EFFECT OF ANTI-TUBERCULOSIS DRUGS ON PATIENTS WITH MULTI-DRUG RESISTANCE TUBERCULOSIS IN MAINLAND HOSPITAL YABA, LAGOS ,Nigeria.

ABSTRACT

The occurrence of multi-drug resistance tuberculosis (MDR-TB) among tuberculosis patients has raised global public health concern, especially in Nigeria. The increase in the number of cases of resistance tuberculosis despite the effort and need to curb the menace in Nigeria led to this study. It was a cross-sectional descriptive study of the already confirmed MDR-TB patients at the Mainland Hospital Yaba, Lagos and the aim was to investigate the effect of anti-Tuberculosis drugs on patients with multi-drug resistance Tuberculosis in Mainland Hospital Yaba, Lagos. One hundred self-structured interview questionairs were randomly administered among already confirmed MDR-TB patients at the hospital to collect bio-data information , and thereafter, received second- line anti-Tuberculosis drugs in phases for 22 months. The patients received the following regimen of treatments based on their weights and ages , the selected regimens administered for 22 months comprised of two phases; first, 8 months of intensive phase of Kanamycin, levofloxacin, cycloserine, prothionamide,and pyrazinamide and second, 12 months of Levofloxacin, cycloserine, prothionamide and pyrazinamide. Post laboratory analysis was used to monitor the effectiveness of the second-line anti-Tuberculosis drugs used. Out of the 92 patients that received the drugs, 89(96.7%) were confirmed negative to MDR-TB , while 3(3.3%) were still positive. The anti-Tuberculosis drugs in the order used is highly recommended for the reduction if not total eradication of MDR-TB in Nigeria. Effort should be geared towards making sure that the MDR-TB patients are confined , proper regimen administered and monitored in order to reduce the rate of spread.

Keywords: Drug resistance, Tuberculoss, Patients, Anti-tuberculosis drugs, Lagos.

INTRODUCTION:

Tuberculosis(TB) is a contagious disease which spreads as a droplet infection and it is the leading killer of young adults worldwide(1). The world Health Organization declared tuberculosis a global emergency in 1993 and it remains one of the world's causes of illness and death (2). Subsequently, multi-drug resistance tuberculosis (MDR-TB) –that is TB resistant to Isoniazid and rifampicin-emerged as a significant global health concern. Moreover, there are alarming reports of increasing drug resistance from various parts of the globe which potentially threaten to disrupt the gains achieved in tuberculosis control over the last decade (3). Begining in the late 1940_s , antibiotics were developed that were effective in curing TB, however, mutant strains of TB that were resistant to one or more of these antibiotics began to be identified as early as 1956 (4). Since then, the evolution of antibiotic resistant among TB has been a growing problem that is now a major public health threat. As the problem continued to grow, the term XDR-TB was coined for extensively drug resistant tuberculosis(5) and this is a resistant to at least four of the first line anti-TB drugs, that is resistance to not only isoniazid and rifampicin, but also resistance to any of the fluoroquinolones and at least one of the three injectable second line drugs (Kanamycin, capreomycin, or kanamycin) and is usually associated with HIV co-infection.

In many countries, the extent of drug resistance is unknown and the management of patients with multidrug resistant –TB (MDR-TB) is inadequate, however, in countries where drug resistance has been identified, specific measures need to be taken within TB control programmes to address the problem through appropriate management of patients, adoption of strategies to prevent the propagation and dissemination of drug resistant TB, since MDR-TB is a man made problem (6). For instance, in one of the studies where prescriptions of 449 doctors were analyzed, 75% of the doctors were found to have made some prescription erros (7), also non-adherence to instructions by the patients and thier families.

In 2010, the top five countries in terms of total number of MDR-TB cases were India, China , Russian Federation, South Africa and Bangladesh [8] . Moreso, estimates for the incidence of drug-resistant TB are difficult to obtain due to insufficient laboratory facilities for drug susceptibility test in most endemic countries (8). Besides,co-infection with HIV, globally. TB is also complicated by increasing drug resistance that first developed against the highly effective first line drugs. An estimated 5% of all TB cases are now MDR-TB and there were approximately 440,000 new cases of MDR-TB reported for 2008 (9).

