

MDR-TB is a *Mycobacterium tuberculosis* strain that is resistant to rifampicin (RIF) and isoniazid (INH), two of the most effective anti-TB drugs. XDR-TB, a subset of MDR-TB is resistant to RIF, INH, any fluoroquinolone, and at least one of three injectable drugs (i.e. capreomycin, kanamycin, or amikacin) [4,5]. According to the WHO (2013), at least one case of XDR-TB was reported in 92 countries at the end of 2012. An estimated 9.8% of all MDR-TB cases develop into XDR-TB [6,7].

MDR-TB is a critical threat to public health, and MDR-TB care control programs in various countries are associated with high mortality and failure rates, especially in presence of HIV-infected patients [8]. Moreover, treatment for patients with MDR-TB strains is more expensive, complicated, and toxic and less effective than treatment for susceptible TB strains and MDR-TB strains are transmittable over long periods of time, even under treatment [8]. Primary and acquired drug resistance are common, with the latter caused by inappropriate regimen prescription or patient non-adherence [6].

Early publications on the treatment response of MDR-TB report a considerable mortality rate of 37% compared with susceptible strains [9,10]. However, XDR-TB treatment is more challenging than MDR-TB treatment. XDR-TB treatment commonly fails and leaves only a few categories of drugs available to which patients can still respond. A study reported that XDR-TB carries a five-fold increase in death risk compared with MDR-TB [10].

Poor treatment outcomes are influenced by several potential factors, such as previous treatments, smear positivity during treatment, Adverse drug reaction, co morbid conditions, treatment interruptions during the intensive phase of the disease, alcohol or drug addiction, and defaulting from TB treatment, which likely causes the proliferation of a large number of MDR-TB strains. Primary MDR-TB transmission also plays a critical role in treatment outcomes. However, all the factors mentioned (previous TB treatment, primary resistance, treatment interruptions, etc.) are well established predictors of poor outcomes [3,11-13].

Differences in treatment outcomes can help identify the causes of treatment success or failure and guide policy-making. Data on MDR-TB treatment outcomes in Nigeria are insufficient. Therefore, this study looked into treatment outcomes and potential associated factors between patients with MDR-TB.

Despite lengthy treatment with costly second-line drug regimens, curing MDR-TB remains a challenge in the resource constrained countries [3]. The World Health Organization (WHO) defines “cure” as “treatment completion” with at least three negative cultures after the intensive phase of therapy in the absence of “treatment failure”. The definition of “treatment failure” requires early termination of treatment or the need for permanent regimen change of at least two anti-tuberculosis drugs. “Treatment success” is defined as the sum of cure and treatment completion, loss to follow-up was defined as a patient on second line anti TB regimen whose treatment was interrupted for two or more consecutive months for any reason [14].

Materials and Methods

This study was a retrospective study from all DR-TB cases were identified from the National e-Tb manager data base from July 2010 to December 2017, medical records of all registered DR-TB patients at communities in States and treatment centers across the country was also used to make clarifications in situations where data on e-Tb manager was incomplete or required clarification.

All cases were diagnosed by Xpert MTB/RIF assay and confirmed by positive sputum culture for *M. tuberculosis*. Line probe assay (LPA), Drug sensitivity testing (DST) against first- and second-line drugs was also conducted for the *Mycobacterium* isolated. The study participants were all confirmed MDR-TB and XDR-TB cases that has been enrolled on treatment and data captured into National DR-TB register and e-TB manager. This include data from both inpatients and outpatient’s records, data on patients who were deceased, and those who had defaulted treatment within the study period were captured, patients record on commodity and ADR was also obtained. Patients considered were those treated with 20 months (8 months intensive and 12 month continuation phase) conventional regimen between 2010 and 2017 and Shorter (9 - 11month)/individualized (20 months) regimens between 2017 till date based on LPA, DST results and patient history of TB drug use. Directly observed therapy-plus (DOT-Plus) were applied on all patients confirmed with MDR-TB infections. Treatment was administered to patients via mix model of care which include in-hospital and community based model of care, patient were initiated either on treatment in hospital treatment centers or community. Patient initiated in the treatment centers were sent to communities after completion of intensive phase of treatment, in the same vein community patients who became sick were sent to treatment centers for expert care.

