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Measurement of CD_4+ Cells and Liver Functions in HIV Patients on Antiretroviral Therapy.

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ABSTRACT

Background: Highly active antiretroviral therapy (HAART) is widely used in the treatment of Human Immunodeficiency Virus (HIV) infection but toxicity is widely reported amongst patients. Hepatotoxicity is commonly reported among HIV patients on treatment with HAART, but there is lack of consensus between authors on whether liver disease seen in these patients is as a result of HAART or HIV infection itself. This study examined the possible effect of HAART on activity of liver enzymes, bilirubin level and Cluster Differentiation of Antigen (CD4+) in HIV patients on drug treatment. **Methods:** Forty (40) HIV patients on HAART (Group 1), forty (40) treatment naïve HIV patients (Group 2) were recruited from the Institute of Human Virology of Nigeria (IHVN) Clinic, Ladoke Akintola University Teaching Hospital, Osogbo while forty (40) HIV negative subjects (group 3) served as control. Activities of Alanine aminotransferases (ALT), aspartate aminotransferases (AST) and bilirubin level were determined spectrophotometrically while CD4+ count was by flow cytometry. **Results:** Results from this study showed that mean activities of the enzymes ALT and AST were significantly different among the groups studied ($p < 0.0001$). Mean total bilirubin concentration highest in group 1, followed by group 2 and then group 3. When means of conjugated bilirubin fraction were compared in all the groups, significant difference in means was observed ($p<0.0001$). The mean CD4+ count was highest in group3, followed by group 1 and least in the HIV treatment naïve group ($p<0.0001$). **Conclusion:** The increases in ALT, AST, CB and TB seen in HIV patients on HAART treatments may be due to HIV infection and HAART treatments, which could be attributed to liver damage observed in these patients.

Keywords: Human Immunodeficiency Virus (HIV), HAART, Liver Enzymes, Bilirubin, CD_4+ count.

INTRODUCTION

The use of Highly Active Antiretroviral Therapy (HAART) has resulted in profound and durable HIV suppression, so that progression to AIDS and the occurrence of opportunistic infections has declined in regions where HAART is readily available. However, despite these successes, drug toxicity is widely reported amongst patients on HAART treatment.[1] Many antiretroviral medications have been associated with liver enzyme elevations to varying degrees.[2] In addition, comorbidities, such as chronic hepatitis B (HBV), hepatitis C (HCV) and tuberculosis (TB) infections may predispose patients to antiretroviral drug-related liver injury (ARLI).[3,4] ARLI is a common cause of morbidity, mortality and treatment discontinuation in HIV-infected patients.[5]

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Hepatotoxicity is one of the most serious complications of highly active antiretroviral therapy (HAART) and previous studies showed that liver related mortality accounts for 30%–55% of all deaths in patients with HIV infection.[6,7,8] In some HAART series, nearly half of deaths among hospitalized HIV-infected patients on ART have been attributed to liver disease.[7, 9]

Hepatotoxicity has been reported in the use of the six classes of drugs approved by the United States Food and Drugs administration (USFDA) namely:nucleoside reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); Protease inhibitors (PIs); integrase inhibitors; fusion inhibitors and CCR5 receptor antagonists.[10,11] Some mechanisms by which ART can lead to liver damage include: direct drug toxicity and/or drug metabolism, hypersensitivity reactions, mitochondrial toxicity, inhibition of human mitochondrial DNA γ-polymerase and more mitochondrial damageand IRIS.[12,13,14]

Increases in activities of serum and plasma alanine amino transaminases (ALT) and aspartate amino transaminases (AST) directly reflect a major

permeability abnormality or cell rupture. AST exhibits high activity in cytoplasm, mitochondrion and microsomes of liver, heart, kidney and brain while ALT is hepato-specific and cytosolic.[15] Elevated ALT levels are associated with acute liver and cholestatic disease while elevated levels of conjugated bilirubin occur in intrahepatic cholestasis.[16] Elevated activities of these enzymes indicate cell damage which result from several mechanisms such as generation of toxic species, peroxidation of membranes. On the other hand, defects in metabolism of bilirubin generally reflect defective metabolic capacity of the liver.[17] In HIV infected patients, abnormalities in liver function tests could be produced exclusively by direct inflammation in the hepatocytes caused by the virus leading to apoptosis.[18]

