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Prevalence of Human Immunodeficiency Virus Infection among Tuberculosis Patients at Infectious Disease Hospital, Kano State, Nigeria

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Abstract
The epidemic of Human Immunodeficiency Virus (HIV) and the emergence of drug resistant Mycobacterium tuberculosis strains have been recognized as the most important factors contributing to increasing resurgence of tuberculosis (TB). This study was conducted to determine the prevalence of HIV among tuberculosis patients and drug sensitivity pattern of some of the mycobacterial isolates. One hundred and sixty eight (168) sputum samples from tuberculosis patients attending Infectious Diseases Hospital, Kano were collected and processed for the presence of Mycobacteria. Blood samples of the patients were also screened for the presence of HIV. The drug susceptibility test (DST) was performed using the BACTEC Mycobacteria Growth Inhibitory Test (MGIT) M960 technique. Results revealed that out of the 168 patients studied 24 (14.29%) were TB and HIV co-infected and 135 (68.88%) were males while 61 (31.12%) were females (P = 0.001). Majority of the studied cases were of the age groups 15-24 years and 25-34 years (P = 0.001). Ten (58.82%) of the 17 isolates that were subjected to DST against the first-line anti-TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) were found to be resistant against the various drugs to which they were tested; out of which 7 (41.17%) exhibited a primary drug resistance pattern, 3 (17.65%) exhibited acquired drug resistance pattern and 2 (11.74%) were multi-drug resistant TB. The highest drug resistance of 23.53% was recorded against isoniazid, followed by rifampicin, ethambutol and pyrazinamide each with a resistance of 17.65%. The study recommends screening of all TB patients for early diagnosis of HIV co-infection as well as conducting DST which will inform prompt management of the infected individuals and designing appropriate treatment schedule for effective TB/HV control as well as preventing transmission of drug resistant TB.
***Key words**: **Tuberculosis**, **Human Immunodeficiency Virus**, **Infection**, **Prevalence**, **Drug Susceptibility**.*

INTRODUCTION

Earlier projections that tuberculosis might be eliminated by the year 2010 have been replaced by the increasing concern that TB could be on the rise again. The emergence of drug resistant strains and the epidemic of HIV have been recognized as the most important factors that contribute to the increasing resurgence of TB. The world health organization (2019) stated that drug-resistant TB threatens global TB care and prevention, and it remains a major public health concern in many countries. Awofala and Ogundele (2016) stated that HIV infection has spread over the last 30 years and has a great impact on health, welfare, employment and criminal justice sectors; affecting all social and ethnic groups throughout the world. So far, TB/HIV is the most common co-infection which still carries high mortality and morbidity worldwide (Gunda *et al.*, 2018).

In 2019, the WHO documented that globally an estimated 10.0 million people fell ill with TB with an estimated 8.6% of them co-infected with HIV and 251,000 TB/HIV deaths accounting for 17.2% of the total TB death (WHO, 2019). Nigeria has been identified among the 30 high TB burden countries and together with eight other countries accounted for two thirds of the global TB burden, with Nigeria accounting for 4% with an estimated 251,000 incidence of TB cases out of which 53,000 (21.1%) are co-infected with HIV (WHO, 2019). The WHO (2019) also reports that Nigeria record a Multidrug resistant (MDR)/Rifampicin resistant (RR) TB of 4.3% and 15% among new and old TB cases, and recorded 32,000 deaths attributed to TB/HIV co-infection.

Earlier studies by Manjareekaa and Nandab (2013); Wang, *et al.* (2010) revealed that each case of TB-HIV co-infection and/or drug-resistant tuberculosis severely aggravates the global TB situation and that the prevalence of the virus in TB patients is a sensitive indicator of the spread of HIV into the general population in many regions. Manjareekaa and Nandab (2013) further stated that, learning the prevalence of HIV infection in active TB patients is imperative, as such information have been recognize to encourage planning and may

also be necessary for determining the appropriate treatment regime in addition to providing comprehensive HIV/AIDS care and support, including anti-retroviral therapy (ART), to HIV-positive TB patients. Oladeinde, *et al*. (2014) further reiterated that collaboration between TB and HIV/AIDS programs provides the needed support to health care providers in delivering the full range of HIV and TB prevention as well as care interventions.

