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Full Length Research Paper

Liver Damage and HIV Viral Load Correlation in Untreated Patients in North-eastern Nigeria

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Alanine aminotransferase (ALT) is a hepatic enzyme that could be used as markers of hepatocellular injury. Liver enzyme elevations are frequent in human immune deficiency virus (HIV)-infected patients which may be caused by the HIV virus in those without other risk factors for liver damage. This study was designed to evaluate the correlation between HIV viral load and serum levels of ALT, a marker of hepatic damage. This was a cross-sectional analytic study performed among HIV infected naive patients without other risk factor for liver disease. The results of the study shows that of the 166 participants recruited into this study, 104 (62.7%) were females. The participants' mean CD4 count was 180.04 ± 38.08 (95% confidence interval (CI), 164.11 to 195.96). The mean viral load log_{10} (copies/ml) was 5.18 ± 4.28, and ALT (UI/L) was 24.80 ± 1.29 (95% CI, 22.26 to 27.35). Sixty (36.2%) of the studied participants had high viral load ≥ 100,000 copies/ml, while 22 (13.3%) had high ALT (≥ 40 IU/L). A positive correlation (Pearson correlation coefficient, r = 0.274, P = 0.000) between HIV viral load and ALT was observed. After adjusting for age, sex and CD4 count in a multivariable linear regression model, the correlation between HIV viral load and ALT remained significant (p = 0.003). The finding of positive correlation between HIV viral load and ALT levels in HIV infected naive patients suggests a linear relation between ALT level and HIV-1 viral load in HIV patients without other risk factor for liver damage. We recommend evaluating patients with high ALT for early anti-retroviral therapy (ART) in those without risk factor for liver damage regardless of the CD4+ cell count, especially where facility for estimating viral load is not available.

Key words: Alanine aminotransferase, human immune deficiency (HIV), viral load, CD4 count.

INTRODUCTION

Liver dysfunction is a major challenge in the management of human immune deficiency (HIV)-infected patients. Among HIV patients, it could be due to opportunistic infections (for example, with cytomegalovirus (CMV) or leishmaniasis), acquired immune deficiency syndrome (AIDS)-related cholangitis associated with parasitic infections (Schistosoma mansoni**,** cryptosporidiosis and microsporidiosis), viral infections (for example, with herpes simplex), mycobacterial infections, tumors (lymphoma and Kaposi sarcoma) and drug-related hepatitis (caused by trimetoprim- sulfamethoxazole and other antibiotics, anti tuberculosis medication or anti retroviral therapy (ART). (Price and Thio, 2010; Crum-Cianflone et al., 2010; Ocama et al., 2010; Pol et al., 2004).

The use of ART has completely modified the pattern of hepatic events in HIV infection, and have resulted in a significant decrease in morbidity and mortality among

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HIV-infected patients (Cooper, 2007; Gwet and Koulla Shiro 2010). The liver remains an important organ to consider when treating HIV-infected patients as liver enzyme elevations are frequent in HIV-infected patients, even among those treated with ART (Vogel and Rockstroh, 2007; Mocroft et al., 2005). Liver enzyme elevations are a frequent finding in HIV-infected patients as a consequence of several risk factors, however the analysis of these events is limited as precise aetiology is rarely clearly defined. Abnormalities in liver function tests could be produced exclusively by direct inflammation in hepatocytes, caused by the HIV virus. Although the mechanisms by which HIV causes hepatic damage are still unknown, studies have shown that it may be as result of apoptosis (induced by caspases 2, 7 and 8) and mitochondrial dysfunction with decreasing mitochondrial DNA in several tissues. Another injury mechanism is permeability alteration in mitochondrial membrane by HIV proteins which stimulate an inflammatory response (Pol et al., 2004; Miro et al., 2004; Casula et al., 2005; Jacotot et al., 2000). Alanine aminotransferase (ALT) is a hepatic enzyme that may be used as a marker of hepatocellular injury (Pasquazzi and Aceti, 2004). The purpose of the study was to determine the association between HIV viral load with serum levels of ALT as markers of hepatic damage in HIV naive infected patients.

MATERIALS AND METHODS

This cross-sectional analytic study was performed among HIV infected naive patients that presented for care between July, 2011 to August, 2012 at the Infectious Diseases Clinic of the University of Maiduguri Teaching Hospital, a designated centre of excellence for infectious diseases and immunology. Patients aged 18 years and above were consecutively recruited into this study. Exclusion criteria included hepatitis B surface antigen (HBVsAg) sero-positivity or detectable hepatitis C virus (HCV) antibody, alcohol consumption in the last three months due to its hepatotoxicity and presence of active opportunistic infections. Patients on drugs with hepatotoxic potential were also excluded. Socio demographic characteristics and medical history were documented. Each participant underwent physical examination to exclude those with active opportunistic infection or AIDS defining infections.

