

# Liver Enzyme Abnormalities: A Comparative Study between Treatment Naïve HIV and HIV Negative Hospital Patients

Ganiyat Oyeleke<sup>1,\*</sup>, Anele Ihekwa<sup>2</sup>

<sup>1</sup>Lagos University Teaching Hospital, Lagos State, Nigeria

<sup>2</sup>University of Port Harcourt Teaching Hospital, Rivers State, Nigeria

\*Corresponding author: drgoyeleke@yahoo.com

Received August 25, 2018; Revised October 18, 2018; Accepted November 09, 2018

**Abstract Background and Aims:** The prevalence of People living with human Immunodeficiency virus remains considerably high in Nigeria. Liver disease has emerged as an increasingly significant contributor to mortality among HIV-infected patients. The aim of our study was to compare the difference in the prevalence of liver enzyme abnormalities between treatment naïve HIV positive and HIV negative patients. **Method:** The study was conducted at a teaching hospital. The study population consists of 736 patients (368 cases and 368 controls) that were selected from the hospital. The cases were treatment naïve HIV patients and the controls were patients being managed for other diseases. A diagnosis of liver disease was made based on the diagnostic criteria which include; presence of at least one clinical feature of liver disease, two liver chemistry abnormalities and an abnormal hepatic ultrasound report. **Result:** The mean ages of the cases and controls were 35.97±9.77 and 36.08±9.54 years respectively. Liver disease was seen in 277 (75.3%) of the cases and 54 (14.7%) of the controls, this difference was statistically significant ( $p<0.001$ ). Alkaline phosphatase ALP ( $p<0.001$ ) and Gamma-glutamyl transferase GGT ( $p=0.04$ ) were indicative of the presence of liver diseases in univariate analysis. Although Bilirubin was not of statistical significance, all HIV infected patients with total bilirubin  $\geq 25.5\mu\text{mol/L}$  had liver diseases. **Conclusion:** The use of abnormal liver enzymes and clinical features in resource poor settings are valuable screening tools to indicate the presence of liver diseases particularly in HIV – infected patients.

**Keywords:** liver enzyme abnormalities, HIV, treatment naïve HIV patients, Nigeria

**Cite This Article:** Ganiyat Oyeleke, and Anele Ihekwa, “Liver Enzyme Abnormalities: A Comparative Study between Treatment Naïve HIV and HIV Negative Hospital Patients.” *American Journal of Medical Sciences and Medicine*, vol. 6, no. 2 (2018): 45-50. doi: 10.12691/ajmsm-6-2-6.

## 1. Introduction

Globally, it is estimated that 36.7 million (30.8-42.9 million) people were living with human immune deficiency virus (HIV) at the end of 2016. [1] While the burden of the epidemic continues to vary considerably between countries and regions; Sub-Saharan Africa remains the most severely affected and it accounts for nearly two-thirds of the people living with HIV worldwide. [1] Of all the people living with HIV (PLWHIV) globally, 9% of them live in Nigeria [2] and deaths caused by AIDS continue to increase. [2,3] Worldwide, the expansion of antiretroviral drugs (ART) coverage has dramatically improved survival among PLWHIV. [4] In Nigeria, however, the coverage of adults and children receiving ART is 30% and there is 37% late HIV diagnosis (with the initial CD4 cell count  $<200$  cells/mm<sup>3</sup>). [3]

The most prominent feature of this disease is immunosuppression, which stems primarily from the

depletion of CD4 helper/inducer lymphocytes. Consequently, infected individuals develop opportunistic infections and the risk of many HIV-related disease varies with the patients degree of immunosuppression. [5] There are evidences that immunosuppression increases the risk of liver disease. [6,7] Managing liver disease is an increasingly important component to the care of individuals infected with HIV-1. [8] Since the advent of effective ART for HIV, there has been a substantial decrease in deaths related to acquired immunodeficiency syndrome. [8,9] However liver disease has emerged as an increasingly significant contributor to mortality among HIV-infected patients due to high prevalence of viral hepatitis co-infection. [10,11] High level of liver enzymes GGT, ALT and AST are predictive of disease and all-cause mortality and can reflect liver injury, fatty liver and/or oxidative stress. [12] The aim of our study was to compare the difference in the prevalence of liver dysfunctions between treatment naïve HIV positive and HIV negative hospital patients using liver enzyme abnormalities.

