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# Pattern of Multi-Drug Resistant Tuberculosis in HIV Sero Positive Patients in Rivers State Nigeria

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author MAA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NO and OKO managed the analyses of the study. Author MAA managed the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Tuberculosis (TB) presents a major worldwide health concern, especially in immune-suppressed persons, with a high mortality rate. The emergence of drug-resistant variants of TB further weighted down by the high HIV prevalence continues to make it difficult to treat this disease. Nigeria is currently listed among the 30 high burden countries for TB, TB/HIV and drug resistant TB (DR-TB). The current study assessed the resistant patterns of *Mycobacterium tuberculosis* to first-line anti-TB drugs among individuals with tuberculosis and HIV coinfection in Rivers State.
**Methods:** A sample size of 260 HIV sero-positive patients were separated into two groups consisting of 130 patients on anti-TB treatment and 130 individuals yet to commence anti-TB treatment. Sputum samples were collected and processed by line probe assay (GenoType®MTBDR*plus* by HAIN Lifescience).
**Results:** The study showed that about 61.5% of the subjects with TB/HIV coinfection were between the ages of 26 and 40 years, with a mean age of 37.2 ± 9.6 years, (102) 64.1% of the subjects had drug susceptible TB, 24 (15%) had INH mono-resistant TB, 17 (10.7%) had RIF mono-resistant TB and 16 (10.1%) had multi-drug resistant TB. There was no significant difference

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observed in the occurrence of drug resistance between the different sexes. The results also showed that 11.0% of the individuals receiving anti-TB treatment had MDR-TB; INH and RIF mono-resistance were observed in 15.7% and 11.8% of these subjects respectively. Amongst subjects that were yet to receive anti-TB treatment, 6.3% had MDR-TB, 12.5% had INH mono-resistant and 6.3% had RIF mono-resistant TB.

**Conclusion:** The findings of the study indicate that drug-resistant TB appears to be prevalent among persons with TB/HIV coinfection in Rivers State, Nigeria.

*Keywords: Tuberculosis; Drug resistance; MDR-TB; LPA; HIV; Rivers State.*

## 1. INTRODUCTION

Despite targeted efforts towards the reduction and elimination of the tuberculosis [TB] epidemic in 2035 as aimed by the world health organization's [WHO's] END TB strategy, the global burden of TB remains enormous [1,2]. In recent times, the WHO has reported progress in reaching more people with quality TB care, corresponding to reduction in the number of tuberculosis related deaths. However, TB remains one of the most infectious killer diseases globally, with about 10 million TB infections reported in 2018 [2]. Consequently, about 1.2 million TB-related deaths were reported among HIV sero-negative individuals and about 251,000 HIV-positive individuals had died from TB-related illnesses in the year 2018 [2,3]. A significant majority of the TB cases reported in the year 2018 by WHO were recorded in South-East Asia [44%], followed by Africa [24%] and the Western Pacific [18%], while smaller percentages of TB occurrences were reported in Eastern Mediterranean [8%], the Americas [3%] and Europe [3%]. Nigeria together with seven other countries in the African and Asian WHO regions were reported to account for about 2/3$^{rd}$ of the global TB burden, with Nigeria accounting for 4% of the global TB incidence reported by the WHO [2].

The impact of HIV/AIDS pandemic has significantly changed the epidemiology of TB globally. HIV infection is a considerable determinant of TB infection, as HIV poses a great risk for reactivation of latent TB infection and increases the progression of TB disease and *Mycobacterium tuberculosis* (MTB) reinfection [4,5,6]. While individuals infected with MTB alone have 10% lifetime risk of developing TB, those with TB/HIV coinfection have more than 10% annual risk of developing TB [3,7].

Africa has been reported to have high HIV/AIDS burden [2]. In Africa, HIV is the single most important factor contributing to the increase in the incidence of TB since 1990. TB/HIV coinfection rates are also high in Africa and high mortality rates have been reported among people with TB/HIV co-infection in this region [2]. This probably explains why TB is one of the world's foremost causes of death [from a single infectious agent] especially in resource-poor settings or developing countries.

Drug resistant tuberculosis (DR-TB) continues to be a public health challenge, exacerbating the burden of tuberculosis [2,8]. The emergence of drug-resistant forms of tuberculosis in many parts of the world is a threat to public health and global TB control efforts, especially in countries with high HIV burden [6,9]. Its very existence is a reflection of weaknesses in TB control programs, intended to minimize the emergence of drug resistance [7,10]. Notable of these is the fact that the directly observed treatment short course (DOTS) programme that has been developed to streamline the use of first line anti-TB drugs is yet to be perfected in many settings. This has resulted in the widespread misuse of isoniazid (INH) and rifampicin (RIF), the two most potent first line anti-TB drugs [11,10]. The decades of drug misuse has consequently led to the selection and amplification of strains of *Mycobacterium tuberculosis* resistant to one or more anti-TB drugs [2,12].