The definitions of terms used in the study were as follows:

- Cured - A patient on second line treatment regimen who has completed treatment according to the NTBLCP protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment or if only one positive culture is reported during that time, and there is no concomitant deterioration, a patient may be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative samples taken at least 30 days apart.
- Completed Treatment - A patient on second line anti TB treatment regimen who has completed treatment according to the NTBLCP protocol but does not meet the clinical definition of cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- Treatment failure - Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of the therapy are positive or if any of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor response or adverse events. This type of failure should be reported separately for the of sub analysis.
- Loss to follow up (LTFU) - A patient on second line anti TB regimen whose treatment was interrupted for two or more consecutive months for any reason.

- Defaulted treatment- Defined as treated patient who did not come back to complete chemotherapy and there was no evidence of cure through the sputum result during the fifth month of therapy. Whereas the treatment interruption was defined as a patient who did not collect medications for two months or more at a particular time or at interval, but still come back for treatment and in the 8th month of treatment, the sputum result was positive.
- Death was defined as a patient who died during treatment irrespective of the cause.
- Transferred was defined as a patient who was transferred to another treatment center and for whom treatment results were not known.
- TB relapse refers to a patient who had previous TB treatment and was cured but diagnosed again with a new TB infection.
- Poor treatment outcome was defined as unsuccessful treatment leading to death, TB relapse, defaulted treatment, or fail to complete treatment regimen or treatment interruption.

Patient were diagnosed by Xpert/MTB RIF molecular assay in most facilities across the country, sample for culture, LPA and DST were sent to regional TB reference laboratories across the country for analysis. Resistance was defined as at least 1% colony growth at critical concentrations of the drug (0.2 µg/mL INH, 1 µg/mL RIF).

Demographic characteristics, treatment outcome for MDR-TB and potential factors associated with poor treatment outcomes were recorded for analysis.

Data were analyzed using SPSS windows (version 25.0) and double-checked and cleaned to screen for missing values or errors. Multivariable analysis was conducted to determine significant potential factors associated with poor treatment outcomes. The multivariable analysis were included. The results were presented using appropriate tabulations based on determined variables, regression coefficients, and crude or adjusted odds ratio with 95% confidence interval as well as corresponding *p*-values. The significance level was set to 0.05.

Results

A total of 973 data of patient treated for DR-TB were studied with a median age of 34.6ys. There were 62%, males and 38% females 89% of the cases were Tb retreatment cases and 11% were new cases (Table 1). About 56.6% of the study group have completed their treatment. 26% cases were declared cured, 4% of patients were LTFU, 12% of patients died, 1.1% of patients failed treatment and were eventually diagnosed pre-XDR-TB. No case of XDR was notified (Table 2). The total success rate was 83%. About 28% (OR, 0.0479; 95% CI: 0.0412 to 0.0557, Z 39.5; P = 0.0001) had varied comorbid conditions and 47.6% (OR, 0.9078; 95% CI: 0.7782 to 1.0590, Z 39.572, P = 0.0001) of the patients had varying degrees of ADR. There was an increase in mortality (34.2%) in 2013 when 34% and 11% had ADR and co-morbidity respectively, suggesting a linear relationship see figure 1.

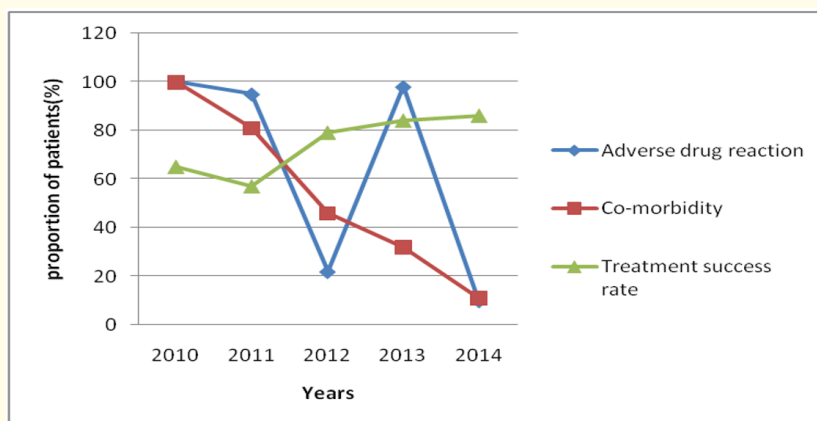


Figure 1: Graph showing the relationship between co morbid condition, adverse drug reaction and treatment success rate.