## 2. Methodology

The study was conducted at the Gastroenterology unit of the university of Port Harcourt, a teaching hospital that is a major referral facility from states in the south-south region of Nigeria. The study population consists of 768 patients that were selected from the Medical Out-Patient clinic, the HIV clinic and the medical wards of the hospital.

### 2.1. Laboratory Investigations

The following investigations were carried out on the cases and controls. HIV screening, Full blood count including platelets and erythrocyte sedimentation rate, Liver enzymes-aspartate amino transferase, (AST) alanine transferase (ALT), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), HBsAg, Anti HCV Antibody using ELISA, Total protein and albumin, Abdominal ultrasonography, and CD4 T-Lymphocyte count (for HIV patients only).

### 2.2. Diagnostic Criteria

Patients were classified as having liver dysfunction if they satisfied the following criteria:

- Clinical: Jaundice, hepatomegaly or reduced liver span, liver palms (palmar erythema) and other signs of chronic liver disease.
- Biochemical: abnormal liver enzymes of greater than one and half times the upper limit of normal; Serum alanine aminotransferase (ALT>63IU/L) [13,14], serum aspartate aminotransferase (AST>52IU/L) [14], gamma glutamyltransferase (GGT>60IU/L) and alkaline phosphatase, ALP>=290IU/L, serum total bilirubin >25.5  $\mu\text{mol/L}$ , conjugated bilirubin>7.6 $\mu\text{mol/L}$ , total protein of less than 62g/l and albumin of less than 35g/l.
- Ultrasonographical: The presence of a space – occupying lesion in the liver, distorted hepatic echo texture, reduced or increased liver size, ascites, and splenomegaly.

A diagnosis of liver disease was made based on the diagnostic criteria which include; presence of at least one clinical feature of liver disease, two liver chemistry abnormalities and an abnormal hepatic ultrasound report.

### 2.3. Selection of Cases and Controls

All consenting patients that were 18 years and above, who were HIV seropositive were recruited for the cases until the sample size of 368 was achieved. The controls were recruited from consenting HIV negative patients both from the medical out patients and those on admission until the sample size of 368 was achieved. These were patients being managed for systemic hypertension, hypertensive heart disease, congestive cardiac failure, left heart failure, diabetes mellitus, diabetic nephropathy, diabetic neuropathy, chronic renal failure, peptic ulcer disease, cerebro-vascular disease. A detailed history was obtained from each subject using a structured questionnaire which included details on demographic, socioeconomic, risk of blood transfusion, intravenous drug use and abuse, previous history of jaundice,

scarification marks, use of alcohol and ingestion of herbal medications and detailed sexual history. Thereafter the investigator in all study subjects carried out a thorough physical examination with emphasis on the signs of liver disease.

Differences between groups were tested using chi-square and the R statistical software was used to get the P values. [15] A p value of 0.05 was considered statistically significant.

The study was approved by the Ethical Committee of the University of Port Harcourt teaching hospital and written informed consent was obtained from all persons included in the study.

### 2.4. Exclusion Criteria

The following exclusion criteria was applied to the cases: currently on antiretroviral drugs, pregnant at the time of recruitment, admitted for a previous history of jaundice, blood transfusion or liver disease, had a significant alcohol history, agreed to a history of intravenous drug abuse or were on potential hepatotoxic drugs or agents, refused consent.