In 2018, there were about half a million new cases of rifampicin-resistant TB [RR-TB] {of which 78% had multidrug resistant TB (MDR-TB)}; defined as tuberculosis caused by MTB strains that are resistant to at least, two first-line anti-TB drugs INH and RIF[1,8,13]. Globally, 3.4% of new TB cases and 18% of previously treated cases had multidrug resistant TB or rifampicin-resistant TB (MDR/RR-TB), with the highest proportions (>25% in new cases and >50% in previously treated cases) in countries of the former Soviet Union [2].

Although MDR-TB is a threat to the global TB control efforts and a cause of morbidity and mortality, its diagnosis remains a worrisome

challenge which further compounds treatment and control efforts. Therefore prospects for reaching the TB elimination target set for 2050 are still not in sight. In addition, the implementation of the World Health Organization's Stop TB Strategy is currently lagging behind the envisioned scale-up pace, particularly with regard to TB/HIV collaborative activities and management of drug resistant TB [13]. This situation is aggravated by inadequacy of diagnostic and treatment services, particularly in the TB high burden regions where they are most required [4].

The various techniques available for TB diagnosis have varied advantages and shortcomings. Conventional microscopy lacks sensitivity while culture is cumbersome and time-consuming; resulting in patients with DR-TB either not being diagnosed at all or receiving a delayed diagnosis, thus further propagating transmission and increasing the severity of the disease. Therefore, rapid tests with high sensitivity and specificity that have the ability to evaluate resistance patterns are the new ideal. This goal has prompted the development and subsequent approval of several genotypic methods by the WHO [14]. One of these methods, the molecular line probe assay [LPA], GenoType®MTBDR*plus*, developed by HAIN Lifescience, Nehren, Germany for the molecular genotypic identification of MTBC and its resistance to rifampicin [RIF] and and/or isoniazid [INH] directly from clinical specimens as well as culture was approved in 2008 [15].

The use of LPA has improved the detection and treatment of drug resistant TB globally [16,17] via early and accurate diagnosis, with significantly lesser turnaround time [48 hours] as compared to conventional DST method [42 days]; thus enabling appropriate medication for treatment, especially in the presence of drug resistance, with a resultant break in the transmission cycle.

While these techniques are readily available and routinely used in developed countries, their availability is still limited in TB endemic areas, including Nigeria, where they would have been more useful, particularly for the diagnosis of DRTB. Therefore, there still exists a wide gap with regards to diagnosis and case detection in these regions [2].

Nigeria is still currently listed among the high burden countries for TB, TB/HIV and MDR-TB [2]. In Nigeria, patients with HIV and TB/HIV are classified as priority groups for presumptive DRTB, who should be screened for DRTB, using rapid genotypic methods [18]. However, under diagnosis is still a major challenge in Nigeria [2]. In addition, the HIV prevalence in Rivers State Nigeria, was reported to be above the National average [19]. This study therefore, adopted the LPA technique with the objective of assessing the prevalence of multi-drug resistant TB among HIV sero-positive patients in Rivers State.

## 2. METHODS

### 2.1 Study Design

This was a cross sectional study carried out in Rivers State, Nigeria to determine multidrug-resistant pulmonary tuberculosis among Human immunodeficiency virus (HIV) seropositive patients in Rivers State using line probe assay (LPA) technology.

Registered adult HIV seropositive patients presenting with symptoms suggestive of broncho-pulmonary infection (cough lasting more than 2 weeks), and those with prior diagnosis of TB were identified.

### 2.2 Study Area

The study was carried out in Port Harcourt, the capital city of Rivers State, Nigeria.

The study was conducted in the directly observed treatment short-course (DOTS) and HIV clinics, located at the University of Port Harcourt Teaching Hospital (UPTH), Central Chest Clinic, Rivers State Ministry of Health (CCH) and the Braithwaite Memorial Specialist Hospital (BMSH) in Rivers State.

### 2.3 Study Population

The study population consisted of 260 adult (≥18 years old) HIV sero-positive patients attending UPTH, CCH and BMSH, who consented to participate in the study and produced sputum for testing.

The patients were separated into two groups consisting of 130 TB/HIV co-infected patients on anti-tuberculosis treatment and 130 HIV seropositive patients, suspected of having tuberculosis who were treatment naive.

