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Impact of HIV and HIV with HBV co-infection on hepatic transaminases and CD4$^+$ T cell counts in Sokoto, North Western Nigeria

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ABSTRACT
Human immunodeficiency virus (HIV) and Hepatitis B (HBV) virus co-infection is not unexpected because both infections have common routes of transmission. The former increases morbidity and mortality of HBV liver related diseases. Alanine aminotransferase (ALT) and Asphatate aminotransferase (AST) are enzymes that reflect integrity of liver cells and whose elevation in the blood indicate liver cell injury. The CD4$^+$ T cells which are often depleted and malfunctioned in HIV infection play a central role in the immunology of HBV infection.
This study aimed at determining impact of HIV and HIV with HBV co-infection on Hepatic transaminases and CD4$^+$ T cell counts. A cross-sectional design was adopted, in which 180 treatment naïve HIV infected adults attending HIV clinics at Usmanu Danfodiyo University Teaching Hospital, Sokoto (UDUTH) and Specialist Hospital Sokoto (SHS), were recruited in the study from March 2014 to October 2015. Alanine aminotransferase and asphatate aminotransferase levels, CD4$^+$ T cell counts, and HBsAg were evaluated.
The prevalence of HBsAg among HIV infected patients was higher among male participants compared to female participants (P=0.016). Mean ALT and AST levels were higher in males compared to females among the study participants (P<0.077; 0.044 respectively). Mean CD4$^+$ T cell counts were significantly higher among female study participants than in male study participants (P= 0.0001). The mean CD4$^+$ T cell counts, ALT and AST levels were higher among patients with HIV and HBV co-infection compared to HIV mono-infected patients (P< 0.022; 0.854; 0.341 respectively). Prevalence of elevated ALT and AST levels were higher among patients with HIV and HBV co-infection than in patients with HIV mono-infection (P< 0.323: 0.074 respectively). Severely immunosuppressed individuals irrespective of Hepatitis B co-infection were more likely to have either higher mean or elevated ALT and AST levels.
Baseline ALT, AST levels and HBsAg screening should be ensured in HIV patients. Treatment options for

patients with severe immunosuppression in either HIV mono-infection or HIV and HBV co-infection should be carefully considered and monitoring of transaminases be ensured.

Keywords; *HIV infection, Hepatitis B virus co-infection, Hepatic transaminases, CD4$^+$ T cell counts.*

INTRODUCTION

Human immunodeficiency virus (HIV) and Hepatitis B virus (HBV) co-infection is common due to their common routes of transmission and the burden is high all over the world. Hepatitis B virus is hepatotrophic, and patients with chronic hepatitis B viral infection have increased risk of developing liver cirrhosis and or hepatocellular carcinoma [1]. Human immunodeficiency virus infection adversely affects the natural history of HBV infection, thereby increasing the morbidity and mortality of HBV related liver diseases [2].

Hepatotoxicity in HIV and HBV co-infected patients may be due to direct effect of anti HIV and or anti Tuberculosis therapy. Sometimes, worsening of liver damage as a part of Immune Reconstitution Inflammatory Syndrome (IRIS) may occur after anti HIV therapy, and this is typical in Acquired Immunodeficiency Deficiency Syndrome (AIDS) caused by HIV infection [3].

Alanine aminotransferase and AST are enzymes that reflect liver cell integrity and are non invasive markers whose elevation in the blood indicate liver cell injury. The actual effect of HIV and HIV with HBV co-infection on hepatic transaminases is best determined prior to commencement of Anti Retroviral Therapy (ART). The CD4$^+$ T cells which are main targets in HIV infection are often depleted and malfunctioned as a result of HIV infection. These CD4$^+$ T cells play a central role in the defense and immunity against HBV infection.

This study therefore aimed to determine the impact of HIV and HIV with HBV co-infection on hepatic transaminases and CD4$^+$ T cell counts.

MATERIALS AND METHODS

One hundred and eighty treatment naïve HIV infected patients attending HIV clinics at Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto and Specialist Hospital Sokoto (SHS) between March 2014 to October 2015 were recruited.

A cross sectional descriptive study method was adopted. Patients who provided written informed consent, and were 18-60 years old were included in the study. Patients who received HBV vaccination were excluded in the study. Convenient sampling technique was adopted.

After normal routine cleaning of the collection site, 5mls of venous blood was taken from each of the study participants and transferred into two specimen tubes. In one specimen tube with no anticoagulant, the blood was allowed to clot and centrifuged at 1500 revolutions per minute for 5 minutes and the serum was used for HBsAg determination, ALT and AST levels estimation.