The WHO (2019) explained that targets for ending the TB epidemic by 2030 are a 90% reduction in the number of TB deaths and 80% reduction in TB incidence rate compared with the levels in 2015. To achieve this, the WHO set new global targets that include; establishment and strengthening the mechanism for delivering integrated TB and HIV services, reducing the burden of TB in people living with HIV and initiating early antiretroviral therapy, reducing the burden of HIV in patients with presumptive and diagnosed TB and sourcing of funds to support TB research (WHO, 2019).

The aim of this study is to determine the prevalence of HIV infection among tuberculosis patients attending Infectious Disease Hospital, Kano and drug susceptibility pattern (DST) of some of the mycobacterial isolates. The study will further reveal the rate of TB/HIV co-infection in the community as well as anti-TB drug resistance pattern of some of the isolates.

MATERIALS AND METHODS

The study was a cross sectional hospital based study that comprised of all tuberculosis patients irrespective of their HIV status who reported to TB outpatients' clinic of Infectious Diseases Hospital (IDH) Kano. Approval for the study was obtained from the Ethical Committee of Infectious Diseases Hospital (IDH), Kano. An informed signed consent was obtained from the participating patients prior to the commencement of the study, which were selected using purposive sampling. A questionnaire was also administered for the demographic information of the patients.

Of the 168 selected patients, 165 had a history of new TB diagnosis with no evidence of previous treatment while 3 had a history of reactivated disease, had earlier received treatment and were discharged from clinic but reported back because they had a relapse.

One hundred and sixty eight (168) early morning spot sputum samples were obtained randomly from the consented patients and processed according to standard mycobacteriological procedures described by National Tuberculosis and Leprosy Control Programme (NTBLC) SOP Manual (2011), National Committee for Clinical Laboratory Standards (NCCLS) (2011) and Kent and Kubica (1985). Accordingly, the sputum samples were decontaminated and concentrated using N-acetyl-L-cysteine (NALC)-NAOH method. Exactly 5mls of sputum was transferred into a labeled 50mls sterile screw-capped conical centrifuge tube, and then an equal volume of 4% NAOH and 2.9% sodium citrate containing 0.5% NALC was added to the tube. The tubes were vortexed for 20 seconds at 2500RPM and repeated three (3) times at regular interval of 5 minutes. Each tube was then inverted 5 times to ensure NALC-NAOH comes in contact with the entire surface of the tube and the tubes were allowed to stand at room temperature (20-25^{o}C) for 15 minutes for decontamination. Phosphate buffer solution (pH 6.8) was then added up to 45mls to reduce the action of NAOH and lower the viscosity of the mixture and the tubes were re-capped and inverted several times to mix the contents, then centrifuged for 15 minutes at 3000rpm. The supernatant were carefully dispensed into discard jar containing Lysol solution, the resulting sediments were then re-suspended with 2mls of phosphate-buffer saline (PBS). A smear of the concentrated specimen was then stained using Ziehl-Neelsen staining procedure and examined for the presence of acid fast bacilli according to Kent and Kubica (1985).

Isolation of Mycobacteria from the processed sputum samples was done using Lowestein-Jensen (LJ) media (Difco. TM Lowenstein Medium Base lot 3023218, ref 24442) which was prepared according to the method described by Kent and Kubica (1985). Exactly, 37.2g of LJ powder was suspended in 600ml of purified water containing 12mls glycerol. It was thoroughly mixed and heated with frequent agitation and allowed to boil for 1 minute and then autoclaved at 121^{o}C for 15 minutes, after which it was allowed to cool to 45-60^{o}C. For LJ media with pyruvate, 2.4mls of the pyruvate was added, after constitution of the LJ media and autoclaved, then allowed to cool. Finally, one litre of fresh, uniform egg suspension prepared under aseptic conditions was then added to both media (i.e. LJ media with glycerol or pyruvate), mixed and then dispensed into 15mls sterile tubes and allowed to coagulate in a slanting position at 85^{o}C for 45 minutes in an insipissator. The processed sputum samples were then inoculated onto the slants of Lowenstein-Jeensen (LJ) medium with glycerol and LJ medium with para-nitrobenzoic acid and incubated at 37^{0}C for up to eight weeks before being considered as negative.