### 2.4 Sample and Sampling

A total of two hundred and sixty (260) subjects were recruited for the study, with sample size

determination based on the expected prevalence of MDR-TB in TB/HIV co-infected patients estimated at 19% (19).

Following formula as stated by Kirkwood *et al*. [20].

$$n = Z^2 * (PQ)/D^2$$

Where:

N= Minimum sample size
Z= Value of reference normal distribution for the desired confidence interval (95 % Confidence Interval)
P= Expected prevalence of MDR-TB in TB/HIV co-infected patients (19% estimated prevalence) by Tukvadze *et al*. [21].
Q=100-P
D= Highest acceptable error in an estimate (1/2 width of the CI measurement of precision).

Therefore; N = 1.962 [0.19 (1-0.19)] / 0.052 = 236.49 ~ 236 + 10% of 236 = 260

### 2.5 Specimen Collection

Duplicate sputum samples (spot and early morning) were collected in sterile, wide-mouthed bottles from patients that were able to produce. The collected sputum samples were preserved in a refrigerator ($4^oC$) at the site of collection and subsequently moved in a cooling box daily to the Medical Microbiology Laboratory of the UPTH for initial processing.

### 2.6 Specimen Analysis

The Ziehl Neelsen (ZN) method was used to confirm the presence of Acid Fast Bacilli (AFB) in the sputum samples. The stained slides were stored in slide boxes. The samples were subsequently subjected to decontamination procedure, repeat ZN staining and AFB microscopy. The decontaminated sputum samples were subjected to both molecular Line Probe Assay (MDRTB*plus* by HAIN Lifescience Germany) for the genotypic identification of MTB and its drug susceptibility testing and culture using established procedures (22).

### 2.7 Data Analysis

The data collected was analyzed and presented using measures of central tendency (mean, frequency and percentage). Chi-square analysis was used to assess the occurrence of TB and drug resistance at a 95% confidence interval and a p-value < 0.05 was considered significant. All data were analyzed with the Epi Info v7 software.

### 2.8 Ethical Consideration

Ethical approvals to conduct the study were obtained from the Ethics Committees of the different study sites prior to commencement of the study. A willing informed consent was obtained from all patients before they were enrolled into the study.

## 3. RESULTS

### 3.1 Demographics of Study Population

The mean age of the study subjects was 37.2 ± 9.6 years, 20.8% (54/260) were within 26-30 years, 19.2% (50/260) within 31-35 years and 21.5% (52/260) within 36-40 years. There were 51.9% (135/260) female subjects and 48.1% (125/260) males (p =0.54). A hundred and thirty-one (50.4%) had secondary education, 55 (21.2%) and 53 (20.4%) had tertiary and primary education respectively while 21 (8.1%) did not have any formal education. One hundred and thirty nine (53.5%, 139/260) and 13.1% (34/260) were in the private sector and public employment respectively, while 33.5% (87/260) were unemployed.

Fig. 1 shows that 159 (61%) of the subjects were infected with MTB and 101 (39%) were not.

Fig. 2 shows the drug susceptibility pattern of the MTB infected persons. One hundred and two (64.2%) had drug susceptible MTB, 24 (15.1%) had INH resistant MTB, 17 (10.7%) had RIF resistant MTB and 16 (10.1%) had Multi-drug resistant MTB.

Table 2 shows that the differences in the pattern of drug resistance between both groups of patients was not statistically significant (p = 0.5257).

Table 3 shows the distribution of drug susceptibility by sex in the MTB infected subjects. Among the 82 male subjects, 12 (15.0%) had INH-R, 10 (12.2%) had RIF-R, 10 (12.2%) had MDR and 50 (61.0%) had drug susceptible MTB. Among the 77 female subjects, 12 (15.6%) had INH-R, 7 (9.1%) had RIF-R, 6 (7.8%) had MDR, 52 (67.5%) had drug susceptible MTB. The occurrence of drug resistance was not significantly different between sexes (p = 0.7025).

