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Research Article
Treatment Duration with Antiretroviral Therapy and Selected Liver Enzymes among HIV Positive Patients

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Abstract

Background and Objective: There is increased awareness in the use of antiretroviral therapy. However, these drugs are to be considered along with their potential adverse effects. Some of these adverse effects which may be hepatotoxic may be associated with the duration of treatment. The study was, therefore, designed to compare duration of treatment of antiretroviral drugs with the selected liver enzymes. **Materials and Methods:** This research was conducted on 276 patients who were HIV positive. Data of patients who finally satisfied the inclusion criteria were analyzed. Aspartate aminotransaminase, ALT and ALP were determined by the use of commercial kits manufactured by Randox Laboratory, Alden, the USA on plasma extracted from an aseptically collected blood sample from each subject. **Results:** There were statistically significant differences (ALT $p<0.001$, ALP $p<0.001$) in the mean values of ALT (male, 30.61 ± 20.63, female, 20.70 ± 15.67) and ALP (male, 15.42 ± 8.14, female, 11.06 ± 7.17) between genders. There were no significant differences observed in the enzymes when duration of therapy was considered. However, the mean values of these enzymes were higher in patients who had taken medication for less than 5 years than those who had taken for more than 5 years. **Conclusion:** There were no statistically significant differences in plasma AST, ALT and ALP in patients on antiretroviral therapy when linked to the duration of treatment. However, non-significant raised values of these enzymes in patients who had taken medication for less than 5 years should not be overlooked.

Key words: HIV/AIDS, antiretroviral drugs, adverse drug reaction, aspartate aminotransaminase, alanine aminotransaminase, alkaline phosphatase

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In most developing sub-Saharan countries, the pandemic of HIV/AIDS is potentially threatening the health sector. It is causing further reduction in life expectancy and stressing the already weak health system[1]. However, access to combination antiretroviral therapy (cART) has changed the natural history of HIV infection and AIDS remarkably. This has led to a dramatic decrease in morbidity and mortality rates and subsequently transforming HIV disease from an acute to a manageable chronic condition[2]. Globally, as at the end of 2020, 36.4 million people with HIV (90%) had access to Antiretroviral Therapy (ART)[3,4]. However, the long-term usage of Highly Active Antiretroviral Therapy (HAART) can induce considerable adverse effects such as abnormal lipid metabolism with associated increased risks of cardiovascular diseases and hepatotoxicity as evidenced by raised liver enzymes[5].

Liver enzymes elevation is a common problem that is encountered in patients on HAART. Highly Active Antiretroviral Therapy (HAART) damages the liver cells by direct toxicity of the parent drug or from its active metabolites [6]. Liver disease has emerged as the most common non-AIDS-related cause of death among HIV infected patients, accounting for 14-18% of all deaths[7]. Antiretroviral therapy has been found to have minimal effects on hepatic enzymes[8]. Injury may occur in the hepatic organ in patients not yet on ART and without any other known associated risk factors[9].

Although, many studies were conducted in different countries to examine the effect of antiretroviral drugs on the liver but the majority of these studies were comparative[6]. This study was however, designed to look into the effects of these combinations of drugs to the duration of treatment on a selected liver enzymes (aspartate aminotransaminase, AST, alanine aminotransaminase, ALT and alkaline phosphatase, ALP).

MATERIALS AND METHODS

Study area: The study site was the HIV clinic and the Department of Chemical Pathology of the Ekiti State University Teaching Hospital, Ado-Ekiti. Records of patients on treatment from HIV clinic were examined in order to recruit patients for the study. This research project was conducted from January-July, 2014.

Experimentation: A research protocol was designed to assess needed variables based on the proposed topic. On this protocol were columns for patient's age, duration of treatment as at the time of collecting this data and gender, after which patients were sent to the laboratory for the analysis of the selected liver enzymes (AST, ALT and ALP). The reference values for these parameters were considered as being used routinely in our center (AST<16, ALT<18 and ALP is 30-120 IU L^{-1}). This research was conducted for 6 months in 2014 of which 276 patients who were HIV positive were recruited into the study. Sixteen of them were found to be $HBsAg^+$ positive and they were subsequently excluded from the study. Patients who were obese as evidenced by increased Body Mass Index (BMI), those on other drugs that are metabolized in the liver, those who are diabetic or hypertensive were also excluded from the study. Patients with obvious liver pathology during the physical examination as seen in the case notes were also excluded from the analysis.

