Multi-Drug Resistance, HIV/AIDS Coinfection and Risk Factors Associated with *Mycobacterium tuberculosis* Infection in Nigeria: A Systematic Review

Kashibu E.[1*] Doughari J. H.[2] and Ja'afaru M. I.[2]

1. Department of Medical Laboratory Science, Taraba State University, PMB 1167, Jalingo, Taraba State, Nigeria.

2. Department of Microbiology, Faculty of Life Sciences, Modibbo Adama University, PMB 2076, Yola, Nigeria.

* Corresponding author: Emmanuel.kashibu@yahoo.com

Abstract: Multi-drug resistant tuberculosis (MDR-TB) and human immunodeficiency virus (HIV) have emerged as major public health challenges facing tuberculosis control programme particularly in Asia and Africa. In Nigeria, the seroprevalence of HIV is 4.4%, the third highest infection burden in the world, with 21% of all tuberculosis patients dually infected with TB and HIV. The impact of MDR-TB is likely to increase if adequate measures are not taken. Despite the high prevalence of MDR-TB in Nigeria, not much effort has been made at tackling the problem. This paper reviews the burden of MDR-TB and the factors that are responsible for the problem particularly in Nigeria. Internet search of studies on MDR-TB was done and those relevant for this study were reviewed. The major risk factors of MDR-TB in Nigeria are previous TB treatment and HIV/AIDS coinfection. Efforts should be made towards proper diagnosis of HIV/AIDS and MDR-TB and adequate treatment given where causes are treatable. Patients should be adequately counseled and where facilities for diagnosis and treatment are inadequate, the government can provide and subsidize the cost for ease of management and treatment.

Key word: Tuberculosis, multi-drug resistance tuberculosis, TB/HIV confection, risk factors.

INTRODUCTION

Pulmonary tuberculosis is a global emergency, one third of the world's population has latent TB infection with about 10% of this population developing active pulmonary tuberculosis (PTB) during their life time (Omote *et al.,* 2018). In 2016 10.4 million new cases was recorded globally with estimated death figure of 1.4 million persons at approximately 4,105 mortality rate per year (Chandreskaran *et al.,* 2017*).* There are several chemotherapeutic agents (antibiotics) available and are used for the treatment of PTB, these agents were helping to record success story against PTB until the advent of drug resistant strains and HIV/AIDS pandemic (Abiodun *et al.,* 2015). Drug resistance PTB can be classified as mono (resistance to a single anti TB drug, multi (resistance to rifampicin and isoniazid) and extensive (resistance to rifampicin, isoniazid, fluoroquinolones and kanamycin) (Ullah *et al.,* 2016). Drug resistance PTB is a serious public health issue. Globally 3.7% of newly diagnosed and 20% of previously treated cases of PTB was estimated to be caused by multi-drug resistant tuberculosis (MDR-TB) strains in 2022. Higher figures were reported for central Asia and Eastern-Europe and the presence of extensive TB strain have been reported in 92 countries (Yoon *et al.,* 2013).

It is believed that immune response is associated or may be responsible for susceptibility to tuberculosis (Chandreskaran *et al.,* 2017*).* Immune responses are broadly divided into two (innate and acquired). While innate immunity includes physical barrier, complement system, macrophages, monocyte system and natural killer cells, acquired immunity comprises of humeral immunity (B-lymphocytes/T-lymphocytes dependent and production) and cell medicated/ T-lymphocytes dependent and functions in antigen presentation as well as cytoxic activities). Immunological parameters such as total white cell count, absolute neutrophil count, absolute lymphocyte counts, monocyte to lymphocytes ratio and neutrophil to lymphocyte ratio are been used as susceptibility markers to certain disease (Yoon *et al.,* 2013). There are several reports associating susceptibility of PTB with these parameters (Afzal *et al.,* 2010).

Drug resistant tuberculosis and its rising incidence and prevalence have become a

global health burden with serious threat to the world economic growth (Naranbhai *et al.*, 2014). In 2016, there was an estimated 4.1% of new cases and 19% previously treated cases of multi-drug resistant tuberculosis. This figure has increased by an annual rate of more than 20% (Lange *et al.*, 2018). According to a world Health Organization 2017 report, 240,000 people died from multi-drug resistant tuberculosis and countries that reported at least one strain of extensive drug-resistant tuberculosis rose from 92-123 (WHO, 2017). Several factors have been linked to the emergence of multi-drug resistant tuberculosis. But within the last three decades, acquisition or emergence of drug resistant tuberculosis has been linked to previous TB treatment, use of inferior regimes, poor adherence to anti-TB drugs, poor access to healthcare and largely due to HIV/AIDS pandemic (Oneydum *et al.*, 2017). In Nigeria, similar risk factors have been associated with emergence of multi-drug resistant tuberculosis. The Economic, social and psychological burden associated with drug resistant tuberculosis therapy is enormous. Patients have to cope with limited treatment options, longer duration of therapy regimes with increased toxicity and the economic burden for those accessing care from private practitioners (Thomas *et al.*, 2016).