Year	Cases	Average	Male	Female	New cases	Re-Rx Cases
2010	23	33.43	8	15	0	23
2011	37	32.16	22	15	0	37
2012	154	35.64	58	95	26	128
2013	337	36.19	227	110	26	311
2014	422	35.79	292	130	52	370
Total	973		607	365	104	869
Mean	194.6	34.64	121.4	73	21	173
%			62%	38%	11%	89%

Table 1: Demography.

Year	Cases	Co-morbidity	ADR	Rx Completed	Cured	LFTU	Pre-XDR	XDR	Died
2010	23	23	23	4	11	1	0	0	6
2011	37	30	35	17	4	3	3	0	10
2012	154	71	34	71	50	5	6	0	22
2013	337	107	329	153	131	11	2	0	40
2014	422	46	42	306	57	20	0	0	39
Total	973	277	463	551	253	40	11	0	117
Mean	194.6	55.4	92	110.2	50.6	8	2.2		23.4
%		28%	47.6%	56.6%	26.0%	4%	4%		12%

Table 2: Outcomes.

There has been a steady increase in presumptive DRTB cases and Rif resistant cases diagnosed with Xpert/MTB Rif assay, equally the number of cases enrolled on treatment has increased over the last 6 years (2010 to 2016) as shown in table 3 below.

Indicator	2010	2011	2012	2013	2014	2015	2016
Presumptive cases	126	129	1647	3531	24313	52566	82771
DRTB/Rif Resistant cases	23	24	185	554	703	1279	1686
Enrolment	23	25	156	345	410	665	1251

Table 3: Indicators.

Discussion

Previous studies in Nigeria have reported treatment outcomes for Drug sensitive patients [15], however none of these studies included treatment outcomes of MDR-TB, nor XDR-TB. The effect of poor treatment outcome indices can be dare to the health and economic burden on the country, therefore poor outcomes can be overcome by strengthening health systems, including better case holding and effective mechanism to trace defaulters in addition to prompt and adequate care for ADR and co-morbidity among patients on treatment [15], published data on treatment outcome of DR-TB patient are limited, this study was therefore designed to look at the outcome and the factors contributing to the poor outcome in view of addressing them for a better treatment outcome among DR-TB cases.

A total of 973 data of patient treated for DR-TB were studied with a median age of 34.6ys. There were 62%, males and 38% females, indicating a male preponderance of DR-TB this is similar to studies done elsewhere [16,17]. About 89% of the cases were Tb retreatment cases were as 11% were new cases, 56.6% of the study group have completed their treatment with 43.4% yet to complete within the

reporting period, there were 26% cases that has been declared cured, this shows a significant improvement in cured cases compared to 11% seen in NTP in Pakistan [18]. It was noted that only 4% of patients were LTFU, this is also similar to a pattern observed in Zhejiang, China [19]. The total success rate was 83%. However similar study in India indicated a 55% cure rate among a cohort of 140 patients [20].

About 28% (OR, 0.0479; 95% CI: 0.0412 to 0.0557, Z 39.5; P = 0.0001) had varied comorbid conditions and 47.6% (OR, 0.9078; 95% CI: 0.7782 to 1.0590, Z 39.572, P = 0.0001) of the patient had varying degrees of ADR. There was an increase in mortality (34.2%) in 2013 with presence of co-morbidity and adverse drug reaction (34% and 11%) respectively, suggesting a linear relationship see figure 1. Similar effect was also noted in similar studies elsewhere [20,21] and based on the National TB case detection and treatment success rates in 2013 (Global TB Report, 2013) stand at 40% and 83% respectively falling short of the National targets of 70% and 85%, However this study concur with WHO global report on treatment success [1].

Paucity of data still exist about the impact of comorbidities on multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB) treatment outcomes. We aimed to examine the effect of human immunodeficiency virus (HIV), diabetes, chronic kidney disease (CKD), Congestive cardiac failure, on MDR/XDR-TB. There was increase in reported mortality (34.2%) among patient with co-morbidity, HIV comorbidity constituted 15% suggesting an increase in mortality among HIV/DRTB Co-infection than other comorbidities, and 1.1% of the study subjects had treatment failure. Some of the notable co-morbidity with negative impact on treatment outcome were HIV, DM, CCF, CKD this is similar to findings in systemic review and meta-analysis done elsewhere [22].