The second tube containing ethylene diethyl tetra acetic acid (EDTA) was used for the assessment of CD4$^+$ T cell counts. The study was approved by the ethical committees of UDUTH Sokoto and Ministry of Health Sokoto. Questionnaire was used for the collection of some information about the study participants as well as other study variables.

HBsAg was determined using Enzyme Linked Immunosorbent Assay (ELISA) method with HBsAg ELISA kit (Fortess diagnostic UK). ALT and AST levels were determined with Agappe Kit (Agappe Diagnostics Switzerland Gmbh), and normal ranges were up to 49 IU/L and 46 IU/L respectively. The CD4$^+$ T cell counts was performed with Cyflocounter (Partec company, Germany).

Data was analysed using Statistical Package for Social Sciences (Version 20, SPSS). Chi-square test and Student's t-test were applied for comparing categorical and numerical variables respectively, and level of statistical significance was set at $P < 0.05$.

RESULTS

Distribution of HBsAg, mean CD4$^+$ T cell counts, ALT and AST levels by sex in HIV study participants.

One hundred and eighty HIV study participants (109 females and 71 males) aged 32 ± 9 years (Mean ± SD) were recruited in this study. About 21(29.6) and 16(14.7) were positive for HBsAg among males and females HIV patients respectively, and the difference was statistically significant (P=0.016). The mean $CD4^+$ T cell counts were significantly higher among female study participants than in male study participants (P= 0.0001). Mean ALT and AST levels were higher in male study participants than in female study participants, however statistically significant difference was observed in AST levels but not in ALT levels (P<0.077; 0.044 respectively). These results are illustrated in Table 1.

Table 1: Distribution of HBsAg, Mean $CD4^+$ T cell counts, AST and ALT levels by sex among HIV study participants

Parameter	Male n=71	Female n=109	P-value
HBsAg n(%)	21(29.6)	16(14.7)	0.016
$CD4^+$ T cell counts (Mean ± SD)	204 ± 175	339 ± 266	0.0001
ALT levels (IU/L) (Mean ± SD)	41.04±-38.63	38.41 ± 29.68	0.077
AST levels (IU/L) (Mean ± SD)	49.26 ± 37.16	42.94 ± 32.15	0.044

Mean $CD4^+$ T cell counts, ALT, and AST levels among HIV with HBV co-infection group and HIV mono-infected group.

The mean $CD4^+$ T cell counts of HIV mono-infected patients were significantly higher compared to HIV and HBV co-infected patients (P< 0.021). Both ALT and AST levels were higher in HIV and HBV co-infected patients compared to HIV mono-infected patients, though were not statistically significant (P= 0.823; 0.321 respectively) as shown in Table 2.

Table 2: Comparison of mean $CD4^+$T cell counts, ALT and AST levels between HIV with HBV co-infection and HIV mono-infected groups.

Parameter	Group	Mean ± SD	P-Value
$CD4^+$ T cell counts (cells/mm^3)	HIV with HBV co-infection	204 ± 199	
	HIV mono-infection	307 ± 249	0.021
ALT levels (IU/L)	HIV with HBV co-infection	36.16 ± 27.27	
	HIV mono-infection	34.96 ± 35.28	0.847
AST levels (IU/L)	HIV with HBV co-infection	47.43 ± 37.54	
	HIV mono-infection	40.51 ± 37.09	0.314

Elevated ALT and AST levels in HIV with HBV co-infection study participants and HIV mono-infected study participants.

The prevalence of patients with elevated ALT and AST levels were higher among patients with HIV and HBV co-infection than in patients with HIV mono-infection, however the differences were not statistically significant (P< 0.323; 0.074 respectively). These results are represented in Table 3.

Table 3: Comparison of elevated ALT and AST levels among HIV mono-infected and HIV with HBV co-infection

Parameter	HIV mono-infected group (n=143)	HIV and HBV co-infected group (n=37)	P-Value
Elevated ALT levels (IU/L)	28(19.6)	10(27)	0.323
Elevated AST levels (IU/L)	40(28.0)	16(43.2)	0.074

Mean and elevated ALT and AST levels between HIV patients (irrespective of HBV co- infection), with and without severe immunosuppression.

The mean ALT and AST levels were significantly higher among severely immunosuppressed patients ($CD4^+$ T cell counts < 200 cells/mm³) than in patients without severe immunosuppression ($CD4^+$ T cell counts ≥ 200 cells/mm³) (P=0.036; 0.001 respectively). The prevalence of elevated ALT and AST levels were significantly higher in severely immunosuppressed patients compared to non-severely immunosuppressed, ALT levels: 24(28.6) Vs 14(14.6) respectively, AST levels: 36(42.9) Vs 20(20.8) respectively (P < 0.022; 0.001 respectively). Table 4 represents these results.