The isolates were further confirmed as *M. tuberculosis* complex (MTBC) using the SD BIOLINE TB Ag MPT64 Rapid test according to manufacturer's specifications (SD Bioline Kit, Standard Diagnostics, Inc., Korea, 2015). The test is a rapid immunochromatographic identification test for the *M. tuberculosis* complex (MTBC) that uses mouse monoclonal anti-MPT64 contained in a cassette. The test was carried out by removing the cassette from the foil pouch and placing it on a flat dry surface thus exposing the sample well. Then four colonies obtained from 4 weeks culture of each sputum sample was suspended in 200µl of the extraction buffer (TB Ag MPT 64 assay diluent) which came with the test kit. Then from this mixture, 100µl of it was added into the sample well of the cassette. The appearance of two colour (purple) bands ("T" test band and "C" control band) within the result window after 15 minutes of sample application was considered a positive result and confirmed as MTBC which were used for further analysis.

The drug susceptibility test was performed using the BACTEC Mycobacteria Growth Inhibitory Test (MGIT)- M960 technique of Scarparo *et al*. (2004); Adjers-Koskela and Katila (2003) and according to SOP of National Institute for Pharmaceutical Research and Development (NIPRD) (2005) manual for conducting drug sensitivity pattern of mycobacterial isolates. Accordingly, the lyophilized anti-TB drugs (BACTEC MGIT, isoniazid-INH, rifampicin-RIF, and ethambutol-ETH and pyrazinamide-PZA) were rehydrated and the final drug concentrations were prepared as follows: 0.1 and 0.4ug/ml for INH; 1.0ug/ml for RIF; and 5.0 and 7.5ug/ml for ETH, while a modified broth at pH 5.9 with a final concentration of 100ug/ml was used for PZA. Then for each concentration of drug, about 100ml of the final antibiotic solution was then added to 0.8ml of the provided enrichment media (BACTEC MGIT 960 INH, RIF, and ETH Supplement and PZA supplement: Becton Dickinson) contained in a labeled M960 tubes. All the drug containing tubes (including the M960 PZA tube) were then inoculated with 0.5ml of 1:100 dilution positive broth MTBC cultures. The INH, RIF, and ETH drug-free controls were inoculated with 0.5ml of 1:100 dilution of the positive culture broth in sterile saline, while the PZA drug-free control was inoculated with 0.5ml of a 1:10 dilution of the positive broth culture. The tubes were then placed in the M960 instrument and continuously monitored until the results indicating susceptibility or resistance were automatically interpreted and reported; which compared growth in the drug containing tube to that in the growth control tube.

About 5mls of blood sample was also collected from the patients in K_2EDTA bottles and screened for the presence of HIV using SD-BIOLINE HIV1/2 3.0 test kit. Positive cases were confirmed using the LAV-BLOT 1 kit (Biorad, France) which confirms HIV status by immunoblotting. Obtainable data were presented using descriptive statistics in form of percentages and analyzed using Chi-square and Student t test where values with $p<0.05$ were considered significant.

RESULTS

The study reveals that 24 of the 168 studied TB patients at IDH, Kano were co-infected with HIV giving a prevalence of 14.29% (Table 1).

Table 1: Prevalence of HIV among TB Patients at Infectious Diseases Hospital, Kano

Number studied	Number positive with TB alone	Number co-infected with TB and HIV
168	144 (85.71%)	24 (14.29%)

The study subjects comprised of 115 (68.45%) males and 53 (31.55%) females (P=0.001). Among the TB+HIV-group 66.67% were males compared to 33.33% females and out of the 24 patients that were co-infected with tuberculosis and HIV, 19 (79%) were males, while 5 (20.8%) were females (Table 2).