About 28% (OR, 0.0479; 95% CI: 0.0412 to 0.0557, Z 39.5; P = 0.0001) had varied comorbid conditions and 47.6% (OR, 0.9078; 95% CI: 0.7782 to 1.0590, Z 39.572, P = 0.0001) of the patient had varying degrees of ADR Most frequent ADRs were related to gastrointestinal system (30.42%), ototoxicity (11.0%), and central nervous system (7.1%). Aminoglycosides, cycloserine, and ethambutol were either reduced or discontinued due to ADR. Majority ADRs (77.04%) were "possible" category by causality assessment and "mild" in severity assessment. Ototoxicity was only severe ADRs observed. This is seen in similar proportion in similar observation elsewhere [23].

Management of MDR-/RR-TB is challenging because it involves the use of second-line drugs that because a high frequency of adverse drug reactions and because the treatment is lengthy it is associated with high incidence of Loss to follow up (LTFU) globally. About 4% of the study subject were loss to follow, this low figure probably is as result of in adequate reporting during the initial stage of the DR-TB care, this is shown by was low data recorded during the 2010 to 2012, however it showed and upward trend between 2013 1nd 2014 see table 2. This is probably due to improvement in M&E activities in the country this was also observed in Taiwan study among DRTB patients [24].

Pre-extensively drug resistant tuberculosis (pre-XDR-TB) is a comparatively new term and is defined as TB with resistance to rifampicin (RMP) and isoniazid (INH) with additional resistance to either a FLQ (Fluoroquinolone) or ISL (Injectable second line) agent but not against both these drugs simultaneously [25]. Thus pre-XDR-TB cases with FLQ or ISL resistance receive less number of effective drugs under standard MDR-TB regimen. It may amplify further resistance to the effective drugs and progression towards XDR-TB (Extensively drug resistant TB).

XDR-TB is defined as TB resistant to RMP and INH (MDR-TB) with additional resistance to second line anti-TB drugs i.e. to any FLQs, and to at least one of the three injectable second-line drugs (ISL) naming amikacin, kanamycin and capreomycin [26]. The prevalence of XDR-TB is 9.5% worldwide [27]. Treatment of XDR-TB is complicated, as it requires the use of second-line drugs that are less effective and more toxic, thus demanding longer treatment duration. Detection of pre-XDR-TB cases among MDR-TB patients is an important step in the prevention of treatment failure of MDR-TB and in addition, it helps to take appropriate measures to halt the progression towards XDR-TB.

So far, no data is available regarding the status of pre-XDR/XDR-TB in Nigeria. There were 11 (4.0%) of patients who failed treatment and were diagnosed with pre-XDR there were no cases of XDR. 12% of patients were not evaluated, this was probably due to in proper evaluation and lack of molecular diagnostics like Second line LPA and DST for first and second line drugs during the reporting period, with the upgrade and establishment of reference laboratories in the country there has been increase in the detection of pre XDR and XDR

cases within the last 3 years. African countries like South African reported high prevalence of pre-XDR-TB and XDR cases. In India 55.65% pre-XDR-TB cases were found among pulmonary MDR-TB patients in a tertiary care hospital in Mumbai [20,27].

There was significant death reported, within the study period 12% of patients died this could have been as a result of delayed access to diagnosis and treatment and partly due to poor management of ADR and comorbidity during the early stage of DRTB care in the country.

By 2015 MDR TB has caused approximately 240,000 death [14]. In this study 12% of patients died. ADR and comorbid conditions was associated with increase mortality among the study group. There was increase in reported mortality (34.2%) among patient with co- morbidity. HIV comorbidity constituted 15% suggesting an increase in mortality among HIV/DRTB Co-infection than other comorbid conditions among the study population [22].

Conclusion

In conclusion this study revealed that the treatment success rate in patients with DR-TB was about the national target. This study also shows an improvement from the previous success rate especially for DSTB and a decline in LTFU which was probably due to inadequate record keeping during the initial stage of commencement of DRTB care in the country. Comorbidity and ADR are associated with poor clinical outcome.

Recommendation

Standardizing TB treatment strategies, improving case detection rates, decreasing treatment default rates, and sufficient political will and financial support must be stressed. Education programs must be developed, evaluated, and implemented to reduce TB treatment default. Furthermore, nationwide research on survival rates and follow up of patient after cure must be conducted on MDR-TB patients, there is also need to incorporate active drug safety management (aDSM) and specialist review and management for co morbidities as part of the management protocol.

Limitation

Early detection of treatment failure through molecular assay and DST among patient could have improve the detection of early mutation.

Effect of ADR and comorbidity on culture conversion and treatment failure could also be investigated.

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Transparency Declaration

This research is an NTP based and neither the author nor any of the corresponding authors has been paid in any form or collected any resource in any form in order to conduct this research.

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