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Variation of Serum Transaminases in HIV/AIDS Patients on Different Antiretroviral Regimens, Attending the Saint Elizabeth Hospital, Shisong, Northwest Region, Cameroon

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Abstract

Antiretroviral drugs help reduce the viral load in HIV patients and prevent further progression of the virus. Hepatotoxicity has been reported among HIV patients receiving Highly Active Antiretroviral Therapy (HAART). There is therefore the need to monitor liver enzyme activity in HIV seropositive patients on different antiretroviral (ARV) regimens. This study thus aimed at determining the variation of serum transaminases; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) amongst HIV/AIDS patients on different ARV regimens at the Saint Elizabeth Hospital, Shisong with respect to different ARV regimens, age groups, gender, and duration on ARV therapy. The results will guide health personnel in administering anti-retroviral therapy to HIV/AIDS patients and bring to focus the need for a liver function test before placing a patient on antiretroviral therapy. In this cross-sectional exploratory hospital and laboratory-based study involving 57 participants, venous blood was collected and the absorbance and concentration of serum transaminases for each subject read using a spectrophotometer. Data obtained were analyzed using SPSS and the Chi-Square test used to determine association and significance at P-value ≤ 0.05. Results showed there was significant elevation of transaminases among study participants. Elevation of transaminases was more pronounced for AST (47.4%) than ALT (19.3%). Regarding the different ARV regimens, participants on a combination of Nucleoside Reverse Transcriptase Inhibitor and Non-Nucleoside Reverse Transcriptase Inhibitor (NRTI+NNRTI) had higher transaminase elevations than those who were on single or triple combinations. With respect to sex, elevation of AST levels was significantly higher (RR=1.0962) in females (48.7%) than males (44.4%). For ALT, males tend to have more elevated levels than females but the difference was not significant (RR=0.8077). There was no significant difference in transaminase levels with age groups (P>0.05).

Keywords: Serum transaminases; HIV/AIDS patients

List of abbreviations:

AIDS: Acquired Immunodeficiency Syndrome; ALT: Alanine Aminotransferase; ARV: Antiretroviral; AST: Aspartate Aminotransferase; AZT: Azidothymidine, GGT: Gamma-Glutamyl Transferase; FI: Fusion Inhibitor; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immune Deficiency Virus; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; PI : Protease Inhibitor

Introduction

The management of HIV/AIDS, which is an important public health problem and remains a major cause of morbidity and mortality, typically includes the use of antiretroviral (ARV) drugs [1]. The introduction of Highly Active Antiretroviral Therapy (HAART) in 1996 and the recommendation of the American Institute of Health and other organizations offering antiretroviral treatment to all patients with AIDS restored hope in HIV/AIDS patients [2]. Despite the unquestioned success of ARV therapy, limitations still persist. Long term treated patients who are on effective regimens often show persistent immune dysfunction and have higher than expected risk for various non-AIDS related complications including heart, bone, liver, kidney, and neurocognitive diseases [2].

Antiretroviral drug-related liver injury (ARLI) is a common cause of morbidity, mortality and treatment discontinuation in HIV-infected patients [3] and its prevention and management have emerged as major issues among these patients in the era of HAART [4]. ARLI is defined by elevations in liver enzymes in serum, with alanine aminotransferase (ALT) characteristically greater than aspartate aminotransferase (AST). There is great variability in the criteria used in clinical studies to categorize the severity of hepatotoxicity [5,6]. In effect, the AIDS Clinical Trials Group (ACTG) has defined a grading scheme against the patient's baseline serum aminotransferase concentrations. For example, in patients with a normal pretherapy ALT or AST, hepatic injury is graded as moderate or severe based on a 5-fold or 10-fold increase in aminotransferases, respectively [7]. In patients with abnormal liver enzymes prior to therapy, a >3.5-fold or a 5-fold increase in ALT or AST is considered indicative of moderate or severe hepatotoxicity, respectively [8].