## 3. Results

There was a total of 368 HIV treatment naïve patients and 368 HIV negative hospital patients in the study. The mean age of the study participants among the cases and the controls were 35.97 $\pm$ 9.77 and 36.08 $\pm$ 9.54 years respectively. They both had the same age range from 18 to 69 years. There were 204(55.4%) and 216(58.7%) females in the cases and control group respectively. 223(60.6%) and 250(67.9%) of the cases and controls were married. 324(88.0%) were HIV 1 positive while 44 (12.0%) were positive for both HIV-1 and HIV-2. None was sero-positive for only HIV-2. The liver size span from 6cm to 19 cm among cases. Table 1 compares socio-demographic and clinical characteristics between HIV- infected (cases) and HIV negative patients (control).

**Table 1. Socio demographic and clinical characteristics of study participants**

	Cases (N=368)	Control (N=368)
<b>Age</b>	36 $\pm$ 9.77	36.1 $\pm$ 9.4
<b>Sex</b>		
Male	164	152
Female	204	216
<b>Liver disease</b>		
Hepatocellular	263	46
Cholestatic	14	8
No liver disease	91	314
<b>Liver Size</b>		
<8	12	2
>8-12	188	41
>12	77	11
<b>Relationship Status</b>		
Married	223	250
Single	108	80
Widowed	22	20
Separated	12	14
Divorced	3	4

### 3.1. Clinical Signs and Symptoms

#### 3.1.1. Gastrointestinal (GI) and Non-gastrointestinal Symptoms

277 (61.7%) cases and 218 (59.2%) controls had gastrointestinal symptoms on presentation. Of the cases, 158 (42.9%) had a single GI symptom, while 69 (18.8%) had more than one GI symptom. The most common GI symptom among cases was anorexia, followed by diarrhoea and abdominal pain. The commonest non-gastrointestinal symptom was weight loss, occurring in 157 (42.7%) of cases and 148 (40.2%) of controls. This was followed by fever, 108 (29.6%) of cases and 80 (23.4%) of controls.

**Table 2. Distribution of clinical signs between cases and controls**

Signs	Cases		Controls	
	N(%)	N(%)	X <sup>2</sup>	P-value
Cachexia	162(44)	94(25.5)	27.7	<0.001
Liver size	91(24.7)	32(8.6)	33.98	<0.001
Pallor	64(17.4)	12(3.3)	39.68	<0.001
Rashes	52(14.1)	60(16.3)	0.68	0.41
Crepitation	48(13.0)	20(5.4)	12.7	0.0004
Icterus	18(4.9)	20(5.4)	0.11	0.74
Oral thrush	18(4.9)	0(0)	18.45	<0.001
Ascites	16(4.3)	42(11.4)	12.65	0.0004
Dehydration	8(2.2)	0(0)	8.09	0.005
Liver Palm	8(2.2)	2(0.5)	3.65	0.06
Pedal edema	7(1.9)	2(2.7)	2.81	0.09
Splenomegaly	7(1.9)	14(3.8)	2.4	0.12
Asterixis	1(0.3)	0(0)	1	0.32

#### 3.1.2. Signs

The commonest sign among the cases was cachexia occurring in 162 (44%). This was followed by abnormal liver size and pallor. Among the controls, the commonest sign was abnormal liver size 132 (35.9%), this was

followed by cachexia in 94 (25.5%) of patients. There was a statistically significant difference in the occurrence of ascites, cachexia, crepitation, oral thrush, liver size, pallor and dehydration between cases and controls. (Table 2)

#### 3.1.3. Liver Size by Palpation

Liver size was grouped based on a normal span of 8cm to 12 cm and abnormal size of less than 8cm or greater than 12cm in cranio-caudal length. An abnormal liver size was found in 91 (24.7%) of the cases, with enlarged liver in 78(21.2%) while reduced liver was present in 13 (3.5%) of the cases studied. 31 (8.7%) of the controls also had abnormal liver size.

