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Impact of Highly Active Antiretroviral Therapy on Hepatic Enzyme Elevation among HIV Seropositive Individuals: A Case Control Study in Ghana

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Authors' contributions

Author LBK contributed to the conception of the research idea, research design, data collection, data analysis, interpretation of results, and first draft of the manuscript. Author CO contributed to the conception of the research idea, interpretation of results, and first draft of the manuscript. Author MAF contributed to data collection, design, and interpretation of results. All authors read and approved the final manuscript.

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ABSTRACT

Background: Increasing access to highly active antiretroviral therapy (HAART) in our population in recent times has necessitated the assessment of the impact of these therapies on hepatic enzymes. We therefore aimed to assess the impact of highly active antiretroviral therapy on hepatic enzymes and to ascertain the trend of hepatic enzyme elevation in HIV disease progression.
Method: 192 confirmed HIV individuals consisting of 104 HAART experienced and 88 HAART naïve patients were recruited into the study. Venous blood was taken for the assay of Alkaline Phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Gammaglutamyltransferase (GGT).
Results: There was a significant increase ($p<0.0.5$) in the median AST, GGT, ALT and ALP in the HAART naïve patients than the HAART experienced patients. There was a significant increase ($p<0.0001$) in the prevalence of AST, ALT, ALP and GGT elevation in the HAART naïve patients (35.2%, 28.4%, 28.4% and 48.9% respectively) than the HAART experienced patients (5.8%,

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1.9%, 5.8% and 10.6% respectively).
Conclusion: It is clear from this study that HAART may have a minimal effect on hepatic enzyme elevation and longer duration of treatment does not result in liver enzyme elevation. Close monitoring of patients receiving HAART is still relevant.

Keywords: HIV; renal function; HAART.

1. INTRODUCTION

Liver enzyme elevations are common disorders associated with HIV infection. In some cases, elevation of hepatic enzymes in HIV infected patients could be secondary to factors such as alcohol consumption, co-infection such as hepatitis B or hepatitis C infection [1]. The genesis of elevated liver enzymes in HIV infected individuals has been attributed to the toxicity of the antiretroviral therapy [2] whiles other researchers have also attributed it to the HIV infection itself [3] but due to the benefit HIV patients derive from the antiretroviral treatment including immunological stabilization, long-term treatment is inevitable [4]. Long term hepatic damage may also result in mitochondrial toxicity, alteration in lipid metabolism and insulin resistance which contribute to the development of steatohepatitis and steatosis [5]. These liver damages resulting from the drug toxicities coupled with drug discontinuation have been shown to be a major cause of death in HIV infected individuals [6]. Hence in this HAART combination era, major issues regarding the management and prevention of HAART induced liver injuries have evolve as public health concern [7].

Whiles studies elsewhere have reported increased prevalence of hepatic damage among HIV individuals on HAART [8-10], other researchers have also reported absence of hepatic damage among individuals on HAART [11] whereas others have reported a minimal hepatic damage among individuals receiving HAART [12]. Considering the fact that HIV infection is mostly endemic in poor developing/third world countries where resources and infrastructures are limited coupled with the increasing access to about 200-fold in the number of HIV patients receiving ART from 197 in 2003 to over 45,000 in 2010 in Ghana [13], has therefore necessitated the assessment of the impact of highly active antiretroviral on hepatic enzymes. Also on the premise of the conflicting reports on liver enzyme during the course of HIV infection in this HAART era, we aimed to assess the impact of HAART on hepatic enzymes among HIV seropositive on HAART and to ascertain the trend of hepatic enzyme elevation in HIV disease progression.

2. MATERIALS AND METHODS

2.1 Study Design

This was a case control study carried out at the ART clinic of the Bomso Specialist hospital in the Ashanti region of Ghana from August 2015 to March 2016.

2.2 Study Setting

Bomso Specialist hospital in Kumasi is staffed by registered general nurses, medical doctors, medical assistance, laboratory technicians, nutritionist, surgeons, health assistants, psychiatrist, optometrist and laborers. The department presently used by the hospital for it service provision are the outpatients department (OPD), in-patient department, maternity wing, laboratory unit, pharmacy department, a theater, a psychiatry unit, an x-ray unit and a mortuary.