ALT and AST are normally contained within the liver, but if the organ is damaged, they are released into the bloodstream. Normal levels of serum AST and ALT may slightly vary depending on the individual laboratory reference values. Typically, the range for normal AST is reported between 10 to 40 units per liter and ALT between 7 to

56 units per liter. Mild elevations are generally considered to be 2-3 times higher than the normal range. Severe elevations, possibly up to 10 to 20 times the normal values, suggest more significant damage to the liver [9,10].

Several studies have reported increased incidence of liver injury in HAART-treated patients and identified life-threatening hepatotoxic events and end-stage liver disease in patients on antiretrovirals [11]. With the widespread use of HAART and the availability of new antiretroviral medications, ARLI has gained much attention owing to its negative impact on clinical outcomes. Drug-associated hepatotoxicity also increases the economic burden on already strained medical budgets, since additional visits and hospital admissions are often required for appropriate patient care and management [3]. Furthermore, antiretroviral drug discontinuation hampers maintenance of HIV suppression. The severity of ARLI may range from the absence of symptoms to liver decompensation, and the outcome can range from spontaneous resolution to liver failure and death [12].

Transaminases play vital roles in various metabolic pathways especially in the production of amino acids. The association of different ARVs with elevated transaminases is not a good prognosis in the management of HIV/AIDS given that direct damage by these drugs or the elevated transaminases can worsen the health condition of patients. Monitoring the variation of these enzymes in HIV seropositive patients on different ARV regimens is important to check the side effects of recently started medications as well as to diagnose and track many diseases. This will enable health personnel to take special care when administering ARV therapy to HIV/AIDS patients and to discontinue medications promptly and use alternatives. This study was aimed at determining the levels of serum transaminases in HIV/AIDS patients attending the St. Elizabeth Catholic General Hospital Shisong, and to find out if age, sex, class of ARV and duration of ARV therapy are risk factors of ARLI in this study population.

Materials and Methods

Study design and population

This study was a cross-sectional exploratory hospital and laboratory-based study that lasted for four months (January to April, 2015). The study was carried out at the Saint Elizabeth General Hospital Shisong (SEGHS), situated in Kumbo, in the North West Region of Cameroon. The hospital has an Integrated Day Care Centre (IDCC) that caters for the diagnosis, follow up and management of HIV and tuberculosis cases, and hence was a suitable site for the study. The population for this study comprised all HIV/AIDS patients, irrespective of age, sex, race, occupation and religion, who came for ARV refill and initiation at the IDCC of the SEGHS within the study period. HIV Patients suffering from viral hepatitis A, B or C were excluded from the study. All 57 patients who gave consent were selected for the study.

Ethical considerations

Ethical clearance to carry out the study was obtained from the Institutional Review Board of St. Monica University Buea, after the proposal was reviewed and approved. Administrative clearances were sought and obtained from the Matron of the SEGHS and the Director of the integrated Day Care Centre. All participants gave their consent to the study by signing an informed consent form. All test results and sociodemographic information were treated with absolute confidentiality.

Laboratory procedure

About 4 ml of blood was collected by venipuncture into coded dry test tubes. Blood samples were allowed to coagulate after which they were centrifuged at 3000 rpm for 5 minutes to obtain sera.

The level of AST and ALT in each patient's serum was determined by spectrophotometry. The reagent kits used were the AST LAB CARE and ALT LAB CARE kits manufactured by LAB CARE (Lab Care Diagnostics, Munbai-India). The test was carried out using the mono-reagent procedure according to manufacturer's instructions [13]. A Standard Curve was generated by dilution of 0.1 M Glutamate standard using assay buffer to different concentrations with a final volume of 50 µl/well. Quality control sera were included to verify the reliability of the results. Results were analysed using the Statistical Package for Social Scientist (SPSS) version 20.0. The Pearson's Chi Square was used to establish association and results were considered significant at P-value ≤ 0.05.

Results

Patients data

A total of 57 participants enrolled in the study comprising 18 (31.6%) males, and 39 (68.4%) females. Table 1 details the age and therapy background of the study participants. The ages ranged from 15 -70 years and were grouped into six age brackets. Most patients were within the age group 31- 40 years while the age group 61-70 years had the least number of participants (6; 10.5%). Regarding duration on ARV therapy, 21 (36.8%) patients had been on ARV therapy for 3 years or less while only 2 (1.8%) had received ARV therapy for more than 10 years. Our study participants were either on just one drug or a combination of two or three drugs. They were either on Nucleoside Reverse Transcriptase Inhibitor (NRTI) or Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) only or on a combination of these. A few were on these two plus (Fusion inhibitor) or Protease Inhibitor (PI).