#### 3.1.4. Hepatic Ultrasonography

Among the cases studied, hepatic ultrasound was abnormal in 284(77.2%) of patients, while 84 (22.8%) had normal ultrasonography reports. While among the control group, 59 (16.0%) had abnormal and 309 (84.0%) had normal hepatic ultrasonography reports. This difference was statistically significant (p=0.026). (Table 3)

### 3.2. Liver Function Test

The distribution of liver function tests between the cases and controls are shown in Table 4. There was a high prevalence of elevated levels of ALT and AST in both the cases and controls. Elevated ALT and AST were found in 257(69.8%) and 325(88.3%) of HIV treatment naïve patients and in 236(64.1%) and 316(86.3%) of HIV-negative hospital patients. Elevated ALP and GGT were found in 298 (81.0%) and 106 (28.8%) of HIV treatment naïve patients and in 274 (74.5%) and 76 (20.7%) of the controls. Statistical significance was seen in GGT and ALP. Elevated TB and CB were found in 12 (3.3%) and 6(1.6%) of HIV treatment naïve patients; and in 10(2.7%) and 4(1.1%) of HIV negative hospital patients. There was a prevalence of 7.3% (27) and 52.2% (192) in the cases and 8.2% (30) and 56.0% (206) of controls below the threshold values of 62 and 35 for Total protein and Albumin.

**Table 3. Abdominal ultrasound findings between cases and controls**

	Cases (368)	Cases with liver disease(277)	Controls(368)	Controls with liver disease(54)
<b>Abdominal Ultrasound findings</b>				
Hepatomegaly				
• Homogenous	100	98	19	10
• Focal hyper-echoic	4	4	0	0
• Multiple hyper-echoic	1	1	0	0
Reduced liver size	15	15	3	2
Splenomegaly	87	84	16	8
Gall bladder thickening	5	5	1	0
Biliary dilation	11	11	0	0
Gall stones	6	5	1	0
Ascites	55	54	19	11
Total	284	277	59	31

