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TREATMENT OUTCOMES OF MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS MANAGED IN EBONYI STATE FROM 2017 TO 2020

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Running Title: Nwali Nneka et al; Drug resistance TB.

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ABSTRACT

Background. The emergence and spread of multidrug resistant/rifampicin resistant tuberculosis has posed an unprecedented global public health challenge. So far, there is scarcity of published work on the treatment outcome of the patients managed during the period WHO shorter injectable based regimen was used in Ebonyi State.

Objective. To determining the treatment outcome of this short injectable regimen in Ebonyi State from October, 2017 to September, 2020 and identify the predictors of unsuccessful treatment outcome.

Design. This was a total population study where all the 62 patients enrolled into the treatment during this period were recruited and a retrospective research design was utilized. Data were collected from the State DRTB registration log-book, patients' folders and treatment cards using an adapted checklist. Information obtained were entered into the computer using SPSS version 25 Illinois USA. Simple frequencies, proportions, cross tabulation and logistic regression were used for data analysis and p value <0.05 was considered significant.

Results. Twenty-five patients (40.3%), (14)22.6%, (5)8.1%. and (18)29% were cured, treatment completed, lost to follow up and died respectively. The predictors of unsuccessful treatment outcome were positive HIV status (P=0.042) and poor functional status (P=0.001).

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Discussion. There is need for the State TB program to channel more efforts toward sensitizing the public on the mode of spread of the disease, counselling of already identified cases, regular drugs supply, monitoring treatment progress to break the chains of transmission.
Conclusion. The presence of HIV and poor functional status are major contributors to poor treatment outcomes.

Keywords: Poor outcomes, HIV co-infection, functional status.

INTRODUCTION

Ebonyi State is located in the Southeast geographical zone of Nigeria. The State has thirteen local government areas and is made up of people with diverse cultures and dialects. Majority of its populace are agrarians while greater percentage of the rural dwellers are living in abject poverty which is a driving force to tuberculosis infection and spread. The State TB team comprises the program manager, drug resistant TB focal person, monitoring and evaluation officer, logistic officer, quality assurance officer and the accounting officer. Each of these officers has specific roles to play to ensure the smooth running of the program. The drug resistant tuberculosis unit harbors a consilium of experts (a six-man committee) comprising the Program manager, drug resistant TB focal person, physician focal person from the state referral treatment center, consultants from different fields in medicine especially the public health physician and ear, nose and throat (ENT) surgeon, and the leading community-based officer in the State. The conciliar meet on quarterly bases or whenever there is need to review the management of drug resistant tuberculosis patients in the State. Each of the thirteen local government area is manned by a TB supervisor (LGTBLS) who oversees the activities of tuberculosis control program. Tuberculosis is an infectious disease spread by microscopic droplets that affects the lungs and destroys other organs in the body causing coughing, weight loss, fever, night sweating and sometimes death. Despite progress in tuberculosis (TB) control round the globe, TB continues to be a leading cause of death from infectious diseases, claiming 1.2 million lives in 2018, 214,000 of these deaths were due to drug resistant strains. About 10 million (24%) were in Africa with Nigeria and South Africa contributing most (1). The same year, Nigeria was among the 30 high burden drug resistance TB contributing 4.5% of new cases and 15%of previously treated cases (2). WHO (2017) report showed that the treatment of MDR TB is complex, takes longer time and much more expensive when compared with treatment of non MDR TB and is associated with significant side effects for the patients. The report equally indicated that treatment success rate declines from 83% for patients with newly diagnosed or relapse non-drug resistant tuberculosis who commenced treatment with the first line regimen (2015 cohort) to 54% of MDR/RR TB (2014 cohort) and to 30% for extensively drug resistant tuberculosis (XDR TB) in 2014 cohort (3). WHO in the same report recommended the use of all oral bedaquiline shorter regimen (9 to11 months) for treatment of MDR TB patients and results so far show that patient find it easier to adhere and complete regimen when compared with injectable based or longer regimen that lasts up to 2 years (4). There was no significant association of unfavorable outcomes of multi-drug resistance tuberculosis with age, sex, place of origin, previous treatment, treatment delay, registration pattern, and classes of drugs

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used. Smoking was reported as an independent risk factor for poor treatment outcome of MDR TB (5).

World Health Organization has rolled out community-based programs aimed at improving treatment outcomes by giving the patients the opportunity to receive treatment in their own homes and by so doing address socio-economic barriers to adherence (USAID, 2011). The signs and symptoms of tuberculosis may include – shortness of breath, chest pain, cough of two weeks or more, loss of appetite, fever, weight loss, night sweat, tiredness. It also reported that other signs and symptoms of extrapulmonary TB depend on the part of the body involved (6).

