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Original Article

Exploring the co-infection of tuberculosis and hepatitis B virus in people living with HIV: Implications for diagnosis and treatment

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Abstract

Hepatitis B virus (HBV) and tuberculosis (TB) infections are common causes of liver cirrhosis and hepatocellular carcinoma. First-line anti-TB medications are known to cause drug-induced liver injury (DILI). This study aimed to investigate whether HBV and TB co-infection increase susceptibility to liver failure and poor outcomes during anti-TB treatment in HIV-positive patients. HBV infection was detected using the ELISA method, while TB infection was confirmed through Lowenstein-Jensen (LJ) medium culture. The severity and incidence of liver failure and mortality were compared, and risk factors influencing clinical outcomes were identified. Patients were categorized as new TB cases, relapse TB cases, or defaulters. Among the total cases, 64.5% were classified as new, 18% as relapse, and 17.5% as defaulters TB cases. The prevalence of HBV infection among new, relapse, and defaulter cases was 11.5%, 4.8%, and 1.6%, respectively. In terms of TB classification, the prevalence of HBV infection among patients with pulmonary TB and extrapulmonary TB was 10.6% and 7.1%, respectively, with no cases recorded in the defaulter category. The prevalence of triple infection (HIV-TB-HBV) was found to be 13.3% in new TB cases and 3.3% in relapse TB cases. Patients undergoing anti-TB therapy with chronic HBV co-infection were more susceptible to liver failure and had poorer treatment outcomes. Regular monitoring of liver function is essential, and anti-HBV therapy should be considered for patients with high viral loads before initiating anti-TB treatment.

Keywords: HIV, tuberculosis, hepatitis B virus, drug-induced liver injury, liver failure, clinical outcome

Introduction

The occurrence of both tuberculosis (TB) and concomitant hepatitis B virus (HBV) infection is likely to be associated with poor patient outcomes and poor treatment response. TB and chronic HBV infections are two major global health problems. In 2016, there were an estimated 10.4 million new TB cases worldwide and 1.67 million TB deaths according to the WHO global TB report (WHO, 2017). The incidence of TB-HBV co-infection remains unknown. The treatment for TB patients co-infected with HBV is a challenging health problem worldwide.

Presently, isoniazid, rifampisin, pyrazinamide, and ethambutol are considered the first-line drugs. These drugs are associated with hepatotoxicity exclusive to ethambutol. The occurrence of hepatotoxicity and other adverse effects ranges between 3% and 28% (Hest et al., 2004). TB patients with HBV co-infection are at a higher risk of developing hepatotoxicity (Sharma et al., 2002; Hest et al., 2004). However, limited data are available on the effects of anti-tuberculous treatment in patients with HBV co-infection, particularly in local settings. Hepatotoxicity associated with isoniazid (INH), rifampisin, and pyrazinamide (has been reported more frequently, with an incidence ranging from 3% to 28%, resulting from both idiosyncratic and intrinsic toxic reactions (Sharma et al., 2002; Hest et al., 2004;

Sharifzadeh et al., 2005; Tost et al., 2005). Although HBV is a non-cellular pathogen, active HBV replication can trigger immune-mediated liver injury and, in severe cases, lead to liver failure, particularly in adults (Bertoletti and Kennedy, 2015). Despite the availability of nucleostide analogue anti-HBV drugs, including lamivudine, adefovir, telbivudine, entecavir, and tenofovir, TB patients with chronic HBV co-infection who receive anti-HBV treatment prior to anti-TB therapy remain an overlooked issue in routine clinical practice.

Hepatotoxicity caused by anti-TB medications, combined with immune-mediated liver injury due to HBV replication, exacerbates liver dysfunction (Pan et al., 2005; Patel & Voigt, 2002). In the absence of novel agents to replace first-line anti-TB drugs, identifying and considering risk factors is crucial for preventing drug-induced liver injury (DILI). Notably, regions with a high endemicity of TB often overlap with areas of high HBV prevalence, particularly in Asia and Africa (Patel and Voigt, 2002).