Sample collection: In the laboratory, a minimum of 3 mL of whole blood sample was collected from each subject between the hours of 08.00 and 10.00 am and dispensed inside lithium heparin specimen bottle. This blood sample was centrifuged almost immediately after collection at about 3000Xg for 5 min to harvest supernatant (plasma). The plasma was kept frozen for the maximum period of five days before the analysis of these biochemical parameters (AST, ALT and ALP). Aspartate aminotransaminase, ALT and ALP were analyzed by the use of commercial kits manufactured by, Randox Laboratory, Alden, the USA.

Statistical analysis: Variables were later entered and analyzed using SPSS 23.00. Data were presented in form of flow chat, tables and bar chart. ANOVA was used to compare association within different groups of patients and $p<0.05$ was considered significant.

Ethical approval: Ethical approval (EKSUTH/A67/2020/018) was obtained from Ethic and Research Committee of the Ekiti State University Teaching Hospital, Ado-Ekiti

RESULT

Figure 1 below, out of 276 randomly recruited subjects, 16 (5.8%) was found to be HBsAg+positive also. 21 (8.1%) patients were found to do take alcohol/alcohol-based herbal preparation once in a while. Sixty-six (25.4%) of these patients who are HIV positive are males while 194 (74.6%) of them are females. Thirteen (6.7%), out of the female population had Body Mass Index (BMI) kg m^{2-1} less than 18.5 while 181

Table 1: Comparison of mean distribution of selected liver enzymes

Variables (UI L^{-1})	Male (66)	Female (194)	t-test	p-value
AST	34.77±17.36	29.81±16.96	1.237	0.217
ALT	30.61±20.63	20.70±15.67	4.076	**<0.001
ALP	15.42±08.14	11.06±07.17	4.128	**<0.001