Table 4: Comparison of mean and elevated ALT and AST levels among HIV study participants (irrespective of HBV co-infection), with and without severe immunosuppression

Parameter	Severely immunosuppressed (n = 84) n(%)	None Severely immunosuppressed (n = 96) n(%)	P Value
Elevated ALT (IU/L)	24(28.6)	14(14.6)	0.022
Elevated AST (IU/L)	36(42.9)	20(20.8)	0.001
ALT levels (IU/L) (Mean ± SD)	40.92 ± 38.02	30.21 ± 28.74	0.036
AST levels (IU/L) (Mean ± SD)	52.45 ± 32.73	32.21 ± 27.95	0.001

DISCUSSION

The prevalence of HBV and HIV co-infection was significantly higher among male 21(29.6%) study participants compared to female 7(14.7%) study participants. Similar finding was recorded by some studies [4],[5], however contrary results were also documented by some researchers [6],[7]. Reasons suggested for male preponderance include injury and high risk behavior, which were more common in males [5]. This study suggests that mean $CD4^+$T cell counts of females that were significantly higher than in males in the current study, may explain why female participants had less preponderance of HIV and HBV co-infection, as $CD4^+$ T cells play a central role in the defense and immunity against HBV infection. Mean ALT and AST levels were higher in males than in female participants. Male preponderance for HIV and HBV co-infection may probably explain why ALT and AST levels were higher in male participants compared to female participants.

The study recorded lower mean $CD4^+$ T cell counts and higher mean ALT and AST levels among patients with HIV and HBV co-infection compared to HIV mono-infected patients, though the statistical difference was observed in mean $CD4^+$ T cell counts, but not in mean ALT and AST levels. Idoko *et al*, (2009) in their studies observed similar finding with regard to $CD4^+$ T cell counts, however observed significant difference in relation to ALT levels [8]. Olawumi *et al*, (2014) in their studies documented similar results with regard to $CD4^+$ T cell counts and AST levels [9]. Human immunodeficiency virus infection is primarily known to cause $CD4^+$ T cell depletion. However Hepatitis B e antigen (HBeAg) is also implicated in HBeAg and HBcAg specific Th1 $CD4^+$ T cell apoptosis [10]. Hepatitis B e antigen is a marker of HBV replication, may be present in both acute and chronic HBV infection and its presence is common in HIV with HBV co-infection. The $CD4^+$ T cells apoptosis may be temporal because HBeAg is gradually cleared from the blood. However, the clearance is decreased in the setting of HIV and HBV co-infection [2]. These points may be the reason why HIV and HBV co-infected patients may have had lower $CD4^+$ T cell counts compared to HIV mono-infected patients.

The study also recorded higher prevalence of elevated ALT and AST levels among HIV with HBV co-infection than in HIV mono-infected patients, though the differences were not statistically significant. Transaminases (ALT and AST) are expected to be higher among HIV and HBV co-infected patients than in HIV mono-infected patients due to the hepatotrophic nature of HBV, which leads to immunologically induced hepatic cell damage as a result liver infiltration of cytotoxic cells. Further studies may give insight into other reasons.

Mean ALT and AST levels were significantly higher in patients with severe immunosuppression ($CD4^+$T cell counts < 200 cells/mm³ {Immunologically defined AIDS}) than in patients without severe immunosuppression ($CD4^+$T cell counts $\geq$ 200 cells/mm³), irrespective of HBV co-infection and this is consistent with finding of Olawumi *et al*, (2014) in their study [9]. Elevated ALT and AST levels were also more common in patients with immunologically defined AIDS compared to patients with $CD4^+$T lymphocyte counts $\geq$ 200 cells/mm³, and this represents about 21% and 31% of total patients with elevated ALT and AST levels respectively. Idoko *et al*, (2009), observed 18% of the cohort with elevated ALT levels in their study [8] and this is comparable to the value obtained in the current study. Higher mean and elevated ALT and AST levels among immunologically defined AIDS patients is not unexpected as some opportunistic infections in AIDS patients may secondarily infect liver cells and result to high hepatic transaminases levels due to liver cell injury.

In conclusion, Male study participants were more likely to have HIV and HBV co-infection and higher mean ALT and AST levels compared to females. High percentage of the study participants presented with elevated ALT and AST levels and these were higher among Immunologically defined AIDS patients compared to those with $CD4^+$ T cell counts $\geq$ 200 cells/mm. Human

immunodeficiency virus and HBV co-infected patients were more likely to have lower mean $CD4^+$ T cell counts, however there was no association between higher mean or elevated ALT and or AST levels with HIV and HBV co-infection.

Conflict of Interest: None declared

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