**Table 4. Liver function test between the full analytic sample and the sample with liver disease**

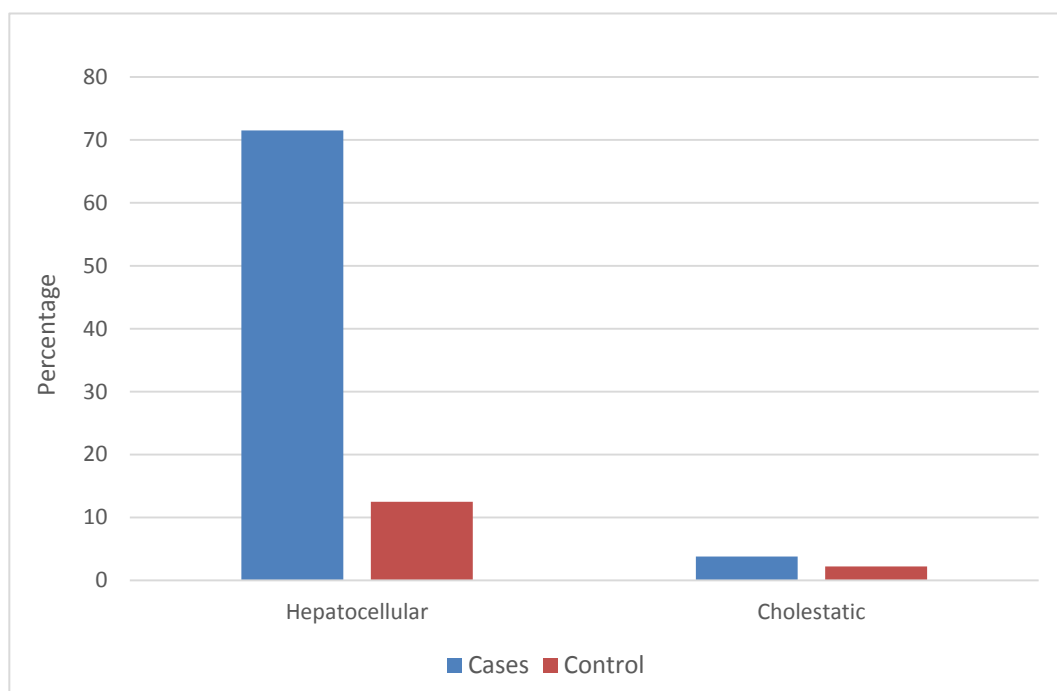
Liver threshold/biomarker	Full analytic sample(n=736)				Sample with liver diseases(n=331)			
	HIV-treatment naïve, n=368 (%)	HIV negative hospital patients, n=368(%)	X2	P-value	HIV-treatment naïve, n=277 (%)	HIV negative hospital patients, n=54(%)	X2	P-value
TB<25.5	356(96.7)	358(97.3)	0.19	0.66	265(95.7)	52(96.3)	0.04	0.84
TB>25.5	12(3.3)	10(2.7)			12(4.3)	2(3.7)		
CB<7.6	362(98.4)	364(98.9)	0.41	0.52	271(97.8)	54(100)	1.19	0.28
CB>7.6	6(1.6)	4(1.1)			6(2.2)	0()		
ALT<63	111(30.2)	132(35.9)	2.72	0.10	77(27.8)	20(37.0)	1.89	0.17
ALT>63	257(69.8)	236(64.1)			200(72.2)	34(63.0)		
AST <52	43(11.7)	50(13.6)	0.60	0.44	27(9.7)	5(9.2)	0.01	0.92
AST>52	325(88.3)	318(86.4)			250(90.2)	49(90.7)		
ALP<290	70(19.0)	94(25.5)	4.519	0.03	30(10.8)	16(29.6)	13.35	<0.001
ALP>290	298(81.0)	274(74.5)			247(89.2)	38(70.4)		
GGT<60	262(71.2)	292(79.3)	6.57	0.01	187(67.5)	44(81.5)	4.16	0.04
GGT>60	106(28.8)	76(20.7)			90(32.4)	10(18.5)		
Tprot<62	27(7.3)	30(8.2)	0.171	0.68	21(7.6)	1(1.9)	2.40	0.12
Tprot>62	341(92.7)	338(91.8)			256(92.4)	53(98.1)		
Alb<35	192(52.2)	206(56.0)	1.08	0.30	145(52.3)	29(53.7)	0.03	0.86
Alb>35	176(47.8)	162(44.0)			132(47.7)	25(46.3)		

CB-Conjugated Bilirubin; TB-Total Bilirubin; AST -Aspartate aminotransferase; ALT - Alanine aminotransferase; GGT-Gamma glutamyltransferase; ALP- Alkaline phosphatase; Alb- Albumin; Tprotein-Total Protein.

### 3.3. Incidence and Pattern of Liver Disease

Based on the diagnosis described in the methodology, liver disease was present in 277 (75.3%) of the cases while 54 (14.7%) of the controls also had liver disease. On a further analysis to determine the pattern of the disease, 14(3.8%) of the cases were classified as

having obstructive / cholestatic liver disease based on their ALT and ALP levels (ALP 3-5\*ULN and ALT 1.5-4\*ULN). [16] While for the hepatocellular disease (ALT>1.5 upper limit of normal and normal or raised AST) was found in 263 (71.5%) of the cases. Isolated elevation of ALP was present in 40 (10.9%) of the cases.



**Figure 1. Pattern of liver diseases**

## 4. Discussion

In this study of Liver dysfunctions in HIV infected and negative patients which was carried out at one of the two referral centres for free antiretroviral therapy in Port - Harcourt, we found some differences in the age and sex representation in the participants of the study. The mean age of the female patients was  $33.27 \pm 9.62$  years and  $39.34 \pm 8.88$  years for the male patients. The most common age group among the cases was 26-35 years occurring in 138(37.5%), while among the controls, the most common age group was 36-45 years which occurred in 130 (35.4%). There were more females than males in this study, with the male to female ratio being 1:1.24. This distribution is representative of the findings from the assessment of national HIV/AIDS response conducted in 2013, which suggests the prevalence of infection is higher for females than it is for male across all age groups except for the 35-44 years age groups [2,3]. Also, globally, women aged 15-24 are infected with HIV at rates twice that of young men, this rate is more pronounced in Sub-Saharan Africa, reasons proposed for this include, multiple concurrent sex partners, income inequality, sexual coercion and partnering with older men [17,18].

