Research Article

Study of Rifampicin resistant pattern of *Mycobacterium tuberculosis* and human immunodeficiency virus co-infected patients using Gene-Xpert assay

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Abstract

Background: A major opportunistic infection among HIV-infected people is tuberculosis. It accelerates the deadly progression of HIV which results in a further decline in the patient's immune status and early death. **Objective:** The objective of the present study was to determine the rifampicin-resistant pattern of MTB and HIV co-infected patients. **Material and methods:** A total of 384 sputa and 384 blood samples were examined from 384 patients (247 male & 137 female) attending north-west zonal tuberculosis reference laboratory of Aminu Kano Teaching Hospital. The patients have a presumptive case of tuberculosis. The research was conducted between March and September 2019. The blood samples were first tested for HIV and sputum samples were analyzed using the GeneXpert machine, a real-time polymerase chain reaction-based equipment. **Results:** Eighty-six (52 male & 34 female) representing 22.4% of the participants are HIV positive. Likewise, 19 (12 male & 7 female) representing 4.9% of the total participants (384) has MTB. The highest rate of MTB was found within the age range of 31 - 40 years. Two (10.5%) samples from the male population are MTB positive and resistant to rifampicin. However, no rifampicin resistance was recorded in the female population. Age group 31 – 40 years are the most affected with pulmonary TB while age groups 21 - 30 and 30 - 40 years are the groups affected with rifampicin-resistant tuberculosis which was 0.38%. There was no detection of RIF/RES at >41 years of age group. **Conclusion:** MTB/RIF assay provide rifampicin resistance directly from the sputum in less than two hours.

Keywords: *Mycobacterium tuberculosis*, Human immunodeficiency virus, Rifampicin, Polymerase chain reaction, sputum

Introduction

Tuberculosis (TB) is a chronic airborne infectious disease caused by the *Mycobacterium tuberculosis* (MTB). According to the World Health Organization (2016), MTB remains a major public health problem, ranking above HIV/AIDS. It is one of the leading causes of morbidity and mortality among infectious diseases worldwide. Most infections do not show

symptoms, and it is therefore regarded as latent TB. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected (WHO, 2016). The classic symptoms of active TB are a chronic cough with blood and fever.

Robert Koch, a physician and microbiologist from Germany, was in 1882 isolated and identified a bacterium responsible for tuberculosis. The causative agent was a year later named as *Mycobacterium tuberculosis*. It is characterized by the formation of nodular lesions (tubercles) in the tissues.

MTB is responsible for most cases of tuberculosis including pulmonary tuberculosis (PTB). Tuberculosis is

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primarily an airborne disease; the bacteria is spread from person-person in tiny microscopic droplet when tuberculosis patient coughs, sneezes, sings, or laughs (Ellner et al., 2011).

The reservoir for the infection is human with active tuberculosis. Tuberculosis is a state in which one or more organs of the body become diseased as shown by clinical symptoms and signs. This is because the tubercle bacilli in the body have started to multiply and become numerous enough to overcome the body defense (Anthony et al., 2004)

Today, tuberculosis tends to be concentrated among the innercity dwellers ethnic minorities and recent immigrants from areas of the world where the disease is still common (WHO, 2002). Though no one is exempted from contracting the disease, alcoholics, who are often malnourished, and people infected with HIV are more prone to disease.

World health organization declared tuberculosis as a global emergency in 1993, however, 21 years after the disease remains a serious and considerable threat to global health. It is also the 10 major causes of mortality among children with the global estimation of 130,000 death per year. Of great concern to the WHO is the emergence of drug-resistant TB strains particularly in developing countries. These strains, especially those resistant to more than one of the usual first line of drugs used to treat the disease, pose a very serious threat if they spread rapidly around the world. Unfortunately, this phenomenon is primarily as the result of incomplete or improper regimens (Ananya, 2014).

Material and methods

Sampling site

Samples for the study were collected from north-west zonal tuberculosis reference laboratory of Aminu Kano Teaching Hospital (AKTH), Kano State, Nigeria.