Hepatotoxicity associated with Protease Inhibitors treatment occurring generally in weeks to months after drug initiation.[13] Atazanavir and indinavir have been observed to cause indirect hyperbilirubinemia but are not associated with liver injury and may not require treatment discontinuation.[19] The nucleoside reverse transcriptase inhibitors (NRTIs) are associated with mitochondrial toxicity while prolonged DDI use has been associated with cryptogenic liver disease and has been linked to non-cirrhotic portal hypertension and oesophageal varices.[20,21] Lamivudine, emtricitabine, and tenofovir can lead to HBV reactivation and severe acute hepatitis if withdrawn in an HBV-infected patient or if resistance develops. The fusion inhibitor enfuvirtide has been rarely associated with hypersensitivity reactions, and the newer drug maraviroc, a CCR5 inhibitor, carries a black box warning for hepatotoxicity as a result of hypersensitivity. Given the high incidence of ART-related hepatotoxicity, all patients should have baseline ALT and AST activities assessed and followed by regular monitoring every 3 months. This present study therefore, measured the CD4+ Cell Count, AST and ALT activities and bilirubin concentration in HIV patients on antiretroviral therapy.

MATERIALS AND METHODS

This study examined the possible effect of HAART on activity of liver enzymes, bilirubin level and Cluster Differentiation of Antigen (CD4+) in HIV patients on treatments. Forty (40) HIV patients on HAART (Group 1), forty (40) HIV patients not yet on treatment (Group 2) were recruited from Institute of Human Virology of Nigeria (IHVN) Clinic, Ladoke Akintola University Teaching Hospital, Osogbo while forty (40) HIV negative subjects served as control. The age range of participants was between 18-55 years and HIV positive status of participants was confirmed with ELISA technique. HIV positive patients had been undergoing treatment in Ladoke Akintola University of Technology Teaching Hospital, Osogbo for a period of at least six months. Subjects with the following manifestations were excluded based on their clinical history and features: Diabetes Mellitus (DM), jaundice, hepatitis, hypothyroidism, hypertensions and nephrotic syndrome.

Sample Collection and Storage

Ten millilitres (10ml) of venous blood was collected from the cubital vein of each subject and dispensed into a test tube containing ethylenediamine tetraacetic acid (EDTA). The plasma was obtained after centrifugation at 400 rpm for 10 minutes and stored at -20°C in plain bottles until the time of analysis.

Methods

ALT and AST activities were measured by the colorimetric method of Reitman and Frankel, (1957) while total and conjugated bilirubin concentrations were analyzed using Powell's method. Bilirubin was estimated by the method of Malloy and Evelyn.[22,23]

CD4+ count was determined using Flow cytometry based on the principle that the fluorescence monoclonal antibody (CD4 mAb PE) binds to the CD4+ antigen on the monoclonal cell i.e. T-lymphocytes and monocytes and in a buffer suspension, the complex is passed through the flow cuvette in a single stream of flow. The complex is excited by the solid state green laser light 532 nm causing the complex to emit light which is captured by a photomultiplier tube and transmitted into digital and read out as count.[24]

Statistical Analysis

Results were reported as mean (±SE). Means of parameters were analysed using the Analysis Of Variance (ANOVA) test and pairwise t-test was used to compare significant variables. Pearson's correlation coefficient (r) was used to determine the relationship between mean of the variables. Results were regarded as significant at $p<0.05$.

RESULTS

Results from this study showed that mean age of the different groups studied did not differ significantly. However, activities of the enzymes ALT and AST were significantly different between the groups studied ($p<0.0001$). Pairwise t test showed that all the groups contributed to the observed significant changes seen in the activity of both enzymes.

Mean total bilirubin concentration in descending order was group 1, 2 and 3. When means of the conjugated bilirubin fraction were compared in all the groups, a significant difference in means was observed ($p<0.0001$).

On the other hand, the mean CD4+ count was highest in group 3, followed by group 1 and least in the HIV treatment naïve group ($p<0.0001$) [Table1].

Pearson's correlation analysis of means of biochemical parameters in HIV subjects on HAART treatment (group 1) showed a significant inverse relationship (r=-253, p<0.05) between CD4+ count and total bilirubin. Similarly, negative relationship between ALT and CD4+, and AST and CD4+ (r=-722, p<0.04 and r=-620, p<0.001 respectively) was seen in this present study [Table 2]

Intra group differences in both the means of age and biochemical parameters were not observed when subjects were classified based on gender into males and females in all the three groups studied [Figures 1, 2 and 3].

Table 1: Means (±SEM), p-value of parameters in groups 1, 2 and 3 using the Analysis of Variance (ANOVA) test.

