ASSESSMENT OF BIOMARKERS IN PATIENTS CO-INFECTED WITH HIV/HBV ATTENDING THE ANTIRETROVIRAL CLINIC IN A TERTIARY INSTITUTION

ABSTRACT

Aim: The level of some biomarkers such as the Lipid profiles and some liver enzymes were checked for in patients who were found to be co infected with HIV/HBV

Study design: The study was conducted among patients infected with the Human Immunodeficiency Virus attending the antiretroviral clinic at the Braith Waite memorial hospital, Port Harcourt, Rivers State. The samples and relevant data were gotten between the months of January and March 2019, using a structured questionnaire

Methodology: The Samples were collected from patients infected with HIV attending the Braith Waite memorial hospital on antiretroviral medication. A total number of 98 samples were collected and analyzed for the presence of HBV IgM core antibody using the ELISA method. The statistical analysis was done using a Stata version 16 and the student T-test was used to determine the P value. A total of 98 samples were collected, 66(67.3%) were females and 32(32.6%) of them were males. Of the 98 samples, 5 (5.1%) of them were positive to HIV/HBV co infection of which 3(3.1%) were females and 2(2%) were males. The age range for those co infected was between 29 – 34 years old. The lipid profile and liver enzymes for the positive samples were analyzed. The result showed an increase in the level of LDL, HDL and triglyceride. The analysis for the liver enzymes showed an increase in the level of AST and ALP while the ALT and GGT remained within the healthy range. The increase in the level of most of the biomarkers, showed that the patients co infected with HIV/HBV were at risk of heart and kidney diseases since they are already immunocompromised. From this result, it shows that patients who are HIV positive should undergo HBV test regularly. Those who are positive should have their biomarkers monitored and put under medication early.

Keywords:
Hepatitis B virus, Human immunodeficiency virus, Liver Enzymes, Lipid Profiles, Biomarkers

1. INTRODUCTION

Hepatitis B virus (HBV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) worldwide [1]. About 15 percent to 25 percent of patient with chronic HBV infection die from cirrhosis or liver cancer [2].

Due to their shared routes of transmission, HIV is common among patients infected with HBV. Approximately, 10% of HIV-infected patients worldwide are thought to be co infected with HBV [3]. Additionally, liver disease has become a major cause of morbidity and mortality in HBV/HIV co infected patients due to prolonged survival with success in antiretroviral therapy (ART) [4]. In HBV/HIV co-infected patients, there is acceleration of the immunologic and clinical progression of HIV infection with an increased risk of hepatotoxicity. HIV infection increases the risk of hepatitis events, cirrhosis, and end-stage liver disease related to chronic HBV infection [5]. Also, co infection with HIV has been found to increase the risk of HBV chronicity (i.e, reduce likehood of HBsAg clearance in unvaccinated patient), increase antiretroviral-related hepatoxicity and increase risk of end-stage liver disease[6]. Patients with co infection have poorer hospital outcomes and higher risk of progression to cirrhosis, HCC, and

death than patients with either HIV or HBV mono-infection[6][7]
Patients co infected with HIV 1 and HBV, especially those with low CD4+ cell counts, have been found to be at an increased risk for liver-related mortality [8]
The liver which is an organ involved in the sequencing, remodeling and redistribution of lipid metabolites which includes the Low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC)[9], receives fatty acids and cholesterol from peripheral tissues and diet, packages them into lipoprotein complexes, and releases these complexes back into the circulation[10]. In a work done by Moustapha *et al*.,[11] the alteration of the lipid metabolism, were shown to promote inflammation, fibrosis and proliferation in a mouse model of chronic cholestatic liver injury. The liver disease is often reflected by biochemical abnormalities of 1 of 2 different hepatic systems or of liver function [12]. HIV co infection with HBV is associated with more frequent flares of hepatic transaminases, which can occur with immune reconstitution inflammatory syndrome (IRIS) owing to ART, interruption of HIV/HBV treatment, or the development of resistance of HIV/HBV treatment; they also can occur spontaneously[13]. Usually elevated AST and ALT levels with mild abnormalities of alkaline phosphatase (ALP) and γ-glutamyltranspeptidase (GGT) levels is an indication of an existing liver disease [14]. Currently in Port Harcour, little or no work has been done on biomarkers associated with liver dysfunction in HIV and HBV co infected patients, hence the need to study these markers in this group of persons so as to proffer the right care for them, thereby reducing mortality rate among them.