Study Population

A total of 384 consented patients were screened and 88 subjects (19.3) of both genders within the age grade of 2–78 years were positive to PTB hence participated in the study. The participants showed a symptom of tuberculosis and were confirmed with GeneXpert system. These symptoms include persistence cough for at least 2 weeks, weight loss, night sweat, swelling at the neck, hand or armpit, and fever. This study involved all presumptive TB patients reported to directly observed treatment, short-course (DOTS) centre at AKTH.

Inclusion criteria

- Subject of all ages with tuberculosis symptoms that agreed to participate in the study by signing patient consent form
- All presumptive DR-TB patients.

- All patients with tuberculosis suspected to have HIV

Exclusion Criteria

- All patients that do not agree to participate in the study
- All patients that attending other hospitals

Sample Size

Fishers formula was used to calculate the sample size as shown below (Fishers et al., 1996):

$$n = \frac{Z^2 PQ}{r^2}$$

Since the entire TB population as of 2018 was above 10,000 (NTBLCP, 2019).

Where n = desired Sample size

Z = standard normal deviation was set at 1.96 which corresponds to 95% confidence

P = proportion of the target population used as 0.50 if no reasonable population estimate (Muhammad et al., 2017)

$$q = 1.0 - p$$

r = degree of accuracy desired (usually 0.05 or occasionally 0.02)

From the above formula :

$$n = \frac{Z^2 PQ}{r^2} = \frac{(1.96)^2 \times (0.5) \times (1.0 - 0.5)}{(0.05)^2} = 0.9604 \div 0.0025 = 384$$

Therefore n = 384 samples

Ethical Clearance

Ethical clearance for the study was sought and obtained from the ethical review committee of Aminu Kano Teaching Hospital. Formal letters were written to the selected health facilities. Before collecting samples, the study participants were informed about the purpose, merit and demerit of the study in local languages, written informed consent was obtained from all participants. Besides, the confidentiality was kept. Participants were given unconditional right of withdrawal at any time and without giving any reason.

Variables

Independent Variables

Age, sex, sign and symptom, occupation, marital status and body mass index.

Dependent Variables

Presence of MTB, HIV, RIF/RES

Data Collection Tools

Data were collected by pre-tested questionnaire and laboratory diagnosis

Data Collection Methods and Laboratory Diagnosis

Data Collection

Structured and standardized questionnaires were used to collect information about the socio-demographic and clinical feature of the study participants. One nurse and one laboratory personnel were recruited from the health facility to assist in the study. Pieces of training were given to them on the objective and benefit of the study, participant's right, informed consent, and techniques of the interview for the collection. The selection of participant were based on the inclusion criteria.

Sample Collection and processing

For the blood sample collection, a tourniquet was wrapped around subjects' upper arm (Ndiok et al., 2012). Then the needle site was cleaned with 70% alcohol. The needle was put into there in. A vacutainer tube was attached to the needle to fill it with. The band was removed from the subject's arm when enough blood was collected (Ndiok et al., 2012). A cotton ball was put over the needle site as the needle was removed. The pressure was put on the site and then a bandage put on. While the sputum sample was collected with a wide mouth leak-proof container for adult, gastric lavage was collected by the pediatricians in children.

The sputum samples were collected and processed as described by National TB and Leprosy Control program SOP NTLCP (2015) and WHO (2012), for Laboratory analysis. Two spot sputum samples are collected from each patient at least one hour apart in a sterile leak-proof (50ml) falcon tube. The patients were instructed to rinse their mouth with water and take 3 to 4 deep breath, holding breath for 3-5 seconds after each inhalation and cough after last inhalation, emptying the sputum into the falcon tube, with care not to contaminate the outside of the tube. The falcon tube screw cap was closed tightly and wiped with cotton wool soaked in tuberculocidal disinfectant (Lysol). The volume of the specimen was between 3-5mls. The entire sputum specimens are produced in an open and well ventilated space.

HIV Status Determination by Rapid HIV tests

The blood was screened for HIV following WHO, 2010 standard of serial all logarithm test method viz: Determine, Unigold, Stat pack. Screening test was carried out using determine HIV kit, then after, reactive sera were further tested using Unigold HIV kit and Stat-Pack was used for inconclusive result and serves as tie-breaker. In the determine test kit, 50µl of the blood sample was added to the sample pad and a drop of chase buffer was added after 60 seconds. Result was read after 15 - 60 minutes with

positive result showing red bar in both patient and control window, and negative result indicated by red bar and no red bar in the control and patient window.