Parameters	Group 1	Group 2	Group 3	F-value	p-value
Age (years)	33.7 ± 1.2	37.2 ±1.3	34.1± 1.3	2.28	0.11
ALT (Ul/L)	33.8 ± 0.4	27.5± 0 .4	8.4±0 .3	1280. 1	<0.000 1
AST (Ul/L)	29.6 ± 0.4	21.8± 0.3	7.7 ±0.5	739.3	<0.000 1
TB (µmol/L)	46.5 ±1.4	13.3 ± 0.4	5.4 ±0.2	660.6	<0.000 1
CB (µmol/L)	26.2± 0.6	7.9 ± 0.3	3.9 ±0.1	921.9	<0.000 1
CD4+	467.3± 19.4	188.5 ± 21.7	886.6 ± 12.6	368.2	<0.000 1

Group1= HIV on HAART treatment, Group 2= HIV treatment naïve and Group 3 = HIV negative, ALT= alanine aminotransferases, AST= aspartate amino transferases, TB= total bilirubin, CB= conjugated bilirubin and CD4+= cluster definition antigen 4

Table 2: Pearson's correlation coefficient of parameters in HIV subjects on HAART treatment group 1.

	ALT(U/l)	AST(U/l)	CB (µmol /l)	TB (µmol /l)	CD4 +	Age
ALT(U/l)	**1**	**.947****	**.747****	**.750****	**-.722****	**.045**
AST(U /l)		1	.783**	.784**	-.620**	.007
CB (µmol/l)			1	.978**	-.245**	-.079
TB (µmol/l)				1	-.253**	-.049
CD4+					1	-.159
Age						1

TB= total bilirubin, CB= conjugated bilirubin, ALT= alanine aminotransferases, AST= aspartate amino transferases and CD4+= cluster definition antigen 4

Significant inter group changes (p<0.0001) were seen when means of albumin, uric acid, catalase and TAS in males were compared between groups 1, 2 and 3. Post Hoc analysis showed that all the groups contributed to the observed significant differences in the means of the biochemical parameters measured [Table 3].

In female subjects, significant inter group changes (p<0.0001) were seen when means of albumin, uric acid, catalase activity, TAS and age (p<0.001) in females were compared between groups 1, 2 and 3. Post hoc test showed that the significant differences was due to changes in all the groups studied while the age difference observed in the age of females was contributed by means of groups 2 versus 3 (p<0.001) [Table 4].

Table 3: Means (SE) of biochemical parameters (ANOVA) in male subjects in the different groups studied.

Parameters	Group 1 (n=20)	Group 2 (n=16)	Group 3 (n=17)	F	p
Age (Years)	34.4±2.1	36.9±2.1	40.4±1.4	2.5	0.09
AST U/l	29.2±0.7	21.6±0.7	8.37±1.0	174. 5	<0.00 01
TB µmol/L	48.2±2.0	13.5±0.7	5.7± 0.4	281. 5	<0.00 01
CB µmol/L	26.6±0.9	7.9±0.7	4.1±0.3	301. 9	<0.00 01
CD4+	464.2±2 5.8	190.8±3 6.5	880.2±1 6.9	153. 7	<0.00 01

Group 1=HIV subjects on HAART treatment, Group 2= HIV treatment naïve and Group 3 = HIV negative, ALT= alanine aminotransferases, AST= aspartate amino transferases, TB= total bilirubin, CB= conjugated bilirubin and CD4+= cluster definition antigen 4

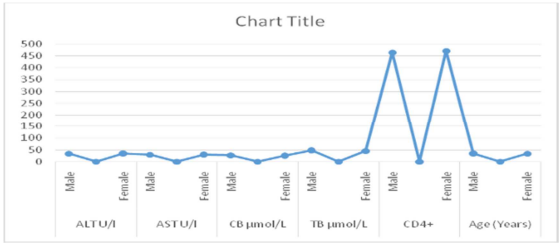


Figure 1: Means of biochemical parameters inHIV subjects on HAART treatment based on gender

ALT= alanine aminotransferases, AST= aspartate amino transferases, TB= total bilirubin, CB= conjugated bilirubin and CD4+= cluster definition antigen 4

Table 4: Means (SE) of biochemical parameters (ANOVA) in Female subject in the different groups studied

Parameters	Group 1 (n=20)	Group 2 (n=24)	Group 3 (n=23)	F	P
Age (Years)	33.1 ±1.4	37.4 ±1.9	28.7 ±1.2	8.2	<0.001
ALT U/l	34.1 ±0.7	28.1 ±0.6	8.3 ±0.4	553. 5	<0.000 1
AST U/l	8.3 ±0.4	30.1 ±0.57	22.0 ±0.5	433. 9	<0.000 1
TB µmol/L	44.8 ±2.0	13.2 ±0.7	5.2 ±0.2	326. 0	<0.000 1
CB µmol/L	25.9 ±0.9	8.0 ±0.5	3.8 ±0.2	397. 8	<0.000 1
CD4+	470.6 ±29.8	178.7 ±27.6	891.3 ±18.3	207. 3	<0.000 1

Group= HIV subjects on HAART treatment, Group 2= HIV treatment naïve and group3 = HIV negative, ALT= alanine aminotransferases, AST= aspartate amino transferases, TB= total bilirubin, CB= conjugated bilirubin and CD4+= cluster definition antigen 4