2.0 MATERIALS AND METHODS

2.1STURDYAREA

The study was carried out in Port Harcourt, Rivers State, which lies along the Bonny River in the Niger Delta region of Nigeria with its co-ordinates: $4^{o}\ 53^{I}\ 23^{II}$ N, $6^{o}\ 54^{I}\ 18^{II}$ E and covers an area of 360 kilometers square. Port Harcourt metropolis consist of Obio akpor Local Government Area and Port Harcourt Local Government Area.

2.2STUDYPOPULATION

The study was conducted among patients infected with the Human Immunodeficiency Virus attending the antiretroviral clinic at the Rivers State University teaching hospital, Port Harcourt, Rivers State. The patients who were within the age range of 18 to 65 years' relevant data were gotten between the months of January and March 2019, using a structured questionnaire. The protocol used for the study was in adherence with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All study subjects gave informed consent. Any subject who did not give consent was excluded.

2.3 ETHICAL APPROVAL

Ethical approval for the study was gotten from the Rivers state ethical health committee

2.4 SAMPLE COLLECTION

All blood samples were collected through venipunture with the patients consent and put into a lithium heparin bottle. The serum was separated using a centrifuge which was spun at 4000 rpm for 5 minutes. The CD4 count was determined using a standard laboratory procedure with the use of a flow cytometer counter (Version 2.4, Partec Germany) after which the serum was stored in another tube at -70^{0} C until analyzed.

2.5 DETECTION OF THE HBV IgM CORE ANTIBODY

The HBV IgM core antibody was detected with the use of a third generation rapid kits which was used to detect the presence of the HBV IgM core antibody which shows a current infection and was confirmed with the ELISA method using a commercially available third generation kit manufactured by Melsin Medical Co., limited. The assay was performed in adherence with the manufacturer's instructions. The optical density was read using the Emax endpoint ELISA microplate reader (Molecular Devices, California, USA) and the result was interpreted according to the manufacturer's instructions.

2.6 DETECTION OF THE LIPID PROFILE

The lipid profile which in includes the Triglycerides, Total Cholesterol, High Density Lipid and the Low Density Lipid levels were detected. The Triglyceride level was determined after enzymatic hydrolysis with lipases. The Cholesterol level was detected using the enzymatic end point method, the High Density Lipid was detected using the precipitant method and the Low Density Lipid was detected using the Freidewald equation method.

2.7 DETECTION OF THE LIVER ENZYMES

Aspartate Transaminase (AST) and Alanine Transaminase **(**ALT) were determined using the Reitman and Frankel method, Alkaline Phospatase (ALP) was determined using the Kochmar and Moss method and Gamma -Glutamyl Transferase **(**GGT) using the Teitz method.

2.8 STATISTICAL ANALYSIS

Stata version 16 was used to analyze the data. The P value was determined using a T- test.

3.0 RESULT

A total population of 98 patients including males and females were involved in the study of which 66[67.3%] were females and 32[32.6%] were males. Of the total population, 93[94.9%] were Hepatitis B negative and 5[5.1%] were Hepatitis B positive of which 3(3.1%) were females, while 2(2%) were males. The age range of patients coinfected was between ages 29 -30.
The mean value for the Lipid profile result was gotten. Total Cholesterol for the patients co infected was 4.4mmol/L, the Triglyceride was 1.7mmol/L, High Density Lipoprotein was 1.7mmol/L and that of the Low Density Lipoprotein was 3.5mol/L.
The mean value for the Liver enzymes was also detected. Aspartate Transaminase (AST) for the Patients co-infected was 50.8u/L. Alanine Transaminase (ALT) was 22.8u/L, the Alkaline Phosphatase (ALP) was 36.4 u/L, Gamma- Glutamyl Transferase (GGT) was 3.28u/L.