Analytical methods

Alanine aminotransaminase (ALT) level was estimated by automated clinical chemistry autoanalyzer (Hitachi 902 Roche Diagnostic GmbH, Mannhein Germany). Normal reference values for ALT in normal Nigerian subjects is 3 to 15 U/L. The CD4+ T lymphocyte cell count was estimated by Cyflow counter (Partec GmbH, Gorlitz Germany). Samples for CD4+ T cell count was collected between 9:00 to 10:00 am and assayed within 6 h of collection of whole blood using standardized flow cytometric Cyflow machine (Cytec, Partec, Germany 2005). Haemoglobin (Hb) and white blood count (WBC) were analysed using a Haematology analyzer (Sysmex®, Corporation Kobe, Japan). Enzyme linked immunosorbent assay kits was employed to detect the presence of HBsAg and HCV antibodies (DIA, PRO, Diagostic Bioprobes Sri, via columella no 20128 Milano-Italy). Plasma HIV RNA levels was measured using freshly frozen plasma specimen separated within 6 h of phlebotomy utilizing the Amplicor HIV-1 Monitor Test, version 1.5 by Roche® Germany, with a minimum cut off value of 200 copies per ml.

Statistical analysis

Results were expressed as mean ± standard deviation (±SD). The strength of relationship between HIV viral load and ALT was estimated by a Pearson correlation coefficient. To adjust for the effects of potential confounders, a linear regression model was used. A p-value of < 0.05 was considered statistically significant.

RESULTS

Clinical and laboratory parameter

One hundred and sixty-six (166) participants that fulfilled the inclusion criteria were consecutively recruited for the study. They consisted of 104 (62.7%) females. The mean age of the studied participants was 39.39 ± 9.21 (95% CI, 38.04 to 40.71). Males with mean age of 43.02 ± 7.50 were significantly older than females with a mean age of 37.28 ± 9.51 ($p < 0.05$). The mean body mass index (BMI) was 20.71 ± 4.50 (95% CI, 19.81 to 21.62). A total of 22 (13.3%) patients had high ALT (≥ 40 IU/L) with overall mean ± SEM of 24.80 ± 1.29 (22.26 to 27.35). The mean ± SEM (95% CI) of the participants CD4 count was 180.04 ± 38.08 (164.11 to 195.96). The viral load $\log_{10}$ (copies/ml) was 5.18 ± 4.28, with 60 (36.2%) of the studied participants having a high viral load of ≥ 100,000 copies/ml. The clinical and laboratory parameters are as depicted in Table 1.

Correlation between serum HIV-1 viral load and alanine aminotransferase (ALT) level

The distribution of participants with high ALT (≥ 40 UI/L) across stratified levels of viral load is as shown in Table 2. Mean ALT level linearly increased with increase in mean HIV-1 viral load. However, linear increase in the frequency of abnormal ALT in cohort with increase viral load ≥ was not observed. As shown in Figure 1, there was also a significantly mild strong, positive correlation between HIV viral load and ALT (Pearson correlation coefficient, $r = 0.274$, $P = 0.000$). Even after adjusting for age, sex and CD4 count in a multivariable linear regression model, the correlation between HIV viral load and ALT remains significant ($p = 0.003$).

DISCUSSION

Our report showed a positive correlation between alanine aminotransaminase and HIV-1 RNA among ART naive HIV positive cohort without viral hepatitis co-infection or opportunistic infections. Our finding is consistent with reports from Mexico (Mata-Marín et al., 2009) and North

Table 1. Baseline characteristics of the study participants.

Clinical characteristic	Mean±SD
Age (years)	39.39±9.21 (95% CI, 38.04-40.71)
Females	37.28±9.51 (95% CI, 35.55-39.00)
Males	43.02±7.50 (95% CI, 41.14-44.89)
Sex	
Females, no (%)	104 (62.7%)
BMI (kg/m^2), mean±SD	20.71±4.50 (95% CI, 19.81-21.62)
Laboratory parameter	
Hb (g/dl), mean±SD	10.58 ± 2.18 (95% CI, 10.28-10.87)
WBC (10^9/l), mean±SD	5.11 ± 2.17 (95% CI, 4.82-5.40)
Platelets count, mean±SD	291.94 ± 103.69 (95% CI, 277.66-306.22)
ALT, mean±SEM	24.80 ± 1.29 (95% CI, 22.26-27.35)
ALT>40 U/L, no (%)	22 (13.3%)
CD4 count (cells/µl), mean±SEM	180.04± 38.08 (95% CI, 164.11-195.96)
Viral load log10 (copies/ml), mean±SEM	5.18±4.28
Viral load>100000, no (%)	60 (36.2%)

SEM standard mean error.

Table 2. Correlation between serum HIV-1 viral load and alanine aminotranferase (ALT) level.