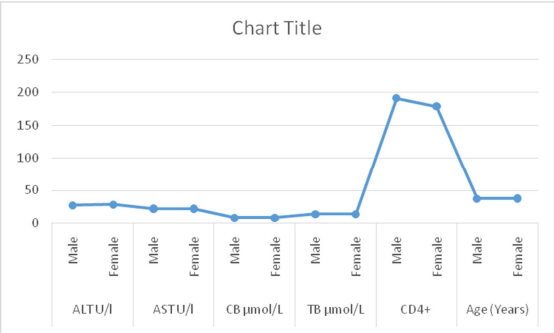


Figure 2: Means of biochemical parameters in HIV treatment naïve subjects based on gender

ALT= alanine aminotransferases, AST= aspartate amino transferases, TB= total bilirubin, CB= conjugated bilirubin and CD4+= cluster definition antigen 4

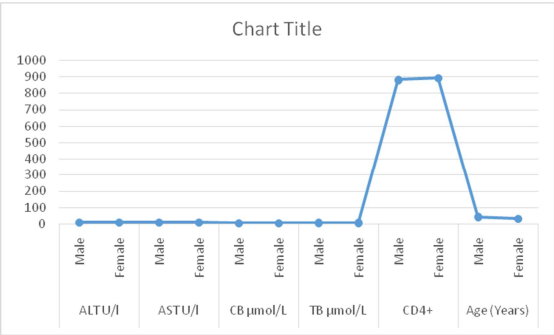


Figure 3: Means of biochemical parameters in HIV - negative subjects based on gender

ALT= alanine aminotransferases, AST= aspartate amino transferases, TB= total bilirubin, CB= conjugated bilirubin and CD4+= cluster definition antigen 4

DISCUSSION

In this study, the means of ALT and AST activities in HIV subjects on HAART treatments were significantly higher than mean enzyme activities in HIV treatments naïve and control subjects. This finding is similar with the report of who reported increases in the activities of ALT and AST and common abnormalities of liver enzymes in HIV patients on HAART treatment.[25] Other researchers also reported elevated liver enzymes activities with specific HAART regimens.[26] Serum aminotransferase levels, ALT and AST are two of the most useful measures of liver cell injury, although the AST is less liver specific than is ALT level. Elevations of the AST level may also be seen in acute injury to cardiac or skeletal muscle. Lesser degrees of ALT level elevation may occasionally be seen in skeletal muscle injury or even after vigorous exercise. Thus in clinical practice, it is not uncommon to see elevations of AST, ALT or both in common non-hepatic conditions such as myocardial infarction and rhabdomyolysis. Diseases that primarily affect hepatocytes, such as viral hepatitis, will cause disproportionate elevations of the AST and ALT levels compared with the alkaline phosphatase level. The ratio of AST/ALT is of little benefit in sorting out the cause of liver injury except in acute alcoholic hepatitis, in which the ratio is usually greater than 2.[27]

Hyperbilirubinemia was observed in HIV patients on treatments when compared with treatments naïve and HIV negative controls. This increase in bilirubin may be due to competitive inhibition of uridylglucuronyl transferases enzymes. Previous reports showed a strong association between the homologous variant allele A (TA) 7TAA and this can increase the risk of developing hyperbilirubinemia.[28] Anoother study showed that unconjugated hyperbilirubinemia has a recognised adverse effect on protease inhibitors therapy containing indinavir (IDV) or atazanavir (ATV).[29] In this study, increases in total and conjugated bilirubin in the HIV patients on treatments may be an indication of liver disease and jaundice. Increase in the level of bilirubin shows the severity of liver damage, excess breakdown of red cells and obstruction of bile flow as caused by hepatic damage.[30] In this present study, the mean CD4+ count was significantly higher in HIV patients on treatments when compared with treatments naive patients. This increase in CD4+ count in HIV patients on HAART treatment has been previously reported.[31] Several other workers showed that long term increases in CD4+ cell counts was seen in HIV infected patients receiving a protease inhibitors-containing antiretroviral regimen and demonstrated CD4+ cell recovery in individuals with advanced HIV- infection receiving potent antiretroviral therapy for 4 years.[32,33]

CONCLUSION

The increases in ALT and AST activities and concentration of total and conjugated bilirubin seen in HIV patients on HAART treatments may be due to combination factors of both HIV infection and HAART treatments, which could be attributed to possible liver damage in these patients and corroborates findings from some previous studies. In addition, HAART had a positive effect on CD4+ count in HIV patients on HAART treatments. Clinicians and other care givers need to assess risks for hepatotoxicity and monitor changes in liver enzyme activities regularly during the course of HAART treatment to ensure optimal patient care.

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