**Table 1. Sociodemographic data of subjects**

| Variables | Frequency (n=260) | Percentage (%) |
|---|---|---|
| **Age group** | | |
| <21 | 4 | 1.5 |
| 21-25 | 15 | 5.8 |
| 26-30 | 54 | 20.8 |
| 31-35 | 50 | 19.2 |
| 36-40 | 56 | 21.5 |
| 41-45 | 27 | 10.4 |
| 46-50 | 20 | 7.7 |
| 51-55 | 13 | 5 |
| 56-60 | 9 | 3.5 |
| >60 | 4 | 1.5 |
| Undisclosed | 8 | 3.1 |
| **Age** | | |
| Mean ± SD | 37.2 ± 9.6 | |
| **Sex** | | |
| Male | 125 | 48.1 |
| Female | 135 | 51.9 |
| **Educational level** | | |
| Primary | 53 | 20.4 |
| Secondary | 131 | 50.4 |
| Tertiary | 55 | 21.2 |
| No formal education | 21 | 8.1 |
| **Occupation** | | |
| Public servant | 34 | 13.1 |
| Private employment | 41 | 15.8 |
| Trading/Self employed | 98 | 37.7 |
| Unemployed | 87 | 33.5 |

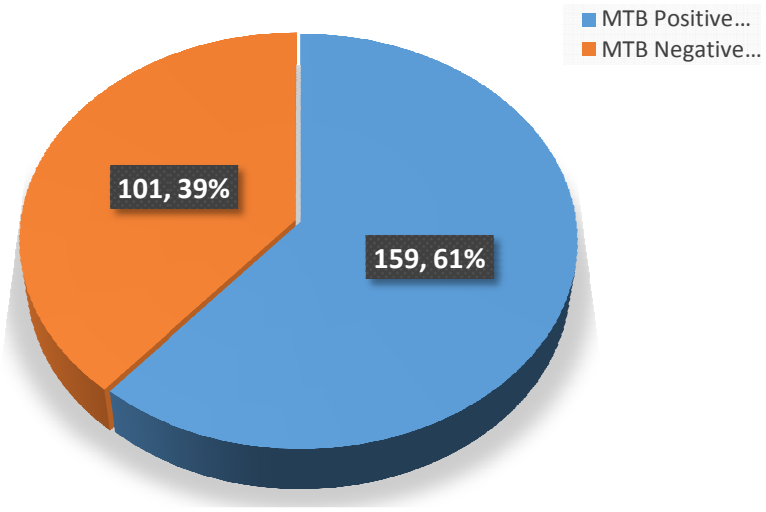


**Fig. 1. Prevalence of TB in the study subjects**

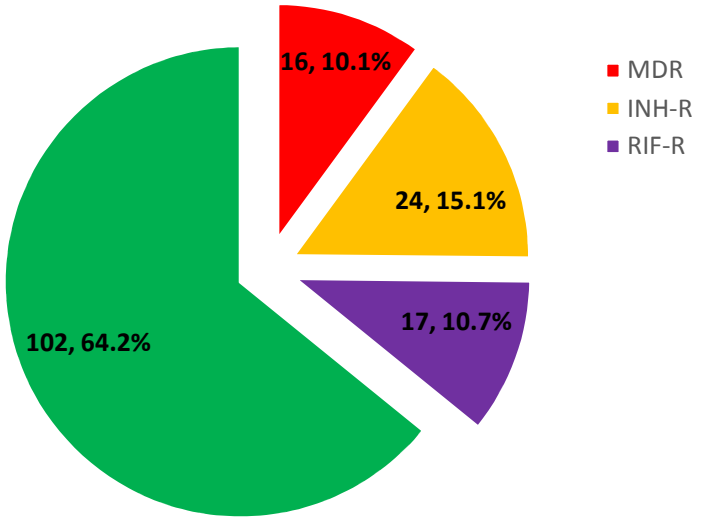


**Fig. 2. Distribution of drug susceptibility patterns**

**Table 2. Pattern of drug resistance according to patients' treatment status**

| Susceptibility pattern | On-treatment (n=127), % | Treatment naïve (n=32), % | Chi-square (p-value) |
|---|---|---|---|
| INH and RIF Resistant | 14 (11.0) | 2 (6.3) | |
| RIF-R | 15 (11.8) | 2 (6.3) | 0.23 (0.5257) |
| INH-R | 20 (15.7) | 4 (12.5) | |
| Susceptible | 78 (61.4) | 24 (75.0) | |

**Table 3. Drug susceptibility pattern by sex**

| Drug susceptibility pattern | Male | Female | Chi-square (p-value) |
|---|---|---|---|
| INH-R | 12 (14.6) | 12 (15.6) | |
| RIF-R | 10 (12.2) | 7 (9.1) | |
| MDR (INH + RIF) | 10 (12.2) | 6 (7.8) | 1.41 (0.7025) |
| SS | 50 (61.0) | 52 (67.5) | |
| TOTAL | 82 (100.0) | 77 (100.0) | |

*INH-R; Isoniazid –resistance, RIF-R; Rifampicin-resistance, MDR; Multi-drug resistance, SS; Drug susceptibility*