Serum HIV-1 viral load (copies/ml)	Serum ALT level, mean±SD (min - max)	Abnormal high ALT level (40IU/L)
<5,000	23.33±15.10 (3-73)	3/33 (9.0)
5000-9,999	17.54±7.85 (8-35)	0/14 (0.0)
10,000-49,999	23.18±15.34 (4-67)	5/38 (13.2)
50,000-99,999	25.52±15.80 (8-59)	4/21 (19.0)
≥100,000	28.05±19.41 (8-114)	10/60 (16.7)

America (DallaPiazza et al., 2010). Alanine aminotransaminase is a marker of liver damage, unlike AST it is not affected by other tissue injuries (muscle, lung, and kidney). Several studies have shown that hepatic cells, Kupffer cells and differentiated tissue macrophages that reside in the liver can be infected by HIV *in vivo* (Cao et al., 1992; Housset et al., 1990; Hufert et al., 1993). *In vitro* studies also suggest that HIV infection of primary Kupffer cells leads to progression of HIV infection and liver injury (Gendrault et al., 1991; Schmitt et al., 1990).

HIV-1 RNA has also been detected in sinusoidal cells and hepatocytes *in vivo* (Cao et al., 1992; Housset et al., 1990). Primary human sinusoidal cells have also been shown to be permissive to HIV infection *in vitro* (Steffan et al., 1992). A number of studies have demonstrated HIV infection of hepatocyte cell lines (Cao et al., 1990). Infection of hepatocyte cell lines is thought to be CD4-independent, as most hepatocyte cell lines, primary hepatocytes inclusive, do not express CD4 (Cao et al., 1990). HIV infection of hepatocytes cells may therefore occur via receptor-mediated endocytosis or alternative co-receptors (Berger et al., 1999). Hepatocytes may act as a transient HIV reservoir and promote CD4+ T cell infection by cell-cell contact (Fromentin et al., 2010). Hepatotoxicity due to ART may be related to agents from a number of classes, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (Núñez, 2010). The severity of hepatotoxicity may range from transient elevations in transaminase levels to hepatic failure and death, via a variety of mechanisms. NNRTI such as nevirapine and efavirenz may cause hypersensitivity (Chu et al., 2010; Coffie et al., 2010; Mbougua et al., 2010). NRTI, primarily didanosine (ddI), may cause direct mitochondrial toxicity leading to abnormal liver function (Murphy et al., 2007). Other mechanisms by which ART causes liver-related toxicity include direct cell stress and disturbances in lipid/sugar metabolism and steatosis, as seen with protease inhibitors (Núñez, 2010). The protease inhibitors ritonavir, tipranavir and darunavir have all been associated with elevations in ALT (Núñez, 2010).

The early recognition and diagnosis of hepatic events will facilitate the safe and effective use of ART and

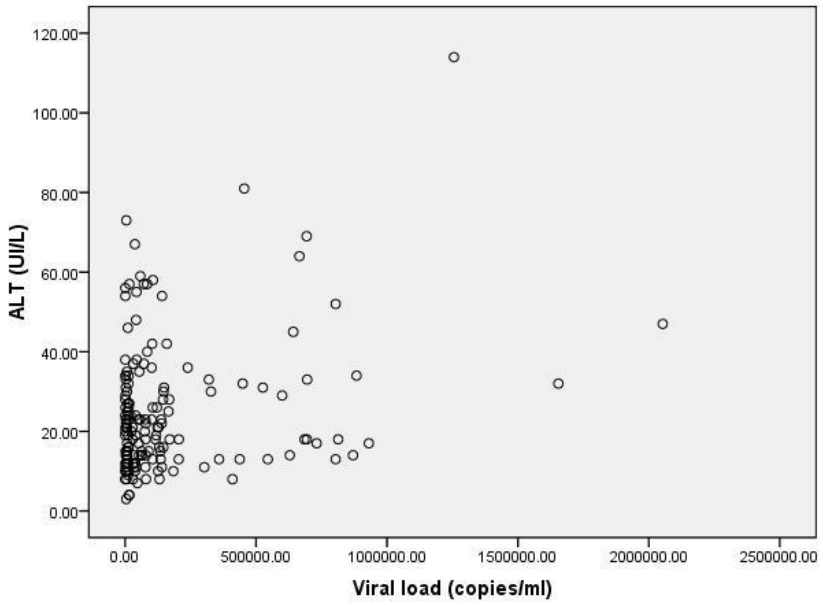

Figure 1. Scatter plot of HIV viral load and ALT. There is a mildly strong correlation between HIV viral load and ALT (r = 0.274, p = 0.000).

enhance the survival of HIV-infected patients. Nevertheless, the intricacies of the various pathogenic mechanisms may result in difficulties in the diagnosis, as well as in the management of such patients with liver abnormalities. We suggest monitoring aminotransferases levels, given the observed positive correlation between the HIV viral load and serum levels of alanine aminotransferase enzyme in HIV infected naive patients. Based on our results, patients with elevated ALT level also have high HIV-1 viral load. Liver function tests should be monitored closely in these patients; and we suggest evaluating patients with high ALT for early start of antiretroviral treatment in those without risk factor for liver damage regardless of the CD4+ cell count, especially where facility for estimating viral load is not available.

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