Many studies had been done for drug resistance TB. A study in south Africa reported high failure rate with the short injectable regimen and better success rate with the Bedaquiline but more loss to follow up and another reported up to 74.2% success rate with Bedaquiline (7-9). Another study, however recorded high success rate (64.5%) with the injectable regimen and attributed treatment failure and death to malnutrition and previous history of treatment (10). Other studies reported treatment failure as related to age above 60 years, co-morbidity, use of second line drugs and loss to follow up (11,12). Systemic reviews with meta-analysis concluded that high prevalence of the disease is associated with the living condition, smoking, alcoholism, drug abuse and co-morbidities. A study recorded low rate of MDR-TB among the young and middle-aged group (13,14). A study also attributed success to incorporation of community initiative into the management (2). Another study reported MDR-TB commoner (14.7%) in age greater than 15years (15).

MATERIALS AND METHODS

A retrospective cohort study design was used for the study. The medical records of groups of individuals who are alike in many ways but differ in certain characteristics were compared for a particular outcome. The study was carried out in Ebonyi State, Southeastern Nigeria. It covers a land space of about 5,533km^2. The population of Ebonyi state from the 2006 census was 2,173,501 with a projected growth rate of 2.8% for the year 2022 (16). About seventy five percent of the entire population are subsistent agrarians that base mainly on rice, yam, cassava and palm oil. The rate of unemployment and underemployment is quite high with more than half of the population living below one United States' dollar per day. The state is made up of three senatorial zones namely north, south and central zones. It consists of thirteen local government areas. The state runs a three-tier health care system which are primary, secondary and tertiary levels. The Federal government is responsible for the activities in the tertiary healthcare centers while the State provides care through the secondary and Primary Health Care centers.

The State is made up of 565 health facilities that offer DOTS (Directly Observed Therapy-Short course) services for tuberculosis and these cuts across the thirteen local government areas. Each of the DOTS facility is spearheaded by a DOTS officer/staff who has been trained on identification, treatment and referral for TB. Each of these-officer collaborate with the local government TB supervisor, linkage coordinator, TB screening officers and other health workers in their respective

ISSN: 0075-5222

LGAs to ensure adequate TB service coverage. The state also has one referral treatment center for managing drug resistant tuberculosis patients. This center is meant to manage drug resistant TB patients who are very ill or complicated cases, patients with co-infection such as HIV, pregnant women, children less than 5 years, patient with history of substance abuse or non-adherent to treatment and patient with serious adverse event. Ebonyi state has nine GeneXpert machine sites where molecular test for TB are run.

The population of study consists of all the patients who were initiated into treatment with WHO injectable based shorter regimen from October, 2017 to September, 2020 in the State. This is a total population study. All Multidrug/Rifampicin resistant tuberculosis patients who were diagnosed through GeneXpert and 1st and 2nd line LPA and initiated into treatment within the period under review were used for the study. A total of 62 patients were recruited for the study. The instrument for the research was a data extraction checklist prepared after reviewing the drug resistance treatment registration log-book, patient treatment cards as well as computer database. The checklist consists of three sections. Section A contains the socio-demographic characteristics (date of registration, sex, age, marital status, occupation and treatment delivery model) section B is made up of clinical characteristics (body mass index, HIV co-infection, ART & CPT intake, functional status, behavioral status, other co-morbid conditions, gap between diagnosis and enrolment and adverse drug reaction), while section C is the treatment outcome. The instrument was sent to five experts in the Public Health Department. Thereafter, all the corrections made were effected and the final version used. Data was retrieved from Patients' personal folders – progress notes, treatment cards, baseline and routine investigations in the treatment center and various out-patient departments (OPD) where the patients were managed. Data was equally extracted from the State DRTB central register. The records of patients who were transferred outside the State after their intensive phase of treatment was obtained by contacting the various authorities concerned.

Drug resistance TB is diagnosed using the sputum, stool mostly from children, other body fluids such as cerebro-spinal, peritoneal, pleural, urine, gastric and joint aspirates from the presumptive person by 'GeneXpert' Mycobacterium tuberculosis/Rifampicin Assay (Xpert MTB/RIF Assay) used as primary diagnostic tool for tuberculosis. This test requires only one clinical specimen and can detect both tuberculosis and rifampicin resistance in less than two hours.