Table 2: Sex Distribution of TB/HIV Cases at Infectious Diseases Hospital, Kano

Sex	Number studied	Infection Status	
		TB+HIV-	TB+HIV+
Males	115 (68.45%)	96 (66.67%)	19 (79.17%)
Females	53 (31.55%)	48 (33.33%)	5 (20.83%)
Total	**168**	**144 (85.71%)**	**24 (14.29%)**

($X^2_{0.05,\ 1}$=85.714; P=0.001)

The infection rates vary significantly among the various age groups of the studied patients (P=0.029). Among both the TB+HIV- and TB+HIV+ groups, the highest number of cases was found among age groups15-24 years 25-34 years, while the least number of cases was among patients in the age groups less than 15 years and 55 years and above. Specifically, out of the 144 patients that were TB+HIV- group those aged 15-24 years and 25-34 years recorded the highest number of cases of 53 (36.81%) and 22 (15.28%) respectively (Table 3). Similarly, among the TB+HIV+ group those aged 15-24 years and 25-34 years recorded the highest number of cases of 6 (24%) and 14 (58.33%) respectively (Table 3).

Table 3: Age Distribution of TB/HIV Cases at Infectious Diseases Hospital, Kano

Age	Number studied	Infection Status	
		TB+HIV-	TB+HIV+
<15	1 (0.59%)	1 (0.69%)	0 (0%)
15-24	43 (25.61%)	37 (25.69%)	6 (24%)
25-34	67 (39.89%)	53 (36.81%)	14 (58.33%)
35-44	25 (14.88%)	22 (15.28%)	3 (12.5%)
45-54	20 (11.90%)	19 (13.19%)	1(4.17%)
55 and above	12 (7.14%)	12 (8.33%)	0 (0%)
Total	**168**	**144**	**24**

($t_{0.05,\ 10}$=2.451; P=0.029)

Majority of the patients in both the two studied groups (TB+HIV- and TB+HIV-) were carpenters, traders, tailors, etc. (31.55%), followed by business men (26.79%) and house wives (26.79%) and the civil servant were the least(2.38%)(P=0.0137) (Table 4). Specifically, among the TB+HIV- and TB+HIV+ groups, 38 (26.37%) and 7 (29.17%) were business men (Table 4). Table 4 also show that 33 (22.92%) of the TB+HIV- patients and 2 (8.33%) of the TB+HIV+ were housewives.Also, 12 (8.33%) of TB+HIV+ and 3 (12.50%) of the TB+HIV- groups were students, while 3 (2.08%) of TB+HIV- and 1 (4.17%) of the TB+HIV+ patients were civil servants (Table 4).

TABLE 4: Distribution of TB/HIV Cases among Various Occupational Groups at IDH, Kano.

Occupation	Number studied	Infection Status	
		TB+HIV-	TB+HIV+
Civil servants	4 (2.38%)	3 (2.08%)	1 (4.17%)
Business men	45(26.79)	38 (26.37%)	7 (29.17%)
Students	15 (8.93)	12 (8.33%)	3 (12.50%)
Housewives	35 (20.83%)	33 (22.92%)	2 (8.33%)
Others	53 (31.55%)	45 (31.25%)	8 (33.33%)
*Not identified	16 (9.52%)	13 (9.03%)	3 (12.50%)
Total	**168**	**144**	**24**

Key: Others (Drivers, Carpenters, traders, tailors and other small business); ($t_{0.05,\ 10}$=2.863; P=0.0137) * Not identified = those who did not state their occupation

Out of the 17 isolates that underwent sensitivity test against the first line ant-TB drugs, 14 were obtained from patients with a history of new TB diagnosis but no evidence of previous treatment. Whereas three patients who had reactivated disease, had earlier received treatment and were discharged from clinic but reported back because they had a relapse. Ten 10 (58.82%) out of the 17 isolates were resistant to one or more of the drugs tested against them, out of which 7 (41.18%) were identified as primary drug resistant cases, while 3 (17.65%) were acquired drug resistant cases (Table 6).

The study further shows that 4 (23.53%) of the resistant isolates exhibited mono-resistance to INH, whereas 3 (17.65%) of the isolates exhibited mono resistance to RIF (Table 6). Additionally, 3 (17.65%) of the isolates were resistant to ETM and to PZA. Finally, 2 (11.76%) of the isolates were found to be MDR-TB and these two isolates were obtained from patients who completed their treatment schedule but reported back with a relapse.