Our study also revealed a higher prevalence of HIV-1 alone 324(88%), while the remaining 44 (12%) were positive for both HIV-1 and HIV-2 infection. No patient was positive for HIV-2 alone. This prevalence follows a similar trend with a study conducted in Burkina Faso, where a prevalence of HIV-1, HIV-1&2 and HIV -2 94%, 3.6%, and 2.5% respectively [19].

### 4.1. Liver Disease

We found a 21.2% prevalence of enlarged liver size (greater than 12cm in cranio-caudal length) among HIV-infected patients, this prevalence is smaller than what was reported in a study conducted by Terzic et al [20]; they found liver enlargement in 63.75% of HIV infected patients. On the basis of the diagnostic criteria of abnormal liver enzymes of greater than one and a half of the upper limits of normal (ULN), presence of clinical features of liver disease, and ultrasound, a total of 277 (75.3%) of the cases were found to have liver disease while 54 (14.7%) of the controls had liver diseases This difference was statistically significant ( $p < 0.001$ ). Liver diseases have been implicated with non-AIDS related morbidities in HIV-infected patients [21].

### 4.2. HIV Type and Liver Disease

Of the 44 cases with HIV 1&2, 34(77.3%) had liver diseases while 243 (75.0%) cases with HIV-1 had liver diseases. Our study suggests that HIV1&2 had a higher tendency to liver disease than HIV-1 alone.

### 4.3. Abnormal Liver Function Tests

Abnormal liver function test may indicate significant liver disease. Skelly et al. found only 6% to have had a normal liver biopsy out of 354 patients with unexplained abnormal liver biochemistry. [22] We found a higher prevalence of ALT and AST when compared to other

studies, we found a prevalence of 69.8% and 88.3% in the treatment naïve HIV patients. Shiferaw et al. found a prevalence of elevated ALT and AST IN 11% and 17.7% of HAART naïve patients in Ethiopia. [23] Lucien et al. who observed a group of 150 HIV infected patients in Cameroun over three years found a prevalence of 54% of elevated AST and 22.7% of ALT at the final phase of the study. [24] Similar trends were found in the controls, a plausible explanation for this is that liver enzymes are often elevated in patients [25]. Higher means of AST and ALT were found in HIV patients compared to controls. These were however not of statistical significance. There was however a statistically significant difference in the mean of AST in HIV patients with liver disease compared to the controls. This study showed that AST was an important determinant of liver disease in HIV patients. Emerging evidences suggests that individuals with ALT values near the upper limit of normal (35-45IU/L) are at a higher risk of liver-related mortality in the long-term. [14] ALT levels are highest with drug-induced or toxin-induced liver injury and ischaemic hepatitis. [14]

Higher means of ALP and GGT were found in cases compared to the controls, with statistically significant levels. Elevated ALP levels  $>290$  IU/L were present in 247(89.2%) of cases and 38(70.4%) of controls with liver disease. This difference was statistically significant. There was also a higher number of HIV patients with liver disease with GGT  $>60$  IU/L than HIV negative controls. Our study also showed that elevated ALP and GGT are strongly predictive of liver disease in HIV patients. Agrawal et al. confirm that raised GGT and ALP confirm hepatic source [14]. A joint elevation of GGT and ALP is indicative of liver disorders [13]. GGT is found in hepatocytes and biliary epithelial cells. Measurement of serum GGT provides a very sensitive indicator of the presence or absence of hepatobiliary disease, but the usefulness of this test is limited by its lack of specificity [13].

We found a higher prevalence of hepatocellular pattern of liver disease than the cholestatic; 263 (71.5%) of the cases studied had the hepatocellular pattern. This result differs from the study conducted by Ocamo et al, they found a higher pattern of Cholestatic liver injury, 63%, and a 8% prevalence of hepatocellular and 19% with mixed pattern, this study was however done on only symptomatic patients [26].