Table 1: Showing age range of HIV mono infection and HIV/HBV co infection

Age Range	HIV mono infection	HIV/HBV Co infection
18 – 20	21	**0**
21 – 30	8	1
31 – 40	35	4
41 – 50	25	0
51 – 60	4	0
Total	93	5

Table 2: Showing gender distribution and CD4 Cell count of non HBV (HIV) infected and HIV/HBV co infection

Gender	HIV Mono infected (%)	HIV/HBV Co infected(%)

Females	51 (52.0)	3(3.1)
Males	42 (42.9)	2(2)
TOTAL	94.9 (96.8)	5(5.1)
CD4+ CELLS COUNT	641.1 cells/μl	403.2 cells/μl

Table 3: Showing the mean value of the biomarkers and their range in healthy individuals

Biomarkers	**Mean Values in HIV/HBV co infection (S.D)**	**Standard Range in healthy individuals**	**Significant Difference (*P* Value)**
LIPID PROFILE			
Total Cholesterol (TC)	4.4 mmol/l (0.396)	6.9mmol/L	Value in the healthy range
Triglyceride(Trig)	1.7 mmol/l (0.148)	1.7mmol/L	0.756
High Density Lipid (HDL)	1.7 mmol/ l(0.322)	1.6mmol/L	0.043
Low Lipid Density (LDL)	3.5 mmol/l (0.272)	0.4mmol/L	0.001
LIVER ENZYMES			
Aspartate Transaminase (AST)	50.8u/L (3.701)	5 – 40u/L	0.003
Alanine Transaminase (ALT)	22.8u/L (1.483)	7 – 55u/L	Within the healthy range
Alkaline Phosphatase (ALP)	36.4u/L (5.550)	9 – 35u/L	0.603
Gamma- Glutamyl Transferase (GGT)	3.30u/L (0.784)	0 – 30u/L	Within the healthy range