In the Uni-gold test, 60µl of the sample was added to the sample pad and 2 drops of wash solution were added to the sample port. Results were reads after 15 - 60 minutes with reactive resulting showing 2 pink/red lines of any intensity in the device window (test window and control window), and the non-reactive result was indicated by pink/red and no line in the control and test window.

In the Stat-Pak test, 5µl of blood was added into the sample pad and 3 drops of running buffer were added into the sample well. Results were reads off after 10 minutes. The reactive result was indicated by the presence of 2 pink/purple lines of any intensity in the device window (test window and control window) and the non-reactive result was indicated by pink/purple and no line in the control window and test window respectively.

Rapid test was conducted to all TB patients suspected with HIV. Most test for HIV antibodies by taking a prick of blood from the finger. These tests are only applicable in three months after exposure.

Molecular Detection of MTB/RIF using Gene Xpert polymerase chain reaction

Sample preparation

Sputum samples were collected from TB patients and TB patients co-infected with HIV; the working area was disinfected using tuberculocidal disinfectant (Lysol) then each Xpert MTB/RIF cartridge was labelled with the laboratory serial number. The lid of sputum collection container was unscrewed and 2 volumes of sample reagent (SR) were added directly into 1 volume of sputum (ratio 2:1) and the lid was closed. Then it was shaken vigorously 20 times (one fourth-and-back movement were counted as one time) and incubated at room temperature for 10 minutes.

After 10 minutes of incubation, it was shaken again vigorously for about 10-20 times and incubated for 5 minutes. After an additional 5 minutes of incubation, samples were be perfectly fluids before being tested, with no visible clumps of sputum. But if it appeared viscous then another 5-10 more minutes was added before inoculating into the cartridge.

Addition of the samples to the cartridges

The sterile pipette was used to transfer 2ml of the liquefied sample into an open port of the Xpert MTB/RIF cartridge

and it was closed immediately, then finally the pipette was immersed into the tuberculocidal disinfectant solution for decontamination

Starting a test

Create test was clicked on a computer. A window requesting to scan the cartridge barcode appeared on the computer screen then barcode scanner was used to scan the cartridge barcode and a window appear requesting to enter patients Name and Laboratory Serial number.

“Start test” was clicked and the assigned module as indicated by the blinking of a green light then the cartridge bay door of the selected module was opened. And the cartridge was loaded carefully. the cartridge bay door was closed and automatically start the test (NTBLCP, 2015).

Statistical analysis

Data generated were collated, entered into SPSS version 16 and evaluated using the chi square method at 95% confidence limit. The results of the analysis are presented in simple percentages and tables for easy comprehension.

Quality assurance

Both SPC and PCC internal controls used during GeneXpert MTB/RIF assay. The specimen was excluded from the analysis if it was an invalid sample for Xpert assay or sample error according to Cepheid package insert. All procedures were done using standard operating methods.

Results and discussion

The result of the socio-demographic background of the study participants as presented in Figure 1 indicated most of the

participants (29.7%) in the age range of 31-40 years. The gender status of the participants under study showed male category to have a higher percentage of 64.3. Majority of them (79.9%) are married. With regards to the level of education of the participants, most of them (52.6%) are secondary school leavers. However, the employment status of the respondents showed most of them as unemployed (68.5%), while few of them are self-employed (15.1%).

The result of the prevalence of HIV infection according to the socio-demographic characteristics of the respondents is presented in Table 1. Eighty-six (86) of the 384 patients are positive to HIV. The prevalence rate was 22.4%. Out of the 86 positives, 52 representing 21.1% of the overall HIV prevalence are male while the remaining (34) are female. However, statistical analysis carried out using the chi-square test of independence showed no significant relationship ($p > 0.05$) between HIV status and gender. Participants within the age range of 31 – 40 years have the highest number of HIV positive.