2.3 Study Population

192 confirmed HIV seropositive individuals consisting of 104 HAART experienced and 88 HAART naïve patients were recruited into the study. Patients who were confirmed HIV seropositive and were between the ages of 18 and 65 were recruited into the study. Patients with coinfection such hepatitis B, C, tuberculosis and pregnant women were excluded from the study. Liver enzymes elevation were defined as follows; ALT > 40.0 U/L for male or > 31.0 U/L for female, AST > 37.0 U/L for male or > 31.0 U/L for female, GGT > 51.0 U/L for male or > 33.0 U/L for female and ALP > 117.0 U/L for adults [14].

All participants were placed into three groups according to the center for disease control classification which indicates the CD4 lymphocytes of patients. The groups were; CD4 counts less than 200mm^{-3}, CD4 count between 200 and 499 mm^{-3} and the third group consisted of patients with CD4 above 500 mm^{-3} [15].

2.4 Data Collection and Laboratory Analysis

A well-structured questionnaire was used to obtain demographic and clinical characteristics from the patients. 4 ml of venous blood were taken from each patient under sterile conditions after a tourniquet has been applied for less than a minute. 1 ml out of the blood taken was placed in an anticoagulated sequestrene bottles-EDTA for CD4 and CD3 analysis using the Becton Dickenson and company haematological analyzer called the BD FACS Count from California in USA. The remaining blood was centrifuged after they have been made to clot in a plain test tube. The serum obtained was stored at -20°C for the assay of AST, ALT, ALP and GGT using an auto-analyzer known as ATAC® 8000 Random Chemistry System from USA by Elan Diagnostic System.

2.5 Data Analysis

The data were presented as median interquartile range (IQR) for non-parametric variables whiles grouped variables were expressed as proportions. Comparison between HAART naïve and HAART experienced patients was carried out using Mann Whitney U test. Kruskal Wallis test was used where appropriate for comparison between more than two groups. Spearman correlation rank test was used to assess correlations between variables. A probability value less than 0.05 was statistically considered to be significant. All the analysis was performed using the statistical package for social sciences version 20.

3. RESULTS

There were more females than males for both the HAART experienced and the HAART naïve patients. The median age of the HAART experienced (41yrs) was statistically (p=0.203) not different from the HAART naïve patients (40yrs). The median CD4 counts of the HAART experienced (458 mm^{-3}) was significantly (p=0.0001) higher than the HAART naïve patients (229 mm^{-3}). Majority of the HAART experienced patients were on TDF+3TC+NVP (57.7%), 17.3% on CBV+NVP, 19.2 % on TDF+3TC+EFV whiles only 5.8% were on AZV+3TC+NVP. Among the studied participants, 33.9% had been diagnosed for more than four years whiles 30.7% had been on the therapy for more than four years [Table 1].

Table 1. Demographic and clinical characteristics of the studied participants

Parameter	HAART group (104)	HAART naïve (88)	P value
Age (yrs.)	41 (35-53)	40 (31.3-50)	0.203
Gender	N (%)		
Male	31(16.1)	27(14.1)	0.895
Female	73(38.0)	61(31.8)	0.895
CD4 (mm^{-3})	458.00(307.50-633.75)	229.00(136.25-338.75)	0.0001
CD3 (mm^{-3})	1216.50(931.00-1765.50)	919.00(667.50-1143.00)	0.0001
BMI kg/m^2)	23.30(20.33-26.85)	22.55(19.13-26.98)	0.521
HAART regime			
TDF+3TC+NVP	60(57.7)	---------	
AZT+3TC+ NVP	6(5.8)	---------	
CBV+NVP	18(17.3)	---------	
TDF+3TC+EFV	20(19.2)	---------	
HAART duration(yrs.)			
Median(IQR)	5(3-7)	--------	
Group1(<2)	10(5.2)	--------	
Group2 (2-4)	35(18.2)	--------	
Group 3(>4)	59(30.7)	--------	
Duration of diagnosis(yrs.)			
Median(IQR)	5(3-8)	1(0.45-2)	
Group1(<2)	6(3.1)	53(27.6)	
Group2 (2-4)	33(17.2)	31(16.1)	
Group 3(>4)	65(33.9)	4(2.1)	

CD4- cluster of differentiation, IQR-interquartile range, CBV: Combivir, NVP: Nevirapine, EFV: Efavirenz, 3TC: Lamivudine, TDF: Tenofovir, AZV: Zidovudine

Table 2 compares the median levels of the liver enzymes between the HAART experienced and the HAART naïve patients. There was a statistically significant increase (p= <0.0001) in the median AST, GGT and ALP of the HAART naïve patients when compared to the HAART experienced patients. ALT was also significantly higher (p= 0.044) in the HAART naïve than the HAART experienced patients.