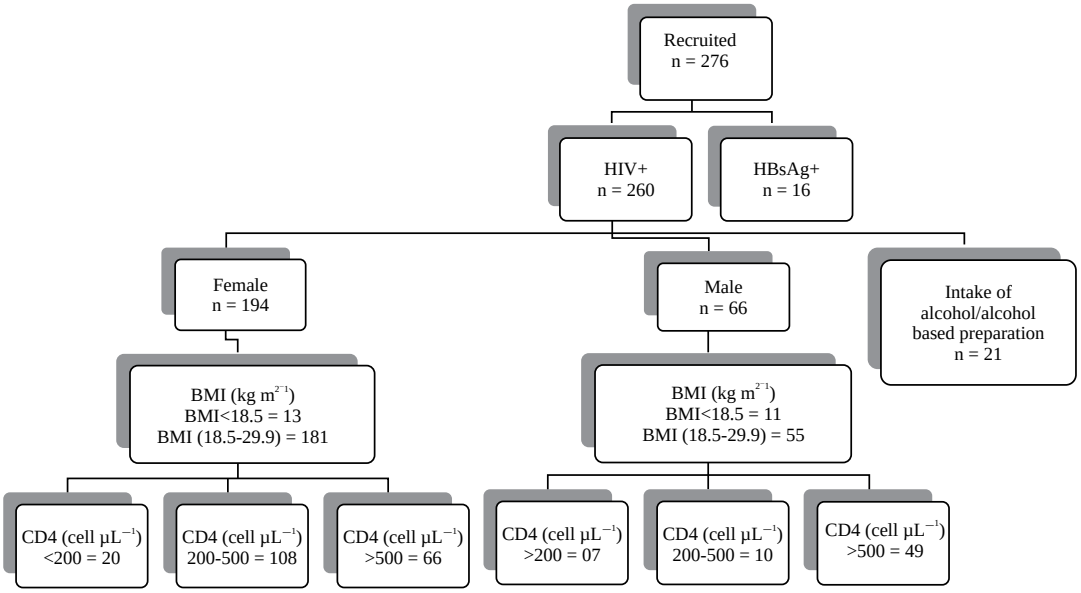

Fig. 1: Socio-demographic data and CD4 (cell µL^{-1}) count of the subjects

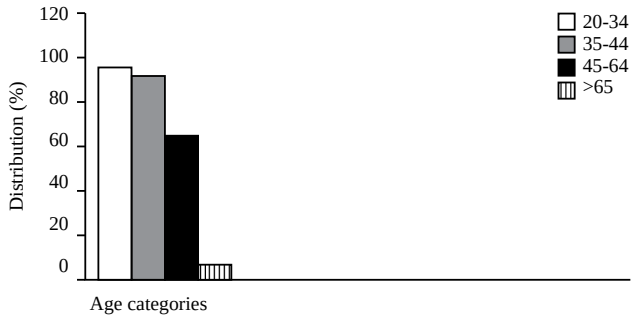

Fig. 2: Age distribution in the studied population

(93.7%) had a BMI between 18.5 and 29.9. Among the male population, 11 (16.7%) had BMI less than 18.5 kg m$^{2-1}$ while 55 (83.3%) had BMI between 18.5-29.9 kg m$^{2-1}$. A greater percentage of the study population as at the time of sample collection had CD4 counts greater than 200 cell µL^{-1} (89.7% for female and 89.4% for male).

In Fig. 2 the age distribution of the studied population was shown. Ninety-seven (37.3%) subjects were between the ages of 20 and 34 years, 95 (36.5%) were between the ages of 35 and 44 years, 62 (23.9%) patients were between the ages of 45 and 64 and 6 (2.3%) patients were of the age greater than 65 years.

Table 1 shows that the mean value of AST was higher in male when compared with the female, although this difference is not statistically significant (34.77±17.36 vs. 29.81±16.96). There were statistically significant differences (ALT p<0.001, ALP p<0.001) in the mean values of ALT (male, 30.61±20.63, female, 20.70±15.67) and ALP (male, 15.42±8.14, female, 11.06±7.17).

There were no significant differences in the mean values of enzymes in different age categories.

The mean plasma value of AST for patients aged 20-34 years was 34.93±17.96, patients aged 35-44 years was 28.36±16.85, patients aged 45-64 years was 29.43±15.43 and for patients greater than 65 years was 29.00±22.39, p = 0.408. The mean plasma value of ALT for patients aged 20-34 years was 22.67±15.87, patients aged 35-44 years was 22.88±17.08, patients aged 45-64 years was 25.20±21.06 and for patients greater than 65 years is 16.71±8.26, p = 0.592. The mean plasma value of ALP for patients aged 20-34 years was 13.22±8.44, patients aged 35-44 years was 10.66±6.44, patients aged 45-64 years was 12.91±7.89 and for patients greater than 65 years was 10.57±6.70, p = 0.098. However, the mean value of ALP was lower than the lower limit of normal expected (30 IU L^{-1}).

There were no significant differences observed in the enzymes when considering the duration of treatment in years. However, the mean values of these enzymes were higher in patients who had taken medication for less than 5 years than those who had taken for more than 5 years. The mean value of AST in patients who had taken medication for less than 1 year was 52.50±23.42, 1-3 years was 29.58±17.61, greater than 3 to 5 years was 30.99±21.96 and for >5 years was 24.00±8.19, p = 0.055. The mean value of ALT in patients who had taken medication for less than 1 year was 22.00±11.93, 1-3 years was 22.05±15.94, greater than 3-5 years was 25.52±20.70 and for >5 years was 18.00±4.00, p = 0.466. The mean value of ALP in patients who had taken medication for less than 1 year was 13.67±9.88, 1-3 years was 11.64±7.19, greater than 3-5 years was 12.93±8.14 and for >5 years was 10.00±6.00, p = 0.504.