Method of Literature Search

PubMed and Google scholar were used to search for literature on multi-drug resistance, HIV/AIDS coinfection and risk factors associated with *Mycobacterium tuberculosis* infection. A total of 1,220 articles were initially obtained. Out of these 48 articles were retrieved and included in the review.

Burden of Multi-Drug Resistant Tuberculosis in Nigeria

According to the World Health Organization (WHO) global report 2016, among 10.4 million incidence of TB cases worldwide, 3.9% are estimated to have had rifampicin or multi-drug resistant tuberculosis (MDRTB) in 2015 (WHO, 2016). Also, 21% of previously treated TB cases were estimated to have MDRTB in the same year (WHO, 2016). Nigeria is one of the countries that is included among the 30 high burden countries for multi-drug resistant tuberculosis (WHO, 2016) The estimated incidence of MDRTB in Nigeria is 4.3% among new cases and 2.5% among previously treated case (WHO, 2016). However, with the advent of newer molecular diagnosis techniques for TB and the current advocacy for a country-wide roll-out by the Nigeria TB program and other partners (FMH, 2015 WHO, 2016), Several studies have reported on the rates of DRTB in different cohorts of TB patients across various setting in Nigeria. A study in the Mid-Western Nigeria in 2018 showed a prevalence of 3.3% which is lower than the national prevalence (Kome *et al.*, 2018). In 2018, a study carried out in South-West of Nigeria recorded a prevalence rate of 23.4%. This is high compared to what was reported in studies from Southern and Northern part of the country (Kuyinu *et al.*, 2018; Vain *et al.*, 2014). However, study from another Southern State in Nigeria indicated a high prevalence than what was found in the Northern part of Nigeria (Osman *et al.*, 2012). In North Eastern Nigeria a study carried out in 2017 showed a prevalence rate of 5.9%. This is comparable to other studies in Nigeria which showed prevalence of 7. 1% and 8.6% respectively (Moss *et al.*,2012, *Rasaki et al.*, 2014). This high prevalence can be attributed to improper prescription of anti-TB treatment regimes, inadequate drug supply poor quality of drug, high default and treatment failure rate (Blondal *et al.*,2017, Jindani *et al.*, 2004, Van der Werf *et al.*,2012). In addition, once selected, drug resistant strain of multi-tuberculosis may be transmitted in the community. Despite the high prevalence of multi-drug resistant TB recorded in Nigeria, no significant efforts have been made in tackling the problem.

Multi-Drug Resistant TB and HIV/AIDS Co-Infection

Drug resistant tuberculosis (DR-TB) is defined as case of TB excreting bacilli that are resistant to one or more anti-TB drug. Drug resistant tuberculosis can exist in

different forms including; mono drug resistant TB, poly drug resistant TB, rifampicin resistant TB, multi- drug resistant TB and extensively drug resistant TB (WHO, 2019). Studies have shown that there is a dynamic interaction between TB and HIV infection. Tuberculosis accelerates the progression of disease in people living with HIV (PLHIV) and people living with HIV have increased susceptibility to TB infection. Tuberculosis has been found to be the major cause of death in PLHIV and TB has been found to be responsible for failure of TB control programs to achieving targets particular in high burden countries. TB and HIV co-infection enhances the risk of acquiring multi-drug resistant TB strains (Wells *et al.,* 2007, Dubrovina *et al*., 2008).

Global Burden of TB and HIV Co-infection

The incidence of drug resistant TB (DR-TB) and HIV coinfection has increased over the past decades as both are strongly linked. It is estimated that PLHIV, especially with fewer 200/cm^3 CD4 counts, show 9-fold increased risk of developing active TB compared to HIV negative patient (Kolo, 1991). World Health Organisation in 2016 reported that 8.6% (7.4-10%) of 10 million incident cases with active TB had coinfection with HIV in 2018. Sub-Saharan Africa is the region with the highest burden of co-infection cases comprising 10% of global co-infected cases of the 30% countries burdened with TB and HIV co-infection. Tuberculosis infection has been detected in 70% of patients with HIV with South Africa reporting the highest number of incidence cases of coinfection (177,000) followed by India (92,000) and Mozambique (N85,000) Also, in 2018, 0.25 million (16.8% of a total 1.5 million deaths from TB shared co-infection with HIV (Kolo, 1991). Out of 862,000 new cases of TB among PLHIV, 477,461 (56%) were established and 86% were placed on antiretroviral therapy (ART) (Kome *et al.,* 2018). In Nigeria, a study in Zaria, North West of the country in 1991 showed a prevalence of 19, 13, and 29% of newly diagnosed patients that are multi-drug resistant (Abdullahi A, 2006). In addition, resistance to isoniazid, streptomycin and pyrazinamide by the isolates had increased to 29, 14, 42% by 2006 (Abdullahi, 2006). This suggests that multi-drug resistant must have been in existence in newly diagnosed patients in Nigeria for some time. But, the WHO without an actual survey put the prevalence in Nigeria at 1.9 and 9.3 for new and previously treated patients respectively. World Health Organization probably underestimated the Nigeria MDR-TB burden. Thus, this brings to fore the need for good clinical practices and cohort drug sensitivity test (DST) survey. It is likely that MDR-TB emerged in Nigeria in 1990s as reported by Idigbe *et al.,* 1999 who reported that 5% of isolated strains were not responding to anti-TB treatment and were resistant to one or more of the drugs used, with 38% being resistant to isoniazid, although 2% were resistant to rifampicin at the time and were not associated with HIV infection (Idigbe *et al.,* 1992*).*