According to World Health Organization (10,11), Nigeria now ranks 10th among the 22 high burden countries of TB in the World. Even though TB control and prevention efforts in Nigeria

have progresed well over the last two decades of the introduction of Directly Observed Therapy Short Course (DOTS) strategy, it still constitutes public health challenge (12).

Resistance to drugs was reported to have increased from 29.14% to 42.00% between 2000 and 2004 respectively (13), this suggests that though MDR-TB may be poorly documented , it is likely to have been present even among newly diagnosed patients in Nigeria.

In 2011, World Health Organization reported that Nigeria is also among the 4 African countries with the highest burden of drug resistant TB. Lawson et al (14), in Abuja pilot study , observed a high co-infection of TB/HIV and 31% of 32 culture positive patients with drug –resistance TB. Despite TB control, major threat is the emergence of drug-resistant MTB strains, that is widespread and caused by TB bacteria that are resisitant to two of the first line anti-TB drugs (rifampicin and isoniazid) (11) .

The emergence of drug resistant TB and relatively high burden of HIV/AIDS have impacted negatively on TB control and prevention efforts in Nigeria. For instance , in 2009, only 24,511 MDR-TB cases were reported to have enrolled for treatment (11) and in 2010, the estimated prevalence of MDR-TB rose to 650,000 cases among which only 46,000 enrolled for treatment . Drug treatment is very effective on the condition of strict patients' adherence which may at times be difficult and prolonged, however, as a result of complexity in taking the drugs, it has been observed that patients' do not adhere strictly to the instructions on the use of their medication , hence, treatment failures, relapse, and the development of drug resistant TB. However,these are in patients who observe their treatments in an irregular and unreliable way (10).

Moreso, extensively drug-resistant tuberculosis (XDR-TB) and multi-drug resistant tuberculosis (MDR-TB) are immense public health issues and debates are unsettled about how to treat the patients, what measures need to be taken to reduce the incidence of drug-resistant TB. All these revelations require urgent need for improving the diagnosis and management of drug resistant TB especially in resource poor country like Nigeria. It is in line with the above inherent problems and our utmost concern in the treatment outcomes of resistant tuberculosis that necessitatd this study.

MATERIALS AND METHODS

This study was carried out between February, 2014 and July, 2016 at the Mainland hospital, Yaba, Lagos. Lagos was chosen because it has a high population density, overcrowded homes, public places, and transportation with a poor level of personal and environmental hygiene, and represents an ideal location for the spread of tuberculosis and multi-drug resistant tuberculosis on the population. And Mainland Hospital Yaba/Ebuta metta as the anchor center because it is a government owned specialist hospital in Lagos Mainland Local Government Area of Lagos, located in Yaba and is considered the MDR-TB treatment center, although, solely designed for the highly infectious airborne MDR-TB disease, also played a positive role in the treatment and containment of the dreaded Ebola Virus Disease (EVD) spread.

STUDY DESIGN.

This is a cross-sectional descriptive study of the already confirmed MDR-TB patients at the Mainland Hospital Yaba, Lagos,Nigeria.

STUDY POPULATION.

This comprised of 100 already comfirmed MDR-TB patients made up of 50 males and 50 females MDR-TB patients at the TB section of the Hospital.

SAMPLE SIZE.

A suitable sample size of already comfirmed 100 MDR-TB patients made up of 50 males and 50 females patients at the TB section of the hospital was calculated and randomly selected.

Categories of respondents	Questionairs administered	Questionairs returned
Males	50	50(100%)
Females	50	42(84%)
Total	100	92(92%

Two female MDR-TB patients selected absconded.

SAMPLE SIZE CALCULATION

Determination of Sample size: A suitable sample size of one hundred (100) already confirmed MDR-TB patients were determined using the formula := $n=Z^2P(1-P)$

$$\frac{\qquad\qquad}{d^2}$$

according to [15], based on prevalence of 7% .

Z=1.96(standard statistical level of confidence at (95%)

P=7% (population based); d=5%(precision or margin error); n=Sample size.

$$n=\frac{(1.96)^2 \times 0.07\ (1-0.07)}{0.0025} = 100.03528 = 100.$$

ETHICAL APPROVAL AND CONSENT

Permission to carry on with this study at the Mainland hospital was obtained from the ethical and research committee of the hospital , while verbal informed consent was also obtained from each of the patients after explaininig the reasons behind the study and what they stand to gain.