As shown in Table 4, these enzymes were compared among patients using different antiretroviral regimen. There were no statistically significant differences observed. The plasma mean values are as follows, for AST (AZT,3TC,EFV = 34.50±20.82, AZT,3TC,NVP = 30.25±29.07, TDF,FTC,NVP = 26.50±10.82, TDF,3TC,ALLUVIA = 20.00±11.48, TDF,3TC,NVP = 40.08±16.93, TDF,3TC,EFV = 35.63±9.12 and Others = 37.29±32.15, p = 0.794), for ALT (AZT,3TC,EFV = 26.22±23.46, AZT,3TC,NVP = 23.11±17.47, TDF,FTC,NVP = 22.33±10.69, TDF,3TC,ALLUVIA = 14.80±4.55, TDF,3TC,NVP = 25.08±20.61, TDF,3TC,EFV = 23.25±17.84 and Others = 22.14±8.57, p = 0.934) and for ALP (AZT,3TC,EFV = 13.00±9.97, AZT,3TC,NVP = 12.07±7.62, TDF,FTC,NVP = 11.00±5.90, TDF,3TC,ALLUVIA = 10.20±6.69, TDF,3TC,NVP = 15.58±8.02, TDF,3TC,EFV = 13.50±4.24 and others = 7.71±5.12, p = 0.458).

DISCUSSION

This study observed more female subjects with HIV infection than male subjects. Despite the reducing prevalence rate of HIV infection in Nigeria, the male to female ratio has not changed, females are three times affected than males. This is similar to what was reported by UNAIDS in 2019[10]. In their release, women age 15-49 years were twice affected as men of the same age group. Also, in the same release, women age 20-24 years were three times more affected than men of the same age group. Our findings in this regard can be said to agree with the report from UNAIDS as the greater percentage of our recruited subjects were between the ages of 20 and 34 years. This is also similar to the prevalence reported in most places in the world [11,12]. This group of people is still presently being affected by HIV infection. This may be because they belong to the age range of sexually active members of society. Females occupy the majority of general prevalence of HIV infection of 1.4% in Nigerian adults and adolescence [13]. Females continue to have a greater burden of HIV infection especially in sub-Saharan Africa[14]. There is a greater risk of a female being infected by a positive male than a male being infected from a positive female. Also, women tend to engage in commercial sex activities in which they may allow sexual intercourse without adequate protection for financial gain from men. Males can control this act. The practice of polygamy among Africans could also be a factor, in the sense that, a single HIV positive man may infect all his wives with the virus.

As presented in Table 1, the mean plasma levels of ALT and ALP were found to be significantly higher in males than females. These findings are similar to some reports in the literature. The study by Solomon *et al*.[15] reported a higher serum level of ALP in males than females[16]. This was linked to higher Pack Cell Volume (PCV) in males than females because the study observed a linear correlation between ALT and hemoglobin concentration levels. These differences, though pack cell volume was not done in our subjects can also be linked as such because, naturally males do have higher pack cell volume than females. Other risk factors for elevated serum ALT such as obesity, liver pathology, hypertension, diabetes and the use of other potential hepatotoxic drugs were excluded in our recruited subjects. A number of antiretroviral drugs such as didanosine, stavudine, nevirapine and efavirenz have been linked to hepatotoxicity with associated elevated liver enzymes[17,18]. This, however, may not be an explanation as to why we have elevated ALT higher in males than females as almost equal number of males and females were placed on the same antiretroviral regimen. It may therefore be said that, males are more engaged in the consumption of hepatotoxic chemicals such as a local concussion or any other alcoholic drinks. This can as well explain raised plasma ALP observed in our study among male subjects. A check on plasma Glutamyl Transferase (GGT) enzyme would have helped to a beat more certain about this raised ALP value in male subjects. When considering reference interval, the mean plasma levels of ALP across genders is lower than lower limit of normal of 30 IU L^{-1}. It is of note in this regard that the reference values for most parameters that we use locally were borrowed from previous researches that didn't consider our biological peculiarities. This finding, we consider a pointer to the need to design our own local reference values for not only ALP but other biochemical parameters. In this, those factors that can naturally affect some biochemical parameters such as environmental and genetic factors can be taken into consideration[19].