Association between DR-TB Epidemiology and HIV and Risk factors

There are several epidemiological reasons that DR-TB may be associated with HIV. Among the reasons are i) rapid progression of disease due to harbouring of drug resistant strains, particularly in the immune compromised compared to the immune competent state, ii) malabsorption of anti-TB drugs such as rifampicin and ethambutol, leading to drug resistance and treatment failure, iii) early reactivation of an infection due to increased vulnerability in an immune compromised state acquired from community or institution transmission, iv) direct contact with DR-TB cases, suggesting primary or transmitted resistance, v) co-founding by common risk factors such as intravenous drug abuse imprisonment, vi) low socio-economic status, vii) alcoholism, viii) frequent hospitalization, ix) repeated exposure to DR isolates and x) poor adherence to treatment. The effect of global burden of DR-TB and HIV co-infection has not been effectively defined due largely to lack of sufficient data. The primary reasons

for the lack of data is that HIV infection and anti-TB drug susceptibility testing (DST) are not adequately accessed from joint surveillance under routine conditions. Epidemiological studies from different countries have shown discordant associations. There have been differences in setting, demographic profile, methodology and analysis of data. In the fourth WHO international union against tuberculosis and lung disease global drug surveillance report, 24 countries reported data on MDR-TB by HIV status (Busillo *et al.*, 2011*)* Of these countries only eleven (11), majority from East European and Central Asian regions, reported strong association between HIV and drug resistance. This has made existing data to be sparse as implementation of tests such as automated GeneXpert MTB/RIF assays and polymerase chain reaction-based line probe assay (LiPAS) remain sparse and sub-optimal, particularly in resource-limited settings assumed to have a high burden disease (Busillo *et al.*, 2011) . Community based surveillance at national level should be conducted for all regions worldwide to estimate the burden co-infection in near future.

Table 1: Ten-year study reports on multi-drug resistant tuberculosis in Nigeria

Authors	Study Design and topics
Omote *et al.* (2018)	Pulmonary tuberculosis among suspected cases in Delta State, south Southern Nigeria
Abiodun *et al.* (2015)	Incidence of HIV and Pulmonary tuberculosis co-infection among patients attending out-patients clinic in a Nigerian Hospital.
Oneydum *et al.* (2017)	Prevalence of drug resistant tuberculosis in Nigeria.
Kome *et al.* (2018)	Multi-drug resistant *Mycobacterium tuberculosis* in Port-Harcourt Nigeria.
Kuyinu *et al.* (2018)	Characteristics of *Mycobacterium tuberculosis* positive patients screened of drug resistant tuberculosis.
Osman *et al*. (2012)	Resistance of *Mycobacterium tuberculosis* for first- and second-line Anti Tuberculosis drugs.
Rasaki *et al.* (2014)	Rifampicin Resistant Tuberculosis in a second Health Institution in Nigeria.
Kolo *et al*. (1991)	Bacteriological and drug sensitivity studies on *Mycobacterium* isolates from patient and their close contacts in ABU Teaching Hospital, Zaria.
Idigbe *et al.* (1992)	Resistance to anti-tuberculosis drugs in treated patients in Lagos Nigeria.
Akinyele *et al.* (2020)	Risk factors associated with MDR-TB among Tuberculosis patients in Ibadan

Risk Factors Associated with Multi-Drug Resistant TB

Drug resistant tuberculosis is a serious global health issue with alarming morbidity and mortality figures. There are established risk factors associated with MDR-TB and this include; i) previous TB infection, ii) poor TB drug regime, iii) poor adherence to TB treatment, iv) contact with MDR-TB patient and v) HIV pandemic. Despite the publicity by health workers on the importance of taking precautional measures regarding this risk factors, DR-TB is still with us. This may not be unconnected with the socio-economic condition globally in diagnosed cases of MDR-TB and lack of awareness and inaccessibility of health services. For example, in Ethiopia in 2012, WHO estimated that the number of patients in Ethiopia tested for MDR-TB was <1% of new and <4% of retreatment case (WHO, 2015).