This followed by 41–50 years group. However, the adolescent group have no HIV positive. The HIV status is significantly associated ($p < 0.05$) with age groups. Sixty-two (62) of 86 HIV positive patients are reported as been married. In relating marital status with HIV, no significant relationship ($p > 0.05$) was observed. Amongst the 86 HIV positive, 46 are secondary school leavers, 24 obtained primary school leaving certificate, 10 were opportune to get tertiary education certificate, whilst the remaining have no formal education. Significant association ($p > 0.05$) was observed between the HIV status and level of education.

Figure 1. Sample preparation demonstration (Cepheid, 2010)

Table 1. Prevalence of HIV infection associated with socio demographic characteristics of the respondents, and statistical parameters

Variables	Respondents Number (%)	Prevalence Number (%)	X ²	Df	P-value
Gender					
Male	247 (64.3)	52(21.1)	0.4518	1	0.5015
Female	137 (34.7)	34 (24.8)			
Total	384 (100)	86(45.9)			
Age group (years)					
10 - 20	63 (16.4)	0 (0)	32.957	5	0.0001*
21 - 30	98 (25.5)	9 (9.2)			
31 - 40	114 (29.7)	37 (32.5)			
41 - 50	50 (13.05)	21 (42.0)			
51 - 60	40 (10.4)	13 (32.5)			
61 - 70	19 (4.9)	6(31.6)			
Total	384(100)	86			
Marital status					
Single	77(20.1)	24(31.2)	2.570	1	0.1089
Married	307(79.9)	62(20.2)			
Total	384(100)	86(51.4)			
Educational level					
No formal education	23(5.10)	6(26.1)	11.638	3	0.0087*
Primary	61(15.9)	24(39.3)			
Secondary	202(52.6)	46(22.8)			
Tertiary	98(25.5)	10(10.2)			
Total	384(100)	86(22.3)			
Occupational status					
Civil servant	16(4.2)	8 (50.0)	79.806	3	0.0001*
Self employed	58(15.1)	27(46.6)			
Private employed	47(12.2)	36(76.6)			
Unemployed	263(68.4)	15(5.7)			
Total	384(100)	86 (22.4)			

The p values with an asterisk (*) are considered significantly associated.

The occupational status of 86 HIV tested participants was also determined. Thirty-six (36) of them are working in private organization, 27 are self-employed, 15 are unemployed, and the remaining 8 are working for the government. Statistical analysis indicated significant association ($p > 0.05$) between the status of the deadly virus and the occupational status of the participants.

The overall prevalence of MTB in the study area was 4.9% with 19 of the 384 samples testing positive for *M. tuberculosis* as shown in table 2. Out of the 19 positive samples that tested positive for tuberculosis, 12 (4.9%) were males while 7 (5.1%) were females. There was no statistical relationship between tuberculosis and gender ($p > 0.05$) (Table 2). Out of the 19 positive samples, 4 samples were from individuals with no formal education, 8 from individuals whose highest level of

education is primary, 6 from individuals with secondary education, and only 1 with tertiary level of education. Statistically, there was a significant relationship between tuberculosis and level of education ($p < 0.05$).

The highest rate of tuberculosis was found within the age range of 31 - 40 years. Statistically, there was no significant relationship between tuberculosis and age ($p > 0.05$). The highest number of the tuberculosis cases was found among unemployed, 7 (2.7%). This was followed by the self-employed with 8.6% and public servant, where 25 % of those tested were positive for TB. Thirty percent (6.3%) of the private employed are tested positive. There is a significant relationship between tuberculosis and occupation ($p < 0.05$).

Table 2. Prevalence of MTB infection associated with Socio demographic characteristics of the respondents, and statistical parameters