SAMPLING METHOD.

This was done by random sampling.

STUDY INSTRUMENT.

A structured interview self-administered questionair was designed and used for collection of information fromt the patients.

POST LABORATORY ANALYSIS.

Post laboratory analysis was used to monitor the effectiveness of the second-line anti-TB drugs used.

The sputa of the MDR-TB patients who received the drugs were analyzed using both culture and staining methods(Ziehl Neelsen smear microscopic technique and culture 2 lowenstein Jensen slopes as in NIMER) to monitor the effectiveness or otherwise of the drugs. These were done at the Nigerian Institute of Medical Research (NIMER) Laboratory,Yaba Lagos .

DATA ANALYSIS.

Statistical analysis was based on simple percentages among related variables.

REGIMEN AND DURATION OF TREATMENT.

Drugs used are Kanamycin, Levofloxacin, Cycloserine, Prothionamide and Pyraznamide.

The patients received the following regimen of treatments based on their weights and ages , and the selected regimen were administered for 22 months in two phases:

(a) First 8 months of intensive phase, includes: Kanamycin, Levofloxacin, Cycloserine, Prothionamide and Pyrazinamide.
(b) Second 12 months of continuation phase includes: Levofloxacin, Cycloserine, Prothionamide and Pyrazinamide.

In addition to the regimen, there was proper intensive monitoring, moreso, nutritional support to ensure the provision of diet rich in protein and vitmin B6 to prevent neurological effects in patients due to Cycloserine/terizidone.

RESULTS.

Out of the 92 MDR-TB patients that received the drug regimen, 89(96.7%) were confirmed negative to MDR-TB.

Table 1: **AGE RELATED RESPONDENTS**

Age range	Frequency(%)
Below 20	8(8.7)
20-29	9(9.8)
30-39	18(19.6)
40-49	36(39.1)
50-59 and above	21(22.8)
Total	92(100.0)

The ages and weights were taken because they are necessary in the administration of anti-TB drugs, and the ages that are mostly affected are those in the range of 40-49(39.1%) and 50-59 and above(22.8%)

Table 2: Respondents marital status

Status	Frequency(%)
Single	17(18.5)
Married	52(56.5)
Widower	11(12.0)
Divorcee	12(13.0)
Total	92(100)

The table 2 showed that out of 92(100%) respondents , 52(56.5%) were married

Table 3 : Smoking hahits

Smoking	Frequency(%)
Never smoked	25(27.2)
Occasionally	27(29.3)
Often	26(28.3)
Very often	14(15.2)
Total	92(100.0)

Table 3 is the pattern of smoking and consequences, occasionally (29.3%) and often(28.3%) smokers had more MDR-TB than the other groups.

Table 4: Alcohol consumption

Consumption of alcohol	Frequency(%)
Yes	72(78.3)
No	20(21.7)
Total	92(100.0)

Table 4 is the consumption of alcohol and the effects, this result by implication suggests that consumption of alcohol by those who suffer from TB infections is highly risky, because it increases the rate of TB progressing to MDR-TB. And it is important to note that smoking and alcohol consumption has a positive relationship with drug resistance (16,17).

TABLE 5: Adherence to prescribed drugs.

Adherence	Frequency(%)
Yes	83(90.2)
No	9(9.7)
Total	92(100.0)

Table 5 showed that 83(90.2%) take their prescribed drugs as when due while 9(9.7%) do not.

Table 6 : Reasons for non-adherence(common reasons for non-adherence)

Reasons	Frequency(%)
Always forgot	15(16.3)
Drugs are too expensive	40(43.5)
Poverty	21(22.8)
Non-availability of the drugs	16(17.4)
Total	92(100.0)

Table 6 X-rays the factors that militate against the effective treatment of TB infections in Nigeria. The cost of the drugs(43.5%) and Poverty(22.8%) were the most potent factors and may cause ordinary TB infection to metamorphose to MDR-TB if not checked.

Table 7: Co-habitation

No of people	Frequency(%)
Living alone	13(14.1)
Up to 4	22(23.9)
5 and above	57(62.0)
Total	92(100.0)

Table 7 is how crowded homes aid in the disemination of TB and consequently MDR-TB infections within the environment since this disease is airborne . 62.0% of 5 and above people respondents live in one room or apartment , 23.9% of up to 4 people of the respondents live in one room while 14.1% of the respondents live alone .