Numerous epidemiological studies have examined whether HBV infection increases the incidence and severity of anti-TB DILI; however, the findings remain inconsistent (Isa et al., 2016; Kim et al., 2016). A recent meta-analysis suggested that HBV infection may elevate the risk of DILI during TB treatment (Wang et al., 2016). However, the study included only articles published in English and lacked multiple subgroup analyses to explore clinical variability. Given the substantial burden of TB and HBV co-infection, especially in Nigeria, this issue requires further investigation and attention. This study aimed to investigate whether HBV and TB co-infection increase susceptibility to liver failure and poor outcomes during anti-TB treatment in HIV-positive patients.

Methods

Study design

The study employed a cross-sectional design to assess the association between HBV and TB co-infection with liver failure and poor outcomes during anti-TB treatment in HIV-positive patients. A structured questionnaire was administered by a clinician, covering various aspects such as the subject's biodata, educational attainment, socio-economic background, clinical symptoms, and knowledge of TB and HBV. The questionnaire also included questions about the type of patient, site of disease, and modes of transmission for both TB and HBV. The data collected through the questionnaire were used to identify risk factors and determine the awareness level of participants regarding the diseases. This study was conducted at a designated health facility where HIV-positive patients with suspected TB and/or HBV co-infection were enrolled for evaluation.

Study area

This study was conducted at Mangu Rehabilitation Centre, located in Mangu, Plateau State, in north-central Nigeria. Mangu serves as the headquarters of Mangu Local Government Area and is situated in the central part of Plateau State. Plateau State is one of the 36 states of the Federal Republic of Nigeria and is home to a diverse range of ethnic groups. According to the 2006 Nigerian census, the total population of Plateau State was recorded at 3,178,712, with current estimates placing the population at approximately 3.5 million. A notable geographical feature of the state is the Jos Plateau, the highest elevated landform in Nigeria, with an altitude ranging from 1,000 to 1,500 meters. Covering an area of approximately 4,000^2 km, the Plateau State is regarded as a distinct geographic unit, rising prominently above the extensive plains of Hausa Land.

Ethical consideration and informed consent

Ethical clearance/approval was be obtained from the human ethical research committee of Mangu rehabilitation centre, Mangu, Plateau State before the commencement of the study. All participants have the right to accept or reject enrolment into the study. All procedures were done in accordance with the Helsinki

Declaration of Human experimental research as revised in 2003. A verbal/written informed consent form containing the research topic, the investigator's name and the purpose of the study was administered to participants for their voluntary participation.

Sample size and patients criteria

The sample size was determined by the method used by Daniel (2004) for calculating sample size using the formula yielding a sample size of 350. The study included both male and female participants who provided informed consent to take part. Eligible participants were between the ages of 15 and 64 years. However, certain individuals were excluded from the study. HIV-positive patients who were not receiving treatment at the selected hospital were not eligible to participate. Additionally, individuals who did not provide informed consent were excluded, as well as those who fell outside the specified age range.

Sample collection

A total of 5 mL of early morning sputum were collected from HIV-confirmed patients into clean, sterile, wide-mouthed plastic bottles. Each sample was properly labelled with the patient's name and the date of collection before being transported to the laboratory for analysis. This procedure was repeated for two consecutive days, following WHO guidelines (2004). Similarly, 5 mL of blood serum were collected in sterile plain tubes for screening of hepatitis B surface antigen (HBsAg) (WHO, 2004). A total of 50 sputum and 50 blood samples were collected over one month, and the study continued for a duration of seven months. A standard HIV-positive control was included for comparison.

Tuberculosis Microscopic examination

Sputum samples were collected from patients after a deep cough. The samples varied in consistency, including purulent, mucopurulent, and salivary types. A purulent portion was selected and spread as a thin smear (2 × 3 cm) on a glass slide using an inoculation applicator. Each subject provided three slides, which were stained using the Ziehl-Neelsen hot staining technique according to WHO standards (WHO, 2004). For staining, slides were flooded with concentrated carbol fuchsin and gently heated over a Bunsen flame until vapours appeared (approximately 60°C). The stain was left for five minutes before decolorization with 3% acid-alcohol, followed by rinsing with water. The smear was then counterstained with 0.3% methylene blue for one minute, washed with water, air-dried, and examined for acid-fast bacilli.