Following result of MDR/RR-TB detection, both local government TB supervisor and the state program are notified. This is followed by patient enrolment in the community or state treatment center as the case may be. Patient receives counselling on the treatment regimen. Commencement of baseline investigations take place after patient and treatment supporter have signed consent form. These investigations include chest X-ray, full blood count, liver function test, electrolyte urea creatinine, thyroid function test, test for HIV, hepatitis B & C, audiometry test, electrocardiogram, fasting blood sugar, visual acuity, patient height and weight, vital signs check and pregnancy test for women. Sputum samples are collected for culture, smear microscopy, first and second line drug line probe assay (LPA) and phenotypic drug sensitivity test. Some of these tests are repeated after two weeks of commencing treatment and then monthly till the end of treatment. The patients were placed on shorter injectable regimen that lasted for 9 to 11 months; 4 to 6 months intensive phase and 5 months continuation phase. The drugs used were kanamycin [Km]/ capreomycin [Cm]/amikacin [Am], pyrazinamide [Z], ethambutol [E], high dose isoniazid [H^{h}], protionamide [Pto], moxifloxacin [Mfx], clofazimine [Cfz] and vitamin B6. The whole medication was administered during the intensive phase, while Z, E, Mfx, and Cfz were continued

ISSN: 0075-5222

till end of treatment. Directly observed treatment short-course (DOTS) was ensured throughout the treatment.

Data collected were entered into the computer using SPSS version 25. Frequencies and proportions were computed for the univariate analysis. Cross-tabulation was done to determine relationship or association between various variables and treatment outcome. Logistic regression was done to ascertain the predictors of treatment success and a p-value<0.05 was considered statistically significant. The severity of adverse events suffered by the participants were graded using the Division of AIDS Table for grading the severity of adults and pediatrics adverse events.

RESULTS

Almost all the patients (96.8%) were self/unemployed and were into occupations that will give very little income and more than half (56.5%) of the participants were new cases of MDR/RR-TB who had never suffered tuberculosis before. Table 1 depicts the socio-demographic characteristic of MDR TB patients from October, 2017 to September, 2020. A total of 62 patients were recruited for the study aged 15 years and above. Majority of the patients 20(32.3%) were within the age range of 35 to 44 years and mean 43±4 years while three-quarter 50(80.6%) were males. A total of 69.4% were married and up to 91.9% of them were on admission during the intensive phase of treatment.

Table 2 summarizes the clinical characteristics of the patients. The table shows that 26.8% of the patients consumed alcohol, 12.9% had ever smoked while 14.5% could not care for themselves during the period of enrolment and initiation of treatment. Only 29% of the participants had basal metabolic index of 18.5kg/m^2 and above. A total of 56.5% had never suffered tuberculosis before while 38.7% had no co-morbidity. Twelve (19.4%) patients were HIV positive and only 4(33.3%) were on antiretroviral therapy/cotrimoxazole therapy during the period of enrolment. A total of 91.9% were enrolled into treatment within two weeks of diagnosis. Majority 93.5% had adverse drug reactions ranging from mild, moderate, severe, potential life threatening and death in the ratio of 43.1%, 39.7%, 13.8%, 1.7% and 1.7% respectively. Two patients were discontinued from treatment as a result of hepatotoxicity (Jaundice).

ISSN: 0075-5222

Table 1: Socio-Demographic Characteristics of the Patients

Variables	Frequency (N=62)	Percentage
Age (years)		
15 -24	4	6.5
25-34	13	21.0
35-44	20	32.3
45-54	12	19.4
55-64	6	9.7
≥65	7	11.3
Sex		
Male	50	80.6
Female	12	19.4
Marital status		
Married	43	69.4
Single	19	30.6
Occupation		
Employed	2	3.2
Unemployed	60	96.8
Petty trader	18	
Farmer	15	
Barber	1	
Carpenter	1	
Commercial driver	3	
House wife	2	
Student	3	
Apprentice	3	
Tailor	3	
Vulcanizer	1	
Food vendor	2	
Meat butcher	1	
Palm wine tapper	1	
Others	1	
Treatment Delivery Model		
Community based	5	8.1
Hospital based	57	91.9