Table 8: Post treatment laboratory results.

Results	**Frequency(%)**
Negative	89(96.7)
Positive	3(3.3)
Total	92(100.0)

Table 8 showed the effect of the anti-TB drugs on MDR-TB patients after receiving the regimen of the drugs. Out of 92 MDR-TB patients that received the treatments, 89(96.7%) of them with MDR-TB were confirmed negative, that is had their infections totally taken care of . While 3(3.3%) of the remaining patients were still positive. Therefore, this regimen , if properly

harnessed is highly effective against MDR-TB and should be recommended in most of our TB centers.

DISCUSSION.

The effective traetment of 89(96.7%) of MDR-TB patients out of 92 of them in this study(Table 8) has shown the highly efficacy of combined therapy of second-line anti-TB drugs using 8 months of intensive phase of Kanamycin, Levofloxacin, Cycloserine, Prothionamide and Pyrazinamide, and 12 months of second continuation phase of Levofloxacin, Cycloserine, Prothionamide and Pyrazinamide as applied in this investigation, under close monitoring (Directly Observed Therapy Short Course (DOTS), (7) corroborated this result when he said that irregularity in taking the drugs, non-monitoring, poverty , non-availability of drugs are some of the causes of MDR-TB , and is in agreement with Geerligs, (18) who said that MDR-TB is essentially a man-made phenomenom. According to him , other causes are genetic mutation, poorly or inadequate administered treatment regimen , short course therapy, poor infrastructure, unnecessary administrative control on purchases with no proper mechanism on quality control and bio-availability test, manufacturing of drugs of uncertain bio-availabilty in fixed doses or inappropriate drug combinations, poor storage conditions of drugs and substitution by inferior quality drugs as well as improper diagnosis (7).

While MDR-TB is more within the age brackets of 50-59 and above(22.8%), that of 30-39 years has 19.6%. Moreover, ocassional smokers (29.3%) has the highest portion of MDR-TB , often smokers has 28.3% followed by never smokers(27.2%), this descending report corroborates the statement of (16) and (17) who posited that smoking and alcohol are positively associated with drug resistance . (19) supporting this finding said that smoking, impairs clearance of mucosal secretion which agreed with (20) who found out that smoking reduces phagocytic ability of alveolar macrophages which aids in decreasing the immune response and /or CD4 Lymphopenia due to the nicotine in the cigarrettes.

Moreso, table 3, showed that alcohol predisposes TB patients to MDR-TB, and is in conformity with the revelation of (21) who said that alcohol causes alteration in the immune system specifically in altering the signalling molecules responsible for cytokine production thereby reducing the active responses and feedbacks of the immune systems. Furthermore, co-habitation, close contacts/proximity encourages the disemination of MDR-TB , this correlates the observation of (22) who reported on the risk of factors of Mycobacterium tuberculosis infection among children in Greenland.

Furthermore, cost of drugs and poverty (table 6) are serious challenges to eradication of MDR-TB, this is worrisome, laying credence to this assertion are (23), World Health Organization, (24)

and (25) who variously reported that Tuberculosis burden follows a strong social economic gradient between and within countries with the poorest having the highest risk.

It is therefore, true that drug treatment is very effective on the condittion of strict patient's adherence which may at times be difficult and prolonged.

In conclusion, since MDR-TB is a man-made phenomenom, due to perhaps irregularity in medication, non-adherence to treatment and others, effort should be geared towards making sure that the MDR-TB patients are confined , proper regimen administered and monitored in order to reduce the rate of spread. However, the cost of the drugs, poverty, and non-availability of the prescribed drugs may be a battle to fight

It is therefore imperative that patients using the multi-drug resistant TB drugs should make sure that their drugs are used regularly as prescribed, there should be proper public informatin by the government agencies on health about people managing the TB, what to do and the signs, causes and implication of MDR-TB. Again TB patients should always go for proper medical laboratory diagnosis, government should continue to subsidize and monitor the drugs for the TB patients , early information is paramount as it is an effective factor in managing MDR-TB. And DOTS and DOTS-plus TB programs should be integrated with well functioning HIV management programs to ensure that Anti-Retro-virals are widely administered to limit susceptibility to TB diease.

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