The stained smears were examined using a microscope under the oil immersion objectives, scanning all field at high power field (hpf) for the presence of bright red slender rods, the presence, which was indicative of positive for TB bacilli. The positive stained smears were graded based on WHO guideline (WHO, 2003).

Isolation of *M. tuberculosis*

Samples were cultured on Lowenstein-Jensen (LJ) medium using the Petroff digestion and decontamination technique (Farnia, 2009). An equal volume of 4% NaOH was added to the sputum sample, followed by centrifugation for five minutes. The supernatant was discarded, and the pellet was inoculated onto the LJ medium. Cultures were incubated at 37°C for up to 12 weeks, with weekly monitoring for colony growth. The LJ medium initially appeared greenish in colour (OIE, 2004; Ochei, 2004).

Hepatitis B surface antigen screening

Hepatitis B surface antigen (HBsAg) screening was performed by bringing all reagents and specimens to room temperature. Fifty microliters (50 µL) of each control or specimen were added to designated wells, with 50 µL of HBsAg peroxidase solution added to each well, except the blank. The plate was sealed and incubated at 37°C for one hour. After incubation, the plate was washed and TMB Substrate Solutions A and B were added, followed by a 30-minute incubation at room temperature. The reaction was stopped by adding 100 µL of 2 N H_2SO_4 to each well. Absorbance was measured

at 450 nm within 15 minutes using a photometer. Absorbance values below the cutoff were considered non-reactive, while values above the cutoff were considered reactive. If results were within the retest range, the test was repeated in duplicate (Peters, 1979). The test result was statistically non-significant.

Statistical analysis

The data were subjected to statistical analysis using Chi-squared and a $p<0.05$ was considered statically significant. All statistical analyses were conducted using SPSS version 20.0 (IBM, New York, USA).

Results

Out of the 350 HIV patients included in the study, 208 (59.4%) were females and 142 (40.6%) were males, resulting in a female-to-male ratio of 1.5:1 (Table 1). Among the participants, 250 (71.4%) were urban residents, while 100 (28.6%) were rural residents. In terms of educational status, 115 (32.9%) of the patients were illiterate, while 235 (67.1%) were literate. Regarding marital status, 196 (56.0%) were married, 122 (34.9%) were single, 12 (3.4%) were divorced, 13 (3.7%) were widowed, and 7 (2.0%) were separated due to work, education, or religious conflicts. Occupationally, the majority of the subjects were farmers (140, or 40.0%), followed by students (100, or 28.6%). Only 3 (0.9%) were commercial sex workers, while daily laborers and government employees accounted for 15 (4.3%) and 16 (4.9%), respectively (Table 1).

Table 1. Socio-demographic characteristics of the study subjects and assessment of risk factors associated with tuberculosis and hepatitis B among HIV positive individuals in Mangu Rehabilitation clinic, Plateau State, Nigeria (n=350)

Variable	Category	Frequency	Percentage
Gender	Female	208	59.4
	Male	142	40.6
	Total	350	
Residence	Urban	250	71.4
	Rural	100	28.6
	Total	350	
Education	Unable to write and read	115	32.9
	Literate	235	67.1
	Total	350	
Occupation	Farmer	140	40.0
	Student	100	28.6
	Daily laborers	15	4.3
	Merchants	25	7.1
	Commercial sex workers	3	0.9
	Government employee	16	4.6
	House wife	26	7.4
	Others	25	7.1
	Total	350	
Marital status	Married	196	56.0
	Single	122	34.9
	Divorced	12	3.4
	Widow	13	3.7
	Separated	7	2.0
	Total	350	

The patients were categorized as new, relapse, and defaulters. Of the total cases, 64.5% were classified as new, 18% as relapse, and 17.5% as defaulters, with no statistically significant difference (Table 2). Among the patients, 25 (10.6%) had pulmonary tuberculosis (PTB), and 5 (7.1%) had extrapulmonary tuberculosis

(EPTB), with no defaulters in this category. The prevalence of infection among new, relapse, and defaulter cases was 11.5%, 4.8%, and 1.6%, respectively. For PTB and EPTB, the prevalence was 10.6% and 7.1%, respectively, with no infections recorded in the defaulter category. The prevalence of triple infection (HIV-TB-Hepatitis) was 4 (13.3%) in new TB cases and 1 (3.3%) in relapse TB cases, with no triple infections detected in defaulters (Table 2).