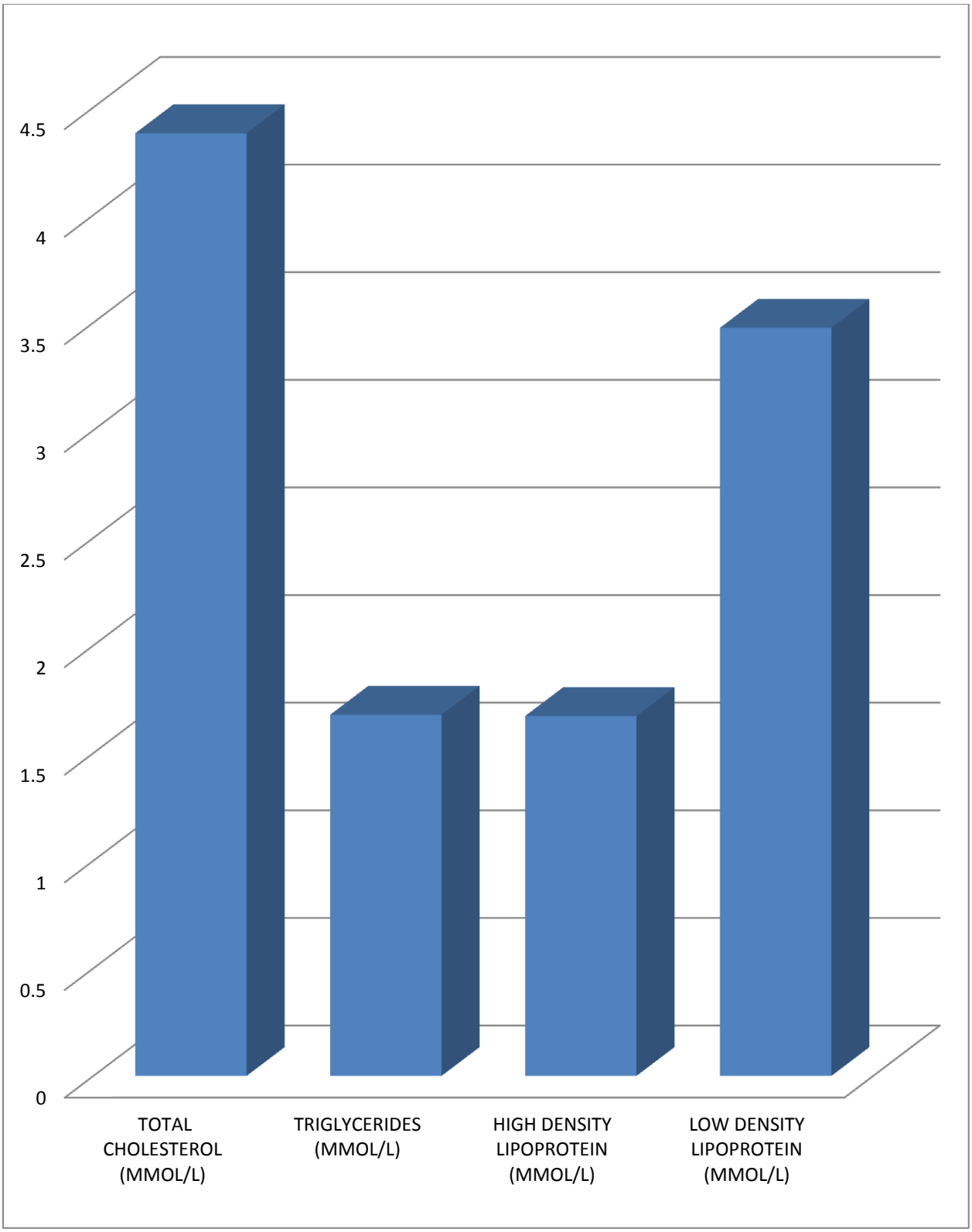

Fig 1: Showing the lipid profile of people co infected with HIV/HBV

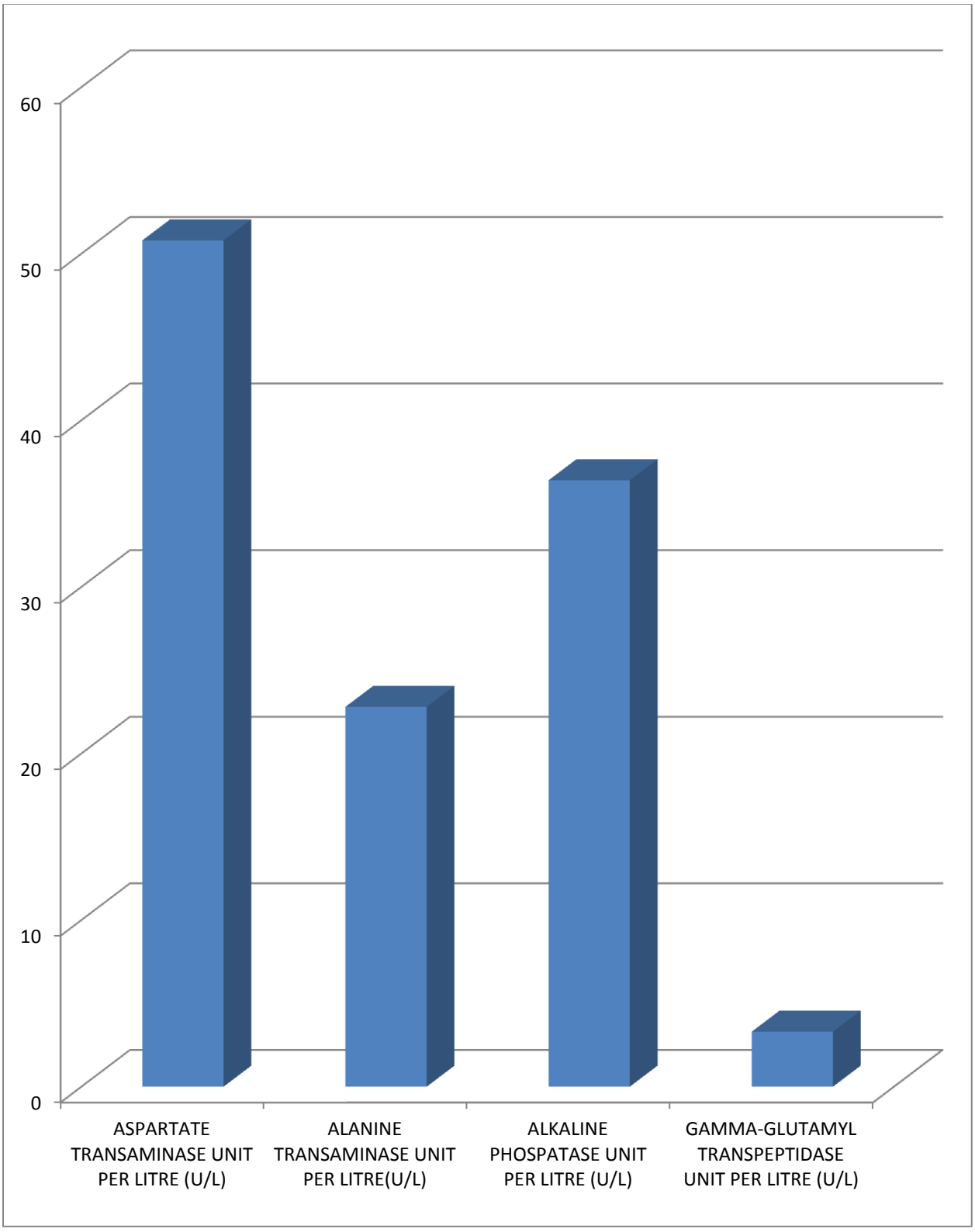

Fig 2: Showing the liver enzymes levels of people co infected with HIV/HBV

4.0 DISCUSSION

Non fasting blood was used for the analysis in line with Langstead *et a*l.,[15] who discovered from their work that there was no significant difference between fasting and non fasting blood and Lucaz *et al.,* 6]whose work showed that non fasting lipid profile is more suggestive of dyslipidemia than fasting lipid.

From the work done as shown in Table 1, the number of patients co infected with HIV/HBV was 5 out of the 98 samples analyzed with a percentage of 5.1. From the work done by Okonko *et al*., [17] in Port Harcourt, in which the prevalence of the co infection of HIV/HBV was detected among HIV seropositive blood donors, 6.1% were co infected. Also, 7.8% were HIV/HBV coinfected in the findings of Anigilaje and Olutola [18] among Children in an Antiretroviral Therapy Programme in Benue State, Nigeria and 8.8% HIV-seropositive persons attending antiretroviral clinics in the Eastern Region of Ghana as reported by Kye-Duodu *et al*.,[19]. All of these findings though within the range of the findings from this work, were slightly higher but the finding from this work agrees with that of Lawal *et al*., [20] in which 5.3% of the patients were co infected. This shows that people are becoming aware of the infection and taking precursions as compared to previous works such as the study carried out in Malawi by Nyirenda *et al*., [21] in which 17.5% among those attending antenatal were co infected with HIV/HBV and a prevalence of 16.7% was found among a Ghanaian HIV-positive cohort hospitalized at a tertiary care institution in Kumasi in the findings of Geretti *et al*., [22], in which there were higher prevalence. Of the five patients co infected, three (3.1%) were females while two (2.0%) were males as shown in table 2. This does not correlate with the findings from the work of Nwolisa *et al*.,[23]carried out in Owerri, south eastern Nigeria in which the prevalence of the co infection was higher among the males than the females with a percentage of 8.2 to 3.8 but agrees with the work done by Boateng *et al*., [24]in which the female co infected were 56% while the percentage of males co infected were 46% and that of Marceline *et al*.,[25] in which the female were prevalent by 12% against the men who were 4% in Younde, Cameroon.

From the analysis as shown in Table 3 High density Lipoprotein [HDL] showed a significant increase with a *P* value of 0.043 above the normal healthy range with the mean value of 1.7mmol/L when compared to the normal range value of 0.9-1.6mmol/L. There was also a significant increase with a *P* value of 0.001 in the level of Low Density Lipoprotein [LDL] with the mean value of 3.5mmol/L when compared with the healthy value of 0.4mm. The triglyceride level with the mean value of 1.7mmol/L was on the borderline when compared to the healthy range value. The level of Total cholesterol mean value which was 4.4mmol/L was within the healthy range.