Previous Tuberculosis treatment

Most cases in Nigeria showed a strong association between the occurrence of MDR-TB and previously treated TB with anti-TB drugs (Akinyele *et al*., 2020). This occurs when there is a history of incomplete or inappropriate TB treatment regimens lasting at least 1 month (Gomes *et al.*, 2018). This may be because prior inadequate anti-TB treatment only suppresses the growth of susceptible bacilli and does not affect other resistant strains, leading to suitable conditions for the dominant multiplication of

pre-existing drug resistant mutants (Mc Konen *et al.,* 2015).

Alcohol

Alcohol has been found to be a risk factor occurrence of MDR-TB. Several reports indicated that the use of alcohol increases the risk of developing MDR-TB due to poor adherence to treatment impairment of immune responses and increased risk of adverse drug effects (WHO, 2015, Shin *et al.,* 2010).

Smoking

Smoking has been found to contribute significantly to development of MDR-TB (Gomes *et al.,* 2018). This is because smoking and alcohol have been found to go together. And this increases the risk of developing MDR- TB by poor adherence to treatment and impairment of the immune response and also increasing the risk of adverse drug effect (WHO, 2015, Shin *et al.,* 2010).

HIV/AIDS

The HIV/AIDS has been found in most studies to be significant in the development of MDR-TB *d*espite the availability and access to antiretroviral therapy and prophylaxis to infectious diseases (Marahatta *et al.,* 2015, Andrew *et al.,* 2021). But, findings from a study in South West Nigeria showed that positive HIV status contributes relatively to development of drug resistant tuberculosis (Akinyele *et al.,* 2020). This is an agreement with report of (Mishal *et al.,* 2017) who revealed there is high rate of DR-TB among HIV infected persons. This is as a result of the fact that HIV weakens the immune system and give rise to the rapid progression of latent TB (Mishal *et al,* 2017, Andrew *et al.,* 2021).

Gender

Some studies have shown significant statistical associations between gender and MDR-TB (Fasutini *et al.,* 2006) others show no significant association (Akinyele *et al.,* 2020). A study carried out in Ibadan, Western Nigeria specifically showed that there is no significant statistical association between gender and MDR-TB, though more than two thirds of the MDR-TB cases were male. This was so because the male gender due to the nature of their work are exposed more to external environment than the female and as such are more prone to risk to MDR-TB. On the contrary, a in South Africa reported that more female (63.6%) than males (36.4%) were infected with MDR-TB. They submitted that the reason for this observation was because the male gender had quick access to health care services any time males suffer illness than female. This is because culturally, the female depends on other members of the family to have access to health care as they cannot freely express their help problems (Gomes *et al.,* 2018).

Occupation

The occupation of patients has also been found to have a significant statistical relationship to acquiring MDR-TB. A study in Nigeria showed a significant association with the occurrence of MDR-TB and the occupation of the patients (Akinyele *et al.,* 2020). This is contrary to a study carried out in the United States of America in which no significant difference was found in participant's occupations and occurrence of MDR-TB (Mesfin *et al.,* 2014). The type of job is connected with the income and is an indicator of the socio-economic status of an individual. Several findings indicated high burden of MDR-TB among individuals of low socio-economic status (F.M.H, 2015, Marta *et al.,* 2014). This could be explained because if a family has low income, they might have limited access to medical treatment and health care services. Also, the overcrowded and poor living conditions may facilitate the spread of infectious diseases.

CONCLUSION

Multi-drug resistant tuberculosis in Nigeria has an incidence rate of 4.3% among new cases and 25% among previously treated cases. Nigeria also ranks among the 30 high burden countries for multi-drug resistant tuberculosis in the world . Efforts should be made towards the diagnosis and treatment of the infection. Given that health care facilities are limited in Nigeria, but with the advent of newer molecular diagnostic techniques for

TB diagnosis and the current advocacy for a country wide roll out by the Nigeria TB programme and other partners, this problem could be surmounted. Also, improper prescription of anti-TB treatment regimens, inadequate drug supply, poor quality of drugs, high default and treatment failure rates could be taken care of by increasing direct observation treatment (DOT) centers and provision of treatment clinics whose patients are isolated and treated for the required period of time so as to take care of the associated problems. The government should make anti- retroviral therapy (ART) available for HIV/AIDS patients, since there is significant statistical association between HIV/AIDS and MDR-TB. More HIV diagnostic and counseling units should be provided in most health facilities. Other risk factors can be controlled through public health enlightenment programs in both the urban and rural areas in Nigeria.

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