Transaminase levels greater than or equal to five times the upper limit of normal levels for both AST and ALT were considered elevated. Normal levels were therefore taken to be less than or equal to four times the upper limit of normal.

Parameter	Responses	Proportion
Age (Years)	11-20	10 (17.5%)
	21-30	10 (17.5%)
	31-40	18 (31.58%)
	41-50	17 (29.8%)
	51-60	9 (15.8%)
	61-70	6 (10.5%)
Duration on ARV (Years)	≤ 3	21 (36.8%)
	4-7	22 (38.6%)

	8-10	13 (22.8%)
	>10	2 (1.8%)
ARV Regiments	NRTI	13 (22.8%)
	NNRTI	8 (14.0%)
	NRTI+NNRTI	31 (54.4%)
	NRTI+NNRTI+FI	2 (3.5%)
	NRTI+NNRTI+PI	3 (5.3%)

Table 1: Age and therapy history of participants (n=57).

Variation of transaminases in patients according to gender

Of the 39 female participants, 19 showed elevated AST and 7 showed elevated ALT. While 8 of the 18 males showed elevated AST and 4 showed elevated ALT. More females (48.7%) had elevations in their AST levels than males (44.4%). In contrast, more males (22.2%) had elevated ALT levels than females (18.0%). On the overall however, the number of females with elevated transaminases were approximately equal to the number of males with abnormal transaminase values. For AST, the Risk Ratio was 1.0962 which is greater than one, showing that there is enough evidence to support the claim that elevation of AST values was dependent upon gender. The Risk Ratio for ALT which is 0.8077, less than one, is indicative of the fact that at 95% confidence interval, there was no direct relationship between elevation of ALT values and gender as seen on Table 2.

Gender/ Transaminase Level	AST			ALT		
	Normal	Elevated	% Elevated	Normal	Elevated	% Elevated
Female	20	19	48.7	32	7	18
Male	10	8	44.4	14	4	22.2
Total	30	27	90	46	11	23.9
χ^2=1.187; P=0.172				χ^2=2.387; P=0.072		
OR=1.1875; RR=1.0962				OR=0.7656; RR=0.8077		

Table 2: Variation of transaminase in patients according to gender.

Variation of transaminases in patients with respect to age groups

Amongst the study participants, the age group 21-30 had the highest percentage of patients presenting with elevations in both enzymes with 80.0% for AST and 40.0% for ALT. The age group 51-60 was the second highest with elevations for AST (55.6%) while the age group 41-50 (35.3%) was the second highest with elevations for ALT. The elevations began to drop from age 51 for ALT and 61 for AST. There was no statistically significant difference (P>0.05) in the variation with respect to age groups (Table 3).

Age Group/ Transaminase Level	AST			ALT		
	Normal	Elevated	% Elevated	Normal	Elevated	% Elevated
11-20 Years	3	2	40	4	1	20
21-30 Years	1	4	80	3	2	40
31-40 Years	10	8	44.4	16	2	11.1
41-50 Years	10	7	41.2	11	6	35.3
51-60 Years	4	5	55.6	9	0	0
61-70 Years	2	1	33.3	3	0	0
Total	30	27		46	11	
χ^2=6.382; P=0.0832				χ^2=10.382; P=0.063		

Table 3: Variation of transaminase in patients according to age group.

Variation of transaminases in patients according to class of ARV drug

Regarding the class of ARV, participants who were on a combination NRTI+NNRTI were the only group showing more than 50% elevation of AST (54.8%). On the other hand, no treatment group showed up to 50% elevation in ALT (Table 4). However, there was no significant elevation of transaminases with respect to type of antiretroviral drug taken (P>0.05).