Table 3 describes the number and frequency of individuals with normal and elevated liver enzymes and compares between the HAART experienced and the HAART naïve patients. Comparing individuals with liver enzyme elevation between the HAART experienced and the HAART naïve individuals, there was a significant increase (p=<0.0001) in the frequency of individuals with AST, ALT, ALP and GGT elevation in the HAART naïve patients (35.2%, 28.4%, 28.4% and 48.9% respectively) than the HAART experienced patients (5.8%, 1.9%, 5.8% and 10.6% respectively).

Table 4 describes the trend of liver enzyme elevation in the disease progression and compares between the HAART experienced and the HAART naïve patients. Individuals with CD4 count less than 200 mm^{-3} had the highest prevalence of AST, ALT, ALP and GGT elevation in both the HAART experienced (5.4%, 0.0%, 6.5% and 3.7%) and the HAART naïve patients (51.4%, 59.3%, 58.1% and 48.1% respectively) whiles none of the patients with CD4 ≥ 500mm^{-3} experienced liver enzyme elevation. Hence as the disease progresses, there was a concomitant increase in liver enzyme elevation. Also, among individuals of the same CD4 count categories, liver enzyme elevation were high in the HAART naïve than the HAART experienced patients.

Table 5 describes the correlation between the duration on the highly active antiretroviral treatment with the transaminases. A significant negative (p<0.01) correlation was observed between the duration of therapy treatment and AST, GGT and ALP. Although a negative correlation was observed between ALT and duration of therapy treatment, this was statistically not significant (p= 0.977).

4. DISCUSSION

Liver enzyme elevation during antiretroviral therapy has been documented as one of the major causes of mortality and morbidity [6]. The focus of this study is therefore to assess the impact of HAART on hepatic enzymes and the trend of the prevalence of hepatic enzyme elevation in the disease progression.

Table 2. Comparison of biochemical parameters between HAART and HAART naïve individuals

Parameter	HIV-HAART	HIV-HAART naïve	P value
AST(U/l)	18.00(13.00-25.00)	30.00(25.25-43.75)	<0.0001
ALT(U/l)	25.00(22.00-30.00)	27.50(20.00-34.50)	0.044
ALP(U/l)	43.00(39.50-60.00)	90.00(69.00-123.00)	<0.0001
GGT(U/l)	28.00(21.00-30.00)	39.50(30.00-67.50)	<0.0001

ALP-Alkaline Phosphatase; ALT-Alanine aminotransferase; AST- Aspartate aminotransferase; GGT - Gammaglutamyltransferase

Table 3. Comparison of the prevalence of hepatic enzyme elevation between the HAART and HAART naïve individuals

Parameter	Total (n=192)	HIV-HAART (n=104)	HIV-HAART naïve (n=88)	P value
AST				
Normal	155(80.7%)	98(94.2%)	57(64.8%)	<0.0001
Elevated	37(19.3%)	6(5.8%)	31(35.2%)	<0.0001
ALT				
Normal	165(85.9%)	102(98.1%)	63(71.6%)	<0.0001
Elevated	27(14.1%)	2(1.9%)	25(28.4%)	<0.0001
ALP				
Normal	166(83.9%)	98(94.2%)	63(71.6%)	<0.0001
Elevated	31(16.1%)	6(5.8%)	25(28.4%)	<0.0001
GGT				
Normal	138(71.9%)	93(89.4%)	45(51.1%)	<0.0001
Elevated	54(28.1%)	11(10.6%)	43(48.9%)	<0.0001

Table 4. Hepatic enzyme elevation stratified by the CD4 categories

Parameter	<200	200-499	<500	P value
AST(n=37)				
HIV-HAART	2(5.4%)	4(10.8%)	0(0.0)	0.031
HAART naïve	19(51.4%)	12(32.4%)	0(0.0)	0.009
P value	0.069	0.023	1.000	
ALT (n=27)				
HIV-HAART	0(0.0%)	2(7.41%)	0(0.0)	0.322
HAART naïve	16(59.3%)	9(33.3)	0(0.0)	0.015
P value	0.010	0.021	1.000	
ALP(n=31)				
HIV-HAART	2(6.5%)	4(12.9%)	0(0.0)	0.031
HAART naïve	18(58.1%)	7(22.6%)	0(0.0)	0.001
P value	0.094	0.303	1.000	
GGT(n=54)				
HIV-HAART	4(3.7%)	18(16.7%)	0(0.0)	0.009
HAART naïve	52(48.1%)	34(31.5%)	0(0.0)	<0.0001
P value	0.003	0.051	1.000	