Variables	Respondents Number (%)	Prevalence No (%)	X ²	Df	P-value
Gender					
Male	247(64.3)	12(4.9)	0.01070	1	0.9176
Female	137(35.6)	7(5.1)			
Total	384(100)	19 (10)			
Age group (years)					
10 – 20	63(16.4)	0(0)	6.120	5	0.2947
21 – 30	98(25.5)	4(4.1)			
31 – 40	114(37.5)	6(5.3)			
41 – 50	50(13)	5(10.0)			
51 – 60	40(10.4)	3(7.5)			
61 – 70	19(4.9)	1(5.3)			
Total	384(100)	19(32.2)			
Marital status					
Single	77(20)	5 (6.5)	0.4383	1	0.5080
Married	307(80)	14(4.6)			
Total	384(100)	19(11.1)			
Educational level					
No formal education	23(5.9)	4(17.4)	17.976	3	0.0004*
Primary	61(15.8)	8(13.1)			
Secondary	202(52.6)	6(3.0)			
Tertiary	98(25.5)	1(1.0)			
Total	384 (100)	19(31.5)			
Occupational status					
Civil servant	16(4.2)	4 (25.0)	14.748	3	0.0020*
Self employed	58(15.1)	5 (8.6)			
Private employed	47 (12.2)	3 (6.4)			
Unemployed	263 (8.4)	7(2.7)			
Total	384(100)	19(42.7)			

The p values with an asterisk (*) are considered significantly associated.

The overall prevalence of rifampicin resistance was 0.38%, with 2 out of the 19 tuberculosis positive samples showing resistant to rifampicin (Table 3). The two resistance were both in male. There was no significant association between gender and rifampicin resistance ($p>0.05$) as shown in Table 3. Concerning age group, RIF/resistance was detected between the age groups of 21 - 30 and 31 - 40 years respectively, also the occurrence of rifampicin resistance as related with the level of education shows that rifampicin resistance occurs only among participants with primary and secondary education. Moreover, there is no significant association between marital status and occupation; and rifampicin resistance ($p>0.05$).

The overall overall rate shows that the 86 (22.4%) participants tested

positive of HIV composed of population of 52 males and 32 females and Rifampicin resistance is only present among the males population amongst all of which are HIV positive.

MTB is detected only in 19 (4.9%) of the total participants out of which 2 (0.5%) are resistant to rifampicin. With regards to the TB history, 8 of the 19 MTB positives had and receiving treatments while 11 others not. No significant association was observed between the number of participants having previous treatment and those with no previous history. Closed contact with positive TB patients is associated with contracting the diseases.

With relation to HIV infection, 11 of the 19 MTB positive are HIV positive and 8 are HIV negative, therefore HIV is

Table 3. Prevalence of RIF infection associated with socio demographic factors

Variables	Respondents Number (%)	Prevalence Numbers (%)	X ²	Df	P-value
Gender					
Male	24(64.3)	2(0.8)	1.106	1	0.2929
Female	137(35.7)	0(0)			
Total	384(100)	2(0.8)			
Age group (years)					
10 – 20	63(16.4)	0 (0)	1.636	5	0.8968
21 – 30	98 (25.5)	1(1.0)			
31 – 40	114(29.7)	1(0.9)			
41 – 50	50(13.0)	0(0)			
51 – 60	40(10.4)	0(0)			
61 – 70	19(4.9)	0(0)			
Total	384(100)	2(1.9)			
Marital status					
Single	77(20.1)	0(0)	0.501	1	0.4791
Married	307(79.9)	2(2)			
Total	384(100)	2(2)			
Educational level					
No formal education	23(5.9)	0(0)	2.074	3	0.5571
Primary	61(15.8)	1(1.6)			
Secondary	202(52.6)	1(0.5)			
Tertiary	98(25.5)	0(0)			
Total	384(100)	2(2.1)			
Occupational status					
Civil servant	16(4.1)	0(0)	0.9180	3	0.8211
Self employed	58(15.1)	0(0)			
Private employed	47(12.2)	0(0)			
Unemployed	263(68.4)	2(0.8)			
Total	384(100)	2(0.8)			

The p values with asterisk (*) are considered significantly associated

Table 4. Overall prevalence rate of HIV, MTB and RIF resistance the infectious diseases

Parameter	Detected(positive)		Not detected(negative)	
	(n = 384)	Percentage (%)	(n = 384)	Percentage (%)
HIV	86	22.4	298	77.6
MTB	19	4.9	365	95.1
RIF	2	0.5	382	99.5

Chi-square: 121.92; Degrees of Freedom: 2; The P value is < 0.0001. The row and column variables are significantly associated.

considered significantly associated with MTB at (p<0.05).