Table 6: Drug Susceptibility Test Status of Some of the Mycobacterial Isolates

Drug Susceptibility Test Status	Number	Percentage
Number of isolates tested (N)	17	
Susceptible isolates	7	41.18%
Resistant isolates	10	58.82%
Isolates with primary drug resistance	7	41.18%
Isolates with acquired drug resistance	3	17.65%
Mono-resistance to Isoniazid (INH)	4	23.53%
Mono-resistance to Rifampicin (RIF)	3	17.65%
Mono-resistance to Ethambutol	3	17.65%
Mono-resistance to Pyrazinamide	3	17.65%
Resistance to INH+RIF(MDR-TB)	2	11.76%

DISCUSSION

The study reveals that 14.29% of the studied TB patients were also co-infected with HIV at IDH, Kano and this was found to be higher than the WHO (2019) report which revealed that among all TB cases, 8.6% were people living with HIV. Manjareekaa and Nanda (2013) earlier noted that as the HIV epidemic is fueling the global TB epidemic, the prevalence of the virus in TB patients becomes a sensitive indicator of the spread of HIV into the general population in many regions. However, the prevalence of HIV among TB patients in the current study provides a facility based data on co-infection rates of HIV and TB in the community where the study was conducted; as such for a clearer picture of the extent of TB/HIV association in the general population an epidemiological study involving large number of samples in the population is desired.

Compared with the results of this study Oladeinde *et al*. (2014) and Ranti *et al*. (2016) reported a higher TB/HIV co-infection rate of 32.8% among a rural community, in Edo state and 29.27% among TB patients at the Olabisi Onabanjo University Teaching Hospital (OOUTH) in Ogun State respectively, while Chanda-Kapata *et al*. (2017) reported 23.8% TB/HIV co-infection in Zambia. Lower rates of 7.34% of TB/HIV co-infection were reported among TB infected individuals in Ethiopia (Alene *et al*., 2019) and 11.0% among participants that developed TB while receiving ART in Northwestern Tanzania by (Gunda *et al*., 2018). Similar to the findings of this study, Manjareekaa and Nanda (2013) reported similar TB/HIV co-infection rate of 12.3% in the Central Hospital of South Eastern Railway, India. Oladeinde *et al*. (2014) explained that variation in HIV prevalence among TB infected people couldbe due to differences in location of study population, just like the prevalence of HIV infection which has been reported to have geographical variation in several other African studies.

The observation of the study that more males were significantly more infected than females among both the TB+HIV- (66.67%) and TB-HIV+ (79.17%) groups is slightly above the WHO (2019) report that 57% of all TB cases in 2018 were seen in males. Gunda *et al*. (2018); Neyrolles and Quintana-Murci (2009); Davila *et al*. (2008) explained that hormonal differences due to sex steroid hormones could explain the biological differences in male and female susceptibility to *M. tuberculosis*, in addition to the genetic makeup of the sex chromosomes, the sex-specific metabolic features and social behavior. Similar to the observations of this study, other studies by Manjareekaa and Nanda (2013) and Alene *et al*. (2019) also reported higher infection rates in males compared with females. However, in contrast to the observations of this study, other workers reported higher TB/HIV co-infection rates among females than males and include; Gunda *et al*. (2018) (75.45%), Chanda-Kapata *et al*. (2017) (52.8%), Ranti *et al*. (2016) (36.67%), Oladeinde, *et al*. (2014) (37.3%). According to Nigeria National Agency for the Control of AIDS several reasons that possibly accounted for the gender gap and age distribution of HIV infections comprised of poverty, child marriage, gender-based violence, masculinity and femininity norms, disabilities, harmful traditional rites as well as human rights, legal and political factors (Awofala and Ogundele, 2016).

The findings of the study revealed that the infection rates vary significantly among the various age groups of the studied patients (P=0.029) with the highest number of cases seen among age groups 15-24 years and 25-34 years in both the TB+HIV- and TB+HIV+ groups. This observations are consistent with WHO's observation that majority of TB cases occur among people aged >15 years (WHO, 2019). Other studies by Gunda *et al*. (2018); Chanda-Kapata *et al*. (2017); Ranti *et al*. (2016); Oladeinde, *et al*. (2014) also had similar reports. Besides standing a chance to become co-infected with HIV, Aminu and Habib (2019) explained that the high infection rate seen in patient in this age category may be related to

the fact that these patients are physically active and may be engaged in various sectors of life working experiences as such becoming more exposed to acquire and develop TB.