Table 2. Prevalence of tuberculosis (TB) cases category, form of TB laboratory diagnosis status in HIV positive individuals and associated risk factors in Mangu Rehabilitation Centre Mangu, Plateau State, Nigeria

Category	Diagnosis	Positive no (%)	Negative no (%)	Total
HIV sero-status	HIV rapid test	350 (100.0)	0 (0.0)	350
TB category	New	26 (11.5)	200 (88.5)	226
	Relapse	3 (4.8)	60 (95.2)	63
	Defult	1 (1.6)	60 (98.4)	61
Form of TB	Pulmonary TB	25 (10.6)	210 (89.4)	235
	Extra pulmonary TB	5 (7.1)	65 (92.9)	70
	Disseminated TB	0 (0.0)	45 (100.0)	45
AFB result	Positive	30 (13.0)	200 (87.0)	230
	Negative	0 (0.0)	120 (100.0)	120

Table 3 shows the age distribution of the HIV-positive patients. The age group of 15 to 24 years had a total of 137 (39.1%) HIV-positive individuals, with none testing positive for both AFB and HBV. The age group of 25 to 34 years comprised 110 (31.4%) HIV-positive patients, of whom 15 (4.3%) tested positive for AFB, and 5 (16.6%) tested positive for HBV. In the age ranges of 35 to 44, 45 to 54, and 55 to 64 years, no cases of HBV were recorded. The prevalence of AFB in these age categories was 1 (0.3%), 9 (2.6%), 3 (0.9%), and 2 (0.6%), respectively (Table 3).

Table 3. Age distribution of TB and HBV in Mangu Rehabilitation Clinic

Age group (years)	No examined (%)	AFB positive	AFB negative	HBV positive	HBV negative
15–24	137 (39.1)	0 (0.0)	137 (39.1)	0 (0.0)	0 (0.0)
25–34	110 (31.4)	15 (4.3)	95 (27.1)	5 (16.6)	25 (83.3)
35–44	69 (19.7)	1 (0.3)	68 (19.4)	0 (0.0)	0 (0.0)
45–54	15 (4.3)	9 (2.6)	6 (1.71)	0 (0.0)	0 (0.0)
55–64	16 (4.6)	3 (0.9)	13 (3.7)	0 (0.0)	0 (0.0)
>64	3 (0.9)	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Total	350 (100)	30 (8.67)	320 (91.4)	5 (16.6)	25 (83.3)

In the macroscopic, microscopic, and culturing analysis of sputum samples for the isolation of *M. tuberculosis* from 350 HIV patients, 208 (59.4%) were females and 142 (40.6%) were males (Table 4). Among the 208 females, 20 (5.7%) tested positive for TB, while 10 (2.9%) males were TB positive, resulting in an overall prevalence of HIV-TB co-infection of 30 (8.6%). The statistical analysis, using the Chi-squared test, showed no significant difference between females and males ($p>0.05$).

Table 4. Microscopic examination of sputum samples and culturing of sputum samples for isolation of *M. tuberculosis* in relation to gender

Gender	No examined	AFB positive	AFB negative
Female	208 (59.4%)	20 (5.7%)	188 (54%)
Male	142 (40.6%)	10 (2.9%)	132 (38%)
Total	350 (100)	30 (8.6%)	320 (91.4%)

Discussion

The results of this study highlight several key findings regarding the prevalence of TB, hepatitis, and HIV co-infection among different patient categories. A significant proportion of patients (64.5%) were newly diagnosed with TB, while 18% had a relapse and 17.5% were defaulters. Although there was no statistically significant difference between these groups, the data indicates the need for targeted strategies to address TB management, particularly for new cases and relapsed patients. Among the TB-positive patients, 10.6% had PTB, and 7.1% had EPTB, with no infections recorded among the defaulters.

The prevalence of infection was highest in new cases (11.5%) and lowest in defaulters (1.6%), suggesting that timely diagnosis and initiation of treatment play a critical role in preventing further complications. Notably, the study identified a 13.3% prevalence of triple infection (HIV-TB-Hepatitis) in new TB cases, emphasizing the added complexity of managing multiple infections. In contrast, relapse cases showed a lower prevalence of triple infection (3.3%), and no triple infections were detected among defaulters.