Class of ARV/ Transaminase Level	AST			ALT		
	Normal	Elevated	% Elevated	Normal	Elevated	% Elevated
NNRTI	5	3	37.5	6	2	25
NRTI	8	5	38.5	10	3	23.1
NRTI+NNRTI	14	17	54.8	25	6	19.4
NRTI+NNRTI+FI	1	1	50	2	0	0
NRTI+NNRTI+PI	2	1	33.3	3	0	0
TOTAL	30	27		46	11	
χ^2=1.6627187, P=0.063				χ^2=1.4819, P=0.0931172		

Table 4: Variation of transaminases in patients according to class of ARV drug.

Variation of transaminases in patients according to duration on ARV therapy

The results presented on Table 5 shows participants who had been on ARV therapy for between 8-10 years presented the highest elevation of AST (76.9%), followed by those who had been on therapy for 4-7 years (40.9). With ALT, participants on HAART for 4-7 years presented with the highest elevated values (22.7%), followed by those on therapy for 1-3 years (19.1%). Statistics tested showed that the development of elevated transaminase values were not dependent on duration on ARV therapy (P>0.05).

Duration on ARV in years/ Transaminase Level	AST			ALT		
	Normal	Elevated	% Elevated	Normal	Elevated	% Elevated
1-3	14	7	33.3	17	4	19.1
4-7	13	9	40.9	17	5	22.7
8-10	3	10	76.9	11	2	15.4
>10	0	1	100	1	0	0
Total	30	27		46	11	
χ^2=7.693; P=0.142				χ^2=0.5339; P=0.0632		

Table 5: Variation of transaminases in patients according to duration on ARV therapy.

Discussion

Antiretroviral-induced liver injuries are common, and fatal cases have been reported in medical literature [14,15]. Liver enzyme elevation after ARV initiation is a common reason for HAART modification in clinical practice. The pathogenesis underlying this ARV-induced liver injury is, however, poorly understood.

Our results showing more females with HIV/AIDS are in line with clinical data reporting more HIV infections in females than males in Cameroon [6] and globally [16]. This study reveals that more females (48.7%) had elevations in their AST levels than males with a percentage of 44.4. In contrast, more males (22.2%) had elevated ALT levels than females (18.0). Other researchers have reported similar trends in the variation of AST and ALT with gender [17,18]. Serum ALT levels generally remain constant in women throughout life. In men however, ALT levels increase to about the age of 50 and then begin to decline [19]. Numerous reports also show that people with the highest prevalence of HIV/AIDS fall in the age group 31-40 [20].

Several studies have addressed the effect of different ARVs on the levels of transaminases in serum [21-23]. According to Ikekpeazu et al. [23], the incidence of the elevation of transaminases (ALT, AST and GGT) in patients under ARV regimens ranged from 3 to 10% within the first six months with significant increases in enzyme levels noted at three and six months in Non-nucleoside reverse transcriptase inhibitors (NNRTIs) group and at three months in the nucleoside reverse transcriptase inhibitors (NRTIs) group and Protease inhibitors (PI) group. We recorded much higher elevations in ALT and AST with respect to the different ARV classes among participants (Table 4) and this could be due to much higher durations (Table 5). As a result of the adverse effects caused by transaminase elevations including hepatotoxicity, fatigue, headache and still birth, Nabili [10] recommends medications be discontinued promptly if serum AST or ALT is greater than 10 times the upper limit of the normal, even if the patient is asymptomatic. A variation of transaminases according to duration on ARVs is a drug induced hepatotoxicity. This has become an important public health problem contributing to about 50% of acute liver failure cases [24].

Conclusion

There was significant elevation in serum transaminases in HIV patients receiving antiretroviral drugs at the Saint Elizabeth General Hospital Shisong. The elevation was more pronounced for AST than for ALT. Transaminase elevation was found to vary with sex but not with type of drug combination and age group.

Recommendation

A longitudinal study involving assay of bilirubin, albumin and alkaline phosphatase in addition to transaminases should be carried out to justify the results of this crossectional study in the same population.

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Author's Contributions

The overall implementation of this study including the research design, funding, data collection and analysis, report writing, and manuscript preparation were the results of joint efforts of individuals who are listed as co-authors of the paper.

Declaration of Competing Interests:

The author(s) declare that they have no competing interests, no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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