### 4.4. Total and Conjugated Bilirubin

We also found a higher mean total bilirubin,  $12.65$  IU/L  $\pm 39.16$  was found among HIV-infected cases with liver disease compared to  $11.15$  IU/L  $\pm 10.72$  for HIV-negative controls with liver disease, this was however not statistically significant (data not shown). All the 12 HIV patients with total bilirubin  $\geq 25.5$   $\mu$ mol/L had liver diseases, while 2 out of the 10 controls with total bilirubin of  $> 25.5$   $\mu$ mol/L had liver diseases. Conjugated bilirubin enters urine only in the presence of liver disease that limits excretion of bilirubin into bile [14], all the 6 HIV patients with conjugated bilirubin  $>7.6$  had liver diseases while none of the four (4) controls, with elevated levels of CB, was found with liver diseases. Our study indicates a higher tendency to liver disease in HIV infected patients with higher total bilirubin values.

## 4.5. Albumin Levels

Human serum albumin is a critical plasma protein produced by the liver with a number of accepted clinical indications in chronic liver disease including management of circulatory and renal dysfunction in patients with ascites. [27] Lower than normal levels of albumin indicate liver damage or disease. Patients with advanced cirrhosis almost always have hypoalbuminemia caused both by decreased synthesis by the hepatocytes and water and sodium retention that dilutes the content of albumin in the extracellular space. [28] Although not statistically significant, a higher percentage of the cases and controls with liver diseases in our study had lower than the normal values of albumin.

## 5. Conclusion

The use of abnormal liver enzymes in resource poor settings is a valuable screening tool to indicate the presence of liver diseases and to seek further liver assessment particularly in HIV infected patients.

### 5.1. Limitations

We did not consider the type of HAART used by the HIV infected, this would have been helpful to explain possible interactions with therapy and liver diseases, some drugs have been associated with liver enzyme elevations. [29].

Also, there are various definitions for elevated liver enzymes, it ranges from 1.25 to 1.5 of ULN, standardization of these definitions would make comparison of prevalence across studies easier.

## Conflicts of Interest

None.

## Financial Support Statement

This research was not financed by any organization but self funded.

## Authors Contributions

Ganiyat Oyeleke conducted the design of the study, data collection and drafted the paper. Anele Ihekwa supervised the project. Both authors read and approved the final paper.