The study revealed that the prevalence rate of TB among known HIV infected patients was 13.4%. This is similar to 12.5% earlier reported by (Adetunji et al., 2018) among the same study group in Ibadan, Nigeria, but lower than reports of 43%, (Pablo et al., 2003) and 36% in Italy and the 28.3% reported in Argentina (pablosmandes et al.,1998). Patients infected with HIV have a greater exposure to pulmonary TB as a result of their routine scheduled visits to health-care facilities also attended by TB patients or from combining TB-infected patients together with those infected with HIV in these facilities often as the old method

of putting patients with communicable diseases such as HIV and TB in one and the same place. Practices that speed up TB transmission in developing countries include overcrowding, prolonged clinic waiting periods, and facility sharing (like toilets) (Adetunji et al., 2018).

The 13.4% reported in this current study is consistent with the 13% prevalence rate of co-infection reported in Kano (Onipede et al., 1999). Some researchers reported that 14–54% of HIV-infected people had TB in India (Getahun et al., 2007). Other studies reported 10.5% in Sagamu (Daniel et al., 2004), 15.2% in Nnewi (Okechukwu et al.,

Table 5. Multivariate analysis showing association predictors of mycobacterium tuberculosis

Variables	Detected	Not detected	X ²	Df	P-value
Treatment history with TB					
Previously treated	8	99	2.017	1	0.1556
Previously untreated	11	266			
Contact with TB infection					
Contact	3	16	5.511	1	0.0189*
No contact	16	351			
HIV infection					
HIV positive	11	71	15.892	1	0.0001*
HIV negative	8	294			

The row and column variables with asterisk (*) p are considered significantly associated at that p value.

2011), and 19.5% in the Teaching Hospital of University of Abuja (Okechukwu et al., 2011). These values were obtained among the children population in Nigeria. Comparable studies conducted in South Africa and the United Kingdom documented 5.5% and 48% prevalence of HIV/TB co-infection, respectively, among children (Jeenah et al., 2002). Some authors found a 10% prevalence in Kano (Iliyasu et al., 2009) and Ibadan 28.12% prevalence (Odaibo et al., 2006).

Different research works have demonstrated the interplay HIV/TB co-infection has with malnutrition, illiteracy, unemployment and poverty (Sabhapandit et al., 2017). Of 19 TB positive samples, 2 samples representing 10.5% were resistant to rifampicin. This is similar to 11% reported in Abia State (Okorie et al., 2016), but higher than the 4.4% found in Oyo State, in the same country (Small et al., 1991).

The susceptibility of the host to infection acquisition by MTB or strains of multidrug-resistant (MDR)-TB increases in advanced HIV-infected patients with immune suppression (Pablo et al., 1998). The development of drug-resistant TB is often as result of incomplete treatment of active pulmonary TB and/or poor selection of medications.

Another critical factor is the systemic problem such as lack of adequate resources for public health and inconsistent supply of drug. When *M. tuberculosis* is exposed to insufficient lethal dose for just a short time through selectivity or inconsistency of compliance or patients' defaulting, the bacillus escaped being killed. The resulting consequences could be failure of treatment, development of strains of drug-resistant TB, and of course, expensive treatment. Various studies have suggested a relationship between HIV infection and the development of drug-resistant strains of TB among patients under treatments. A 2.2% was reported in Abia State, Nigeria (Okorie et al., 2016). More so, WHO had in 2015 documented 0–4.3% as the MDR-TB range.

Conclusion

In our setting, rifampicin resistance -MTB is prevalent both among adult and HIV positive patients. Being female and having previous treatment with anti-TB drugs was found significantly associated with rifampicin resistance. The strong association of rifampicin resistance with previous treatment suggests the need for improved monitoring of treatment to limit the emergence of drug-resistant MTB strains.

Strict compliance with the infection control measures is strongly advocated for to prevent further transmission of *M. tuberculosis* to people living with HIV (PLHIV) most of whom have their immune system already weakened.

With the prevalence rate reported in this study, there is the need for surveillance of drug resistance in tuberculosis which could lead strengthening of laboratory networks, enhance the prevention and control of TB.

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Conflicts of interest

The authors declare that we have no conflict interests

Ethical Clearance

An approval of the study was obtained from the research ethics committee of Aminu Kano Teaching Hospital, Nigeria.

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