The study findings indicated that the infection rates varied significantly with regards to the occupations of the studied patients (P=0.0139). Among patients co-infected with TB and HIV, majority (33.33%) of them were documented in the category which comprised of drivers, carpenters, traders, tailors and other small business, closely followed by patients whose occupation was documented as business. This observation is however, not surprising as both TB and HIV have been documented to be influenced by exposure and it is evident from the nature of their work, such category of patient will be in constant contact with different types of people that may likely increase their exposure rate as well as infection rate. In a related study, Oladeinde *et al*. (2014) revealed that although the prevalence of HIV-TB co-infection was not significantly associated with the occupation of the patients, yet it was observed that commercial activity in form of trading and movement were identified to increase risk of exposure and acquisition of HIV infection.

Primary drug resistance was defined as a situation in which the strains of *Mycobacteria* are either naturally resistant to the drug, or have acquired resistance in another person as a result of ineffective chemotherapy. The findings of the study indicated that almost half (41.18%) of the isolates that were tested for dug susceptibility test, exhibited primary drug resistant pattern, with additional 17.65% exhibiting acquired drug resistant pattern out of which two isolates were MDR-TB. This indicated that there is high prevalence of TB drug-resistant isolates circulating which poses greater public health concern. Reports by WHO (2019); da Silva and Palomino (2011) indicated that high prevalence of drug-resistant TB in the community increases the risk of drug-resistant TB exposure in the community and that undiagnosed, untreated, or poorly treated drug-resistant TB contributes to sustained high drug-resistant TB prevalence, as well as high proportions of infectious drug-resistant TB cases among the community.

The study further reports that the rate of mono-resistance to INH, RIF, ETM and PZA was a source of concern. Resistance to these drugs in this study could not be unconnected with patient's non-compliance to anti-TB regiments during the continuation phase of the chemotherapy after successfully completing the initial phase. This is due to the fact that in the hospital where the study was conducted (IDH), the patients were treated in line with WHO TB treatment guideline of 2 months INH, RIF,PZA and ETH, followed by 4 months of INH and RIF. However, upon completion of the two months therapy the patients usually exhibited a lot of improvement and when placed on the continuation phase they tended not to comply especially during the first and last few months of the phase which leads to a break in the course of treatment such patients reported back to the hospital as fresh cases and become a source of infection to others.

Finally, 11.76% of the isolates in the study were found to be MDR-TB with acquired drug resistant pattern. Infection with an *M. tuberculosis* strain that is resistant to the two most commonly used front-line anti-tubercular drugs, INH and RIF, is defined as MDR-TB (Jain and Mondal, 2008). Palmero *et al*. (2003) explained that acquired MDR-TB in patients with previous TB treatment usually reflects shortcomings in current treatment administration such as irregular drug supplies, inadequate treatment regimens, or poor patient's compliance. Additionally, Campos *et al*. (2003) observed unenforced hospital infection control programmes as well as HIV infection as other factors associated with MDR-TB. Finally, one of the MDR-TB cases in this study was found to be HIV positive case who was initially on direct observed therapy (DOT). This implies that the presence of HIV in this patient may have compounded his problem such that even with the DOT the patient still developed resistance.

CONCLUSION

The study revealed that 14.29% of the studied TB patients were co-infected with HIV. Among both the TB+HIV- and TB+HIV+ groups, more males were significantly infected than females (P=0.001) and majority of the infected cases were aged 15-24 years 25-34 years (P=0.029). Majority of the patients were carpenters, traders, tailors (31.55%), followed by business men and house wives while civil servants were the least (P=0.0139). Additionally, 58.82% of the 17 isolates that underwent DST were found to be resistant to one or more of the first line anti-TB drugs, out of which 41.18% were further identified as primary drug resistant cases, 17.65% were acquired drug resistant cases and 11.76% were MDR-TB. The study recommends screening of all TB patients for early diagnosis of HIV co-infection as well as conducting DST which will inform prompt management of the infected individuals and designing appropriate treatment schedule for effective TB/HV control as well as preventing transmission of drug resistant TB which include not only MDR-TB but XDR-TB and XXDR-TB which are more difficult to manage.

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