Table 5. Correlation of the duration on HAART with the hepatic enzymes

Parameter	AST	ALT	ALP	GGT
rho	-0.288	-0.003	-0.384	-0.304
p-value	0.003	**0.977**	<0.0001	0.002

Rho-spearman correlation coefficient

The study found the prevalence of liver enzyme elevation to be higher in the HAART naïve than the HAART experienced patients. This was consistent with reports from Cameroon [9], South Africa [16] and Ethiopia [17]. The increased prevalence of hepatic enzyme in the HAART naive patients might be due to direct inflammation of hepatocytes by HIV through apoptosis, mitochondrial dysfunction, and permeability alteration in mitochondrial membrane that stimulates an inflammatory response [18-20]. The median AST, ALT, ALP and GGT of the HAART naïve patients were significantly ($p<0.05$) higher than the HAART experienced patients. Although studies by [12] reported an insignificant increase in these transaminases in the HAART naïve patients than the HAART experienced patients, the increase in the transaminases in the HAART naïve than the HAART experienced patients is consistent with the findings of this study. This is also inconsistent with a study conducted by [9] who reported increased AST and ALT levels only after the initiation of HAART. A cross sectional case control study in Ghana by [2] also found a significant ($p<0.001$) increase in AST, ALT, ALP and GGT levels among HAART experienced patients compared to HAART naïve patients which contradict the findings of this present study. The difference could be attributed to the fact that in their study about 9% of HAART experienced patients were coinfected with hepatitis B but was not the case in this study which excluded all patients infected with hepatitis B. Other studies on hepatotoxicity have shown the existence of hepatic damage during HAART in the presence of other coinfection such as tuberculosis [21]. Since patients with confections where excluded from this study, the raised ALT, ALP, AST and GGT levels in the HAART naïve patients could be attributed to the HIV infection itself as a result of chronic immune dysfunction associated with raised inflammatory cytokines. These findings buttress the point that HIV patients have the tendency to develop liver enzyme elevation even in the absence of HAART [3]. Correlation analysis of the transaminases (AST, ALT, ALP and GGT) with the duration of therapy treatment was negative. This result is consistent with the findings of [22] where they confirmed decreased concentration of transaminases as the treatment duration increases and inconsistent with reports by [9,12]. The difference could be due to the fact that these studies did not take into account the issue of drug discontinuation among their studied population but contrary to that, none of our studied participant had ever discontinued the therapy. Recently, studies by [13] has established the importance of drug adherence

among HIV patients receiving HAART to be associated with improvement in immunological success and effective suppression of HIV.

In the quest to ascertain the trend of liver enzyme elevation during the course of the HIV disease, we found a significantly high prevalence of hepatic enzyme elevation among patients with CD4 count less than 200 mm^{-3}. This concurs with recent findings by [17] and contradicts the findings by [23]. Hence as the disease progressed, we found the prevalence of hepatic enzyme elevation to be increased. This could be explained by the increased chronic immune activation with increased viral burden which directly attacks the hepatocytes [2]. In the light of these findings, the benefit of HAART became evident as the HAART experienced patients had a significantly reduced prevalence of hepatic enzyme elevation when they were compared with their HAART naïve counterpart within the same CD4 count categories.

5. CONCLUSION

It is clear from this study that HAART may have a minimal effect on hepatic enzymes among the studied population and longer duration of treatment may not result in liver enzyme elevation. This suggests that without the presence of any associated risk factors for hepatotoxity, HIV may itself cause hepatic damage. Close monitoring of patients receiving HAART is still relevant as minimal hepatic enzyme elevation could occur when on HAART.

ETHICAL APPROVAL AND CONSENT

Ethical approval was sought from the management of Bomso specialist Hospital and the committee on human research and publication of the School of medical science, Kwame Nkrumah University of Science and Technology (KNUST). Participation was voluntary and written informed consent was obtained from each participant. Respondents were assured that the information gathered was to be used strictly for research and academic purpose only.

COMPETING INTERESTS

Authors have declared that no competing of interests exists.

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