From the work done among people infected with HIV by Pakhale *et al*., [26], the mean value for the LDL was 1.4mmol/L, TC was 3.5mmol/L, HDL was 1.11mmol/L and Triglyceride was 2.26mmol/L and that done by Nayyar [27] the mean value for the LDL was 1.20mmol/L, TC was 1.11mmol/L, HDL was 0.46mmol/L and Triglyceride was 0.76mmol/L . While the study carried out among hepatitis B viral infected persons by Arain [28] showed a mean value of the lipid profile to be LDL (1.76mmol/L), TC (2.45mmol/L), HDL (0.7mmol/L) and Triglyceride (0.93mmol/L) and that of Quaye *et al*., [29] showed a mean value of LDL to be 2.53mmol/L, TC to be 3.9mmol/L, HDL to be 0.90mmol/L and Triglyceride was 1.07mmol/L. The values for each of the lipids were below that gotten in the result of the co infection in this work. This suggest that the co infection of HIV and HBV escalates the lipid profile in patients co infected thereby subjecting them to dislipidemia, since dislipidemia is described as the elevation of more than one lipid above the normal range.

The increase in the level of LDL has been described by Sarin *et al*.,[30] to cause a subsequent increase in the level of cholesterol in circulation which may accumulate in the arteries thereby blocking blood vessels leading to an increased risk of cardiovascular and coronary heart disease and from the result gotten from this study, the LDL level was detected to be on the high side which may subsequently increase the cholesterol level thereby exposing the patients co infected with HCV/HBV with risk of cardiovascular and coronary heart disease. Moreover, the result gotten, suggest that patients co infected with HIV/HBV are also at a risk of liver and pancrease disease which could also lead to kidney disease based on the high value of most of the lipid levels especial in patients who are already imunocompromised as stated by the studies carried out by Amirzadegan *et al*., [31]and Mayo Clinic [32].

From the analysis as shown in Fig 2, Aspartate Transaminase (AST) showed a significant increase with a *P* value of 0.003, with the mean value of 50.8u/L when compared to the healthy range of 5 – 35U/L. This agrees with the work done by[33], although disagrees with the level of the mean value of ALT in which according to Adewole *et al*.,[33], was higher than the AST mean value. There was also an increase though not significantly with a *P* value of 0.603 in the Alkaline Phospatase (ALP) with a mean value of 36.4 U/L compare to the normal range 9 – 35U/L, while the ALT and GGT mean values were 22.8U/L and 3.3U/L respectively which were within the healthy range. The ALT mean value agrees with the findings in the work done by Puoti *et al*.,[34]in which it was discovered that HIV has a lowering effect on the ALT of patients co infected with HIV/HBV.

One of the ways of defining enzyme elevation pattern as defined by Malakonti *et al* [35]is the mixed pattern which is a combination of the pattern predominantly reflecting hepatocellular injury and pattern predominantly reflecting cholestasis. This involves the elevation of either the AST or the ALT and the ALP. From the findings in this work, the patients' co infected with HIV/HBV showed a mixed pattern of enzyme elevation wherein there was an elevation of both the AST and the ALP showing that the patients were both predisposed to hepatocellular injury and cholestasis.

The increase in the level of ALT or AST in a population with unidentifiable risk factor has been associated with liver related mortality according to Kwo *et al* [36] and from the findings of [37], in a ratio of AST : ALT greater than 1in patients with chronic viral hepatitis, there seem to be a prognosticative poor outcomes with more likelihood of progression to cirrhosis. The outcome of this work, showed an AST : ALT greater than 1in the patients which showed that they are at a risk of progression to cirrhosis as stated by Giannin *et al*.,[37].

5.0 CONCLUSION AND RECOMMENDATION

The result showed an increase in the level of LDL, HDL and triglyceride and also an increase in the level of AST and ALP which are deleterous to the patients who are already immunocompromised due to being at risk of liver, kidney and heart disease since they are already infected with the Human immunodeficiency virus. This result suggests that patients who are HIV positive should undergo HBV test on a regular basis and for those who are co infected should have their lipid profile checked and put under medication to avoid complications due to high level of these lipids which can lead to high mortality rate among HIV/HBV co infected patients.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is

absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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