ISSN: 0075-5222

Table 2: Clinical Characteristics of Patients

Variable	Frequency	Percentage
Behavioral status		
Alcoholic use		
Yes	29	46.8
No	33	53.2
Ever smoked		
Yes	8	12.9
No	54	87.1
Functional status		
Can care for self	53	85.5
Cannot care for self	9	14.5
BMI (kg/m)		
<18.5	44	71.0
≥18.5	18	29.0
Registration group		
Previously treated	27	43.5
New case	35	56.5
Co-morbidity		
Yes	24	38.7
No	38	61.7
Gap (days) between diagnosis & enrolment		
<14	57	91.9
≥14	5	8.1
HIV status		
Unknown	0	0
Negative	50	80.6
Positive	12	19.4
On ART/CPT	4	33.3
Yes	8	66.7
No		
Adverse event (n=58)	25	43.1
Mild	23	39.7
Moderate	8	13.8
Severe	1	3.4
Potential life threatening	0	0
Death		

ISSN: 0075-5222

Majority of the patients had mild gastrointestinal adverse drug reactions such as nausea 16%, vomiting 18.5% and loss of appetite 8.3%. A total of 7(5.9%) had sensorineural hearing loss (both partial and total deafness). A total of 9.2% had skin reactions (rashes and itching). The most common musculoskeletal event experienced by the patients was joint pain (5%). Table 3.

Table 3: Adverse Drug Reactions Observed in Patients during the Period of Treatment

Adverse Event	Frequency	Percentages
Gastrointestinal		
Nausea	19	16.0
Vomiting	22	18.5
Diarrhea	3	2.5
Loss of appetite	10	8.4
Gastritis	2	1.7
Bloody stool	1	0.8
Hematemesis	3	2.5
Hemoptysis	3	2.5
Sensory		
Tinnitus	4	3.3
Hearing loss	7	5.9
Eye pain	2	1.7
Ear pain	1	0.8
Psychiatric		
Insomnia	2	1.7
Depression	3	2.5
Psychosis	1	0.8
Suicidal attempt	1	0.8
Skin		
Rashes	6	5.0
Itching	5	4.2
Musculoskeletal		
Body pain	1	0.8
Back pain	1	0.8
Joint pain	6	5.0
Systemic		
Jaundice	2	1.7
Nephrotoxicity	3	2.5
Total	**119**	**100**

Table 4 shows the treatment outcome of the patients treated during the period under research. Out of a total of sixty-two, 25(40.3%), 14(22.6%), 5(8.1%) and 18(29.0%) were cured, declared treatment completed, loss to follow up and died respectively. Treatment success rate (total number

ISSN: 0075-5222

cured plus treatment completed) was 39(62.9%). Treatment unsuccessful (total number loss to follow up with the addition of those that died and those not evaluated) was 23(37.1%). Logistic regression was utilized to determine the predictors of treatment outcome of TB of this study. Both HIV status and functional status were confirmed significantly related to outcome of treatment (P<0.05).

Table 4: Treatment Outcome of MDR/RR-TB Patients/ Predictors Treatment Outcome

Treatment Outcome	Frequency	Percentage
Cured	*25*	40.3
Treatment completed	14	22.6
Loss to follow up	5	8.1
Died	18	29.0
Treatment failure	0	0
Not evaluated	0	0
Total	**62**	**100**

Predictors Treatment Outcome of the Disease

Variable	Odd Ratio	P-value	95% Confidence interval for Odd Ratio
HIV Status			
Positive (*ref*)	4.67	0.042	1.22 – 17.89
Negative			
Functional Status			
Can't care for self (*ref*)	20.27	0.001	2.33 – 176.28
Can care for self			

Table 5 shows that there is no significant relationship between the socio-demographic characteristic of the patients and outcome of treatment as P value was greater than 0.05 for all the variables tested.

ISSN: 0075-5222

Table 5: Relationship between Socio-Demographic Characteristic (Age, Sex, Enrolment Pattern) and Outcome of Treatment

Variables	Outcome Status		χ2	P-value
	Not successful (n=23)	Successful (n=39)		
Age (years)				
≤40	10	23	1.395*	0.237
>40	13	16		
Sex				
Male	18	32	0.133*	0.715
Female	5	7		
Occupation				
Employed	1	1	0.13*	1.000
Self employed	22	38		
Treatment delivery model				
Community	0	5	1.71*	0.148
Hospital	23	34		

*Fisher's exact point

Table 6: Relationship between HIV/ Functional Status and Outcome of Treatment

HIV Status	Outcome Status		χ2	P-value
	Not successful (n=23)	Successful (n=39)		
Positive	8	4	4.12*	0.042
Negative	15	35		

Relationship between Functional Status and Outcome of treatment

Functional Status	Outcome Status		χ2	P-value
	Not successful (n=23)	Successful (n=39)		
Can't care for self	8	2	9.65*	0.001
Care for self	15	38		

* Fisher's exact point

Table 6 shows no significant relationship between HIV status of the patient and outcome of treatment as P>0.05 but there is a significant relationship between functional status and treatment outcome P < 0.05.