## 4. DISCUSSION

The HIV epidemic is a major barrier in the control of tuberculosis especially in countries with high TB burden. Although the phenomenon of drug resistance is not uncommon, it however poses a serious challenge in the control of tuberculosis. This study assessed the prevalence of drug resistant TB among HIV patients that were already exposed to anti-TB treatment as well as HIV patients that were suspected to be infected with TB, who were treatment naïve in Rivers State. The results showed that about 61.5% of the subjects were between 26 – 40 years, while the mean age of the subjects was 37.2 ± 9.6 years. This is consistent with the findings of previous studies around the world reporting that young people of the reproductive age group are mostly infected with HIV [22–24].

Among the subjects, 159 (61%) had *Mycobacterium tuberculosis* infection. This is higher than the findings of Gyar *et al.,* which reported an MTB/HIV coninfection rate of 34.65% in Lafia, Niger State [5] and Musa *et al.* which reported an MTB/HIV coinfection rate of 13.62%

in Kano, Nigeria [10]. The findings of the current study are relatively higher than prevalence rates reported in different parts of Nigeria ranging between 10.1 – 40% [12,25–27]. Similarly, the prevalence of TB/HIV co-infection in Africa is reported to be 43% and between 50 – 80% in parts of sub-Saharan Africa [8]. The high coinfection rate in this study could be associated with the choice of study subjects; one half of the study population consisted of known TB/HIV co-infected patients who were already on anti-tuberculosis treatment. Additionally, the highly sensitive and specific genotypic LPA employed for the diagnosis of MTB and its drug resistance patterns in this study could have accounted for this. Other reasons could be the differences in health seeking behaviours observed in the inhabitants of the different parts of the country and the air pollution caused by industrial activities such as gas flaring in the Niger-Delta region of the country [26].

Drug susceptibility testing showed an overall prevalence of 10.1% for MDR-TB amongst study subjects with TB/HIV coinfection while prevalence rates of MDR-TB were 11% and 6.3% in treatment experienced and treatment naïve subjects respectively.

The prevalence of MDR-TB found in this study is higher than the estimated national prevalence of 4.5% [2] and 5.5% reported in a similar study using sputum smear and GeneXpert technique carried out by Dinic *et al*. [28]. The observed prevalence is also higher than the 6% prevalence of MDR-TB reported in a retrospective study on drug resistant TB among people living with HIV using GeneXpert diagnostic methods by Nwofor *et al*. [29]. Studies on a similar population of TB/HIV coinfected individuals have been infrequent in Nigeria. However, in the general population comprising coinfected and non-coinfected individuals, rates of 4%, 7.7% and 8% have been reported in Calabar, Nnewi and in a three-city Nigerian study of TB drug resistance pattern using GeneXpert technology among TB/HIV co-infected persons [25].

The current study also recorded rifampin (RIF) mono-resistance and isoniazid mono-resistance of 10.7% and 15% respectively which is higher than 7.0% for rifampin [RIF] and 9.3% for RIF or isoniazid (INH) reported by Dinic *et al*. [28]. However, the prevalence of RR-TB and INH-R reported in this study is consistent with the findings of Otu *et al*. [6] which reported a RIF-R of 17% and an INH-R of 14%. Several biological mechanisms linking drug-resistant TB to HIV infection have been suggested [28]. Drug malabsorption in HIV-infected patients, especially rifampicin and ethambutol, has been shown to lead to treatment failure, which possible consequence could lead to drug resistance. Drug-resistant strains may be less virulent and preferentially lead to disease progression in immunocompromised patients, as opposed to immunocompetent individuals[13].

The high TB drug resistance rates observed in this study reflects the rising trend in other parts of the country and indeed the world at large. The variations observed in this study may have resulted from differences in diagnostic methods. Line probe assays reportedly have a higher sensitivity and specificity in detection of drug resistant *Mycobacterium tuberculosis* in comparison to GeneXpert and Sputum Acid-Fast Bacilli which are still the most frequently used diagnostic methods in many centers across southern Nigeria [8,17,30]. Therefore, TB and DRTB cases which would have been missed with other diagnostic methods may have been detected in this study.

## 5. CONCLUSION

The was a high prevalence of Drug-resistant tuberculosis. The findings of this study showed that the MDRTB prevalence was higher prevalence of multi-drug resistant tuberculosis among HIV infected subjects in Rivers State. This prevalence is higher than the estimated national average. There is therefore, the need to strengthen both the DOTS and HIV/TB linkage services in our setting.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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