## References

- [1] WHO | HIV/AIDS. WHO Available at: <http://www.who.int/gho/hiv/en/>. (Accessed: 6th March 2018).
- [2] Awofala, A. A. & Ogundele, O. E. HIV epidemiology in Nigeria. *Saudi J. Biol. Sci.* (2016).
- [3] Nigeria. Available at: <http://www.unaids.org/en/regionscountries/countries/nigeria>. (Accessed: 18th March 2018).
- [4] Fetting, J., Swaminathan, M., Murrill, C. S. & Kaplan, J. E. Global Epidemiology of HIV. *Infect. Dis. Clin. North Am.* 28, 323-337 (2014).
- [5] Jung, A. C. & Paauw, D. S. Diagnosing HIV-Related Disease. *J. Gen. Intern. Med.* 13, 131-136 (1998).
- [6] Phillips, A. N., Neaton, J. & Lundgren, J. D. The Role of HIV in Serious Diseases Other than AIDS. *AIDS Lond. Engl.* 22, 2409-2418 (2008).
- [7] Sherman Kenneth E., Peters Marion G. & Thomas David. Human immunodeficiency virus and liver disease: A comprehensive update. *Hepatol. Commun.* 1, 987-1001 (2017).
- [8] Price, J. C. & Thio, C. L. Liver Disease in the HIV-Infected Individual. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* 8, 1002-1012 (2010).
- [9] UNAIDS\_Global\_Report\_2013\_en.pdf.
- [10] Weber, R. *et al.* Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch. Intern. Med.* 166, 1632-1641 (2006).
- [11] DallaPiazza, M., Amorosa, V. K., Localio, R., Kostman, J. R. & Lo Re, V. Prevalence and risk factors for significant liver fibrosis among HIV-monoinfected patients. *BMC Infect. Dis.* 10, 116 (2010).
- [12] Beek, J. H. D. A. van *et al.* The Genetic Architecture of Liver Enzyme Levels: GGT, ALT and AST. *Behav. Genet.* 43, 329-339 (2013).
- [13] Pratt, D. S. & Kaplan, M. M. Evaluation of Abnormal Liver-Enzyme Results in Asymptomatic Patients. *N. Engl. J. Med.* 342, 1266-1271 (2000).
- [14] Agrawal, S., Dhiman, R. K. & Limdi, J. K. Evaluation of abnormal liver function tests. *Postgrad. Med. J.* 92, 223-234 (2016).
- [15] R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.
- [16] Ejilemele, A. A., Nwauche, C. A. & Ejele, O. A. Pattern of abnormal liver enzymes in HIV patients presenting at a Nigerian Tertiary Hospital. *Niger. Postgrad. Med. J.* 14, 306-309 (2007).
- [17] Richardson, E. T. *et al.* Gender inequality and HIV transmission: a global analysis. *J. Int. AIDS Soc.* 17, (2014).
- [18] Langen, T. T. Gender power imbalance on women's capacity to negotiate self-protection against HIV/AIDS in Botswana and South Africa. *Afr. Health Sci.* 5, 188-197 (2005).
- [19] Harries, K. *et al.* Baseline characteristics, response to and outcome of antiretroviral therapy among patients with HIV-1, HIV-2 and dual infection in Burkina Faso. *Trans. R. Soc. Trop. Med. Hyg.* 104, 154-161 (2010).
- [20] Terzic, D. *et al.* Liver enlargement associated with opportunistic infections in patients with human immunodeficiency virus infection. *J. Gastrointest. Liver Dis. JGLD* 17, 401-404 (2008).
- [21] Smith, C. J. *et al.* Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet Lond. Engl.* 384, 241-248 (2014).
- [22] Skelly, M. M., James, P. D. & Ryder, S. D. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. *J. Hepatol.* 35, 195-199 (2001).
- [23] Shiferaw, M. B., Tulu, K. T., Zegeye, A. M. & Wubante, A. A. Liver Enzymes Abnormalities among Highly Active Antiretroviral Therapy Experienced and HAART Naïve HIV-1 Infected Patients at Debre Tabor Hospital, North West Ethiopia: A Comparative Cross-Sectional Study. *AIDS Research and Treatment* (2016).
- [24] Lucien, K., Clement, A., Fon, N., Weledji, P. & Ndikvu, C. The effects of antiretroviral treatment on liver function enzymes among HIV-infected out patients attending the Central Hospital of Yaounde, Cameroon. *Afr. J. Clin. Exp. Microbiol.* 11, (2010).
- [25] Ch'ng, C. L., Morgan, M., Hainsworth, I. & Kingham, J. G. C. Prospective study of liver dysfunction in pregnancy in Southwest Wales. *Gut* 51, 876-880 (2002).
- [26] Ocama, P. *et al.* The spectrum of liver diseases in HIV infected individuals at an HIV treatment clinic in Kampala, Uganda. *Afr. Health Sci.* 8, 8-12 (2008).
- [27] Spinella, R., Sawhney, R. & Jalan, R. Albumin in chronic liver disease: structure, functions and therapeutic implications. *Hepatol. Int.* 10, 124-132 (2016).
- [28] Bernardi, M., Maggioli, C. & Zaccherini, G. Human albumin in the management of complications of liver cirrhosis. *Crit. Care* 16, 211 (2012).
- [29] Boyd, A., Lacombe, K. & Girard, P.-M. An improved understanding of severe liver morbidity in HIV-infected individuals. *AIDS* 30, 1843 (2016).