ISSN: 0075-5222

Table 7: Relationship between Registration group for TB Treatment and Outcome

Registration group	Outcome Status		$\chi 2$	P-value
	Not successful (n=23)	Successful (n=39)		
Previously treated	13	14	2.50*	0.114
New case	10	25		

* Fisher's exact point

Table 7 shows no significant relationship between registration group and treatment outcome, P>0.05.

DISCUSSION

Greater percentage (32.3%) fall within the age range of 35-44 years with mean 43±4 years. This result is similar to previous reports (17-19). They were predominantly male (80.6%). This is explained by differences in social/risky behaviors which is higher in males. Evidence also showed that males are less likely to seek or access care for TB. The males are also more concerned with how to cater for their family and low socio-economic status is also a factor. This is similar to previous reports (17,20-23).

The common drug reactions were nausea, vomiting and loss of appetite. However, 7(5.9%) developed hearing loss and this is significant. Previous studies also reported hearing loss especially with aminoglycosides injectable agents (24). Thirty-nine (62.9%) of the patients had successful treatment outcome. This is similar to previous reports (12,24,25). and the WHO global success rate report of 60% in 2019. It is higher compared to some previous studies (26,27). The success rate is however, far below some previous reports (28,29) and WHO target of ≥90%. These variances may be due to differences in the socio-economies of the study location. Poverty may also be the cause of the high death rate recorded in this study. The result is however similar to a previous report in Nigeria (30). There is significant association between HIV status and treatment outcome, especially those not on ART and those not commenced on ART during the MDR TB treatment. From the raw data obtained in this study, deaths of HIV patients were noticed among those that were not already on ART and CPT before diagnosis and initiation of MDR TB treatment. This conforms with previous reports (9,31). There is significant relationship between functional status and outcome of treatment. Those who were stable and could care for themselves had better outcome. This was reported in previous studies (32,33).

Majority of the cases in this study (56.5%) were primary MDR TB. This finding emphasized that the existence of high rates of primary drug resistant TB may reflect active transmission of DR-TB in the community from the infectious individuals with the disease who are not on treatment hence, active case search for drug resistant TB is paramount for the prevention and treatment. This was also reported in a previous study (34). The high rates of primary multidrug resistant tuberculosis in this study is a clear indication that majority of people living in the community are ignorant of the mode of transmission, prevention and control of the disease. Health workers have a great role to play in sensitizing the public on the concept of tuberculosis by so doing disabuse peoples mind

ISSN: 0075-5222

on the misconceptions they have about the disease. The major cause of continued existence and rise in drug resistance tuberculosis as noted by different authors used in this study includes poor adherence to TB medications, inconsistent use of drugs (sometimes due to the large volume of drug and prolonged period of medication or treatment), interrupted drug supplies, physician error, and use of drug without a prescription for adequate treatment. Hence, the health officers should educate the people in this regard and at the same time encourage other health workers especially those who are directly involved in TB management to ensure that proper treatment is given to their clients. There is need for the government to implement laws banning the sale of over-the-counter drugs (antibiotics) to reduce drug resistance.

CONCLUSION

The emergence and continued rise in the prevalence of multidrug resistant tuberculosis in the world is a major cause for concern. Nigeria taking the sixth position of the global record of most highly burdened TB pandemic and number one position in Africa is alarming. The treatment outcomes of multidrug drug resistant tuberculosis as noted by the findings of this study show that Ebonyi State Tuberculosis Control Program still has a long way to go to attain the World Health Organization's estimated treatment success rate of 90%, death rate of less than 6-8% and loss to follow up rate of less than 2%. The high number of new cases of multidrug resistant tuberculosis in this study shows that primary transmission of this micro-organism in the communities is very high. High rate of death was noticed among HIV co-infected and those patients that could not care for themselves (bedridden) during the intensive phase of their treatment. Hence, all hands must be on deck to break this chain of transmission of tuberculosis.

The propositions of the researchers are that this may also be happening in many places as reported by some other article hence other researchers may need to do same for a holistic approach to cub the menace.

CONFLICT OF INTEREST

None declared

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None received

ETHICAL ISSUES

Ethical approval for this study was gotten from the ethical committee, Ebonyi State Ministry of Health to grant the researcher access to the patients' records in the State drug resistant tuberculosis central register and various facilities where the patients were managed. No patient's identity was included in any form and the data was kept confidential and was used for the purpose of the study only.

ISSN: 0075-5222

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