These findings underscore the importance of improving patient adherence to treatment regimens, as defaulters had fewer instances of co-infections. Prevention strategies should focus on improving awareness and access to diagnostic services, particularly in newly diagnosed patients. Additionally, monitoring patients with HIV for signs of TB and hepatitis infections, and vice versa, is essential for preventing the development of severe co-infections. Ensuring that patients receive comprehensive care, including counseling on the importance of adherence to treatment, and addressing barriers to treatment adherence, could significantly reduce the incidence of relapse and defaulters, and ultimately improve overall treatment outcomes.

In addition, the findings of this study reveal important insights into the prevalence of HIV-TB and HIV-HBV co-infections, particularly within different age groups and genders. The highest proportion of HIV-positive individuals falls within the 15-24 age range, but interestingly, none of these individuals tested positive for either AFB or HBV. This finding aligns with the general understanding that TB predominantly affects individuals between the ages of 15 and 59, particularly in sub-Saharan Africa, as reported by the CDC (2007). The 25–34 age group showed a notable prevalence of both TB and HBV, indicating that these individuals are more susceptible to co-infection. The lack of HBV cases in older age groups (35 years and above) further suggests that younger individuals, especially those between 25 and 34 years, may be at a higher risk of acquiring both TB and HBV, which could be linked to higher HIV-associated immunosuppression during this age range.

Additionally, the overall HIV-TB co-infection prevalence of 8.6%, with a higher rate observed in females (5.7%) compared to males (2.9%), highlights the gender-related vulnerability, although statistical analysis showed no significant difference between genders ($p>0.05$). This is consistent with previous research indicating that both males and females in sub-Saharan Africa are at risk, though gender-specific factors such as access to healthcare, socioeconomic status, and cultural beliefs may play roles in the observed prevalence. However, the similar prevalence across genders calls for more focus on the broader social and clinical factors contributing to these co-infections rather than gender alone.

Prevention strategies based on these findings should prioritize targeted interventions for the younger population, particularly those in the 25–34 age range. Given the higher rates of HIV-TB and HIV-HBV co-infections, early screening and monitoring for TB and HBV among HIV-positive individuals in this age group could help mitigate the risk of further complications. Enhanced education on the importance of regular testing for TB and HBV, especially for HIV-positive individuals, is essential in high-risk areas.

Further, interventions to reduce TB transmission, such as increased availability of anti-TB treatment, vaccination campaigns (including the HBV vaccine), and improved access to HIV care, should be expanded, particularly in regions with high HIV prevalence. Additionally, targeted health promotion efforts that encourage young adults to seek regular health check-ups could reduce the burden of co-infections and promote early detection, thus improving overall treatment outcomes. Continued public health campaigns aimed at addressing the stigma surrounding TB and HIV could also increase early diagnosis and treatment adherence.

Conclusion

The rates of Mycobacterium tuberculosis and HBV infection in this study area were 8.6% and 16.6%, respectively. When compared to other studies, the prevalence of both tuberculosis and hepatitis infections appears to be on the rise. This increase can be attributed to the fact that sexual intercourse is a primary mode of transmission for both HIV and HBV, which can subsequently lead to the development of tuberculosis as an opportunistic infection. These findings highlight the need for comprehensive prevention strategies targeting both HIV and hepatitis, as well as proactive screening for tuberculosis in individuals with these viral infections.

Authors' contributions

Study Concept and Design: MLD and AD; Acquisition of Data: HDL and NM; Analysis and Interpretation of Data: AD, and MLD; Drafting of the Manuscript: BES, and VFG; Critical Revision of the Manuscript for Important Intellectual Content: NMG, ZA and CNU; Statistical Analysis: ADNU and NM; Study Supervision: ADAY, and MLD.

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Ethical Approval

Ethical clearance/approval was obtained from the human ethical research committee of Mangu rehabilitation centre, Mangu, Plateau State before the commencement of the study. All participants have the right to accept or reject enrolment into the study. All procedures were done in accordance with the Helsinki Declaration of Human experimental research as revised in 2003.

Conflict of interests

The authors declare that there is no conflict of interest.

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