Table 2: Mean distribution of enzymes among different age groups

Variables	N	Mean	X^2	Df	p-value
AST					
20-34	96	34.93±17.96	769.72	3	0.408
35-44	92	28.36±16.85			
45-64	65	29.43±15.43			
≥65	7	29.00±22.39			
ALT					
20-34	96	22.67±15.87	197.03	3	0.592
35-44	92	22.88±17.08			
45-64	65	25.20±21.06			
≥65	7	16.71±08.26			
ALP					
20-34	96	13.22±08.44	122.59	3	0.098
35-44	92	10.66±06.44			
45-64	65	12.91±07.89			
≥65	7	10.57±06.70			

Table 3: Mean distribution of enzymes considering duration (year) of treatment

Variables	N	Mean	X^2	Df	p-value
AST					
<1	12	52.50±23.42	2000.45	3	0.055
1-3	154	29.58±17.61			
>3-5	91	30.99±21.96			
>5	3	24.00±08.19			
ALT					
<1	12	22.00±11.93	263.21	3	0.466
1-3	154	22.05±15.94			
>3-5	91	25.52±20.70			
>5	3	18.00±04.00			
ALP					
<1	12	13.67±9.88	45.994	3	0.504
1-3	154	11.64±7.19			
>3-5	91	12.93±8.14			
>5	3	10.00±6.00			

As demonstrated in Table 2, there were no significant differences in AST, ALT and ALP among different age groups. As observed, reports to support the contrary are scarce in the literature. The factors that are known to influence plasma levels of these enzymes such as liver pathology was clinically ruled out in our study. Plasma ALP is greatly influenced by age, it is known to be higher in children than adults and the release is mainly from osteoblasts which are utilized in bone development. This may also explain why plasma ALP was not different among the age groups because all the recruited subjects were above 20 years of age[20].

Anti-retroviral drugs metabolize largely by hepatic cytochrome P450 activity. Protease inhibitors (PIs) are known to be metabolized by intestinal and hepatic CYP3A[21]. Plasma drug concentrations are improved by CYP3A inhibitors such as cobicistat and ritonavir (RTV)[22]. Despite having the majority of the drugs administered metabolized in the liver as shown in Table 3 there were no significant differences in the liver enzymes when observed along with the duration of treatment. This observation is contrary to the reports of a study by Melashu *et al.*[9] conducted in an Africa country, Ethiopia. In their study it was observed that plasma AST and ALT were elevated in patients on Highly Active Antiretroviral Therapy (HAART) of which duration of therapy was not put into consideration. The subjects selected in their study probably had a longer duration of treatment than our subjects as 98.8% of our subjects studied had taken medication for less than 5 years. However, in their study, the operational set limit for abnormal liver enzymes was 1.25% higher than the upper limit of normal expected. This set limit, we consider to be on the lower side as what is expected and found in the literature is between 3 and 5 times upper reference limit[23,24]. This in a way made diagnosis of abnormal liver enzymes over-diagnosed. If the expected set limits were to be considered there may not be a significant difference in any of the liver enzymes studied. Furthermore, on a close look, researches that reported raised liver enzymes in patients on antiretroviral therapy[6,25] was based on caparison with controls

Table 4: Mean distribution of AST, ALT and ALP among patients on different anti-retroviral regimen

Variables	N	Mean	X^2	df	p-value
AST					
AZT,3TC,EFV	18	34.50±20.82	416.38	6	0.794
AZT,3TC,NVP	24	30.25±29.07			
TDF,FTC,NVP	6	26.50±10.82			
TDF,3TC,ALLUVIA	5	20.00±11.48			
TDF,3TC,NVP	12	40.08±16.93			
TDF,3TC,EFV	8	35.63±09.12			
Others	7	37.29±32.15			
ALT					
AZT,3TC,EFV	18	26.22±23.46	95.632	6	0.934
AZT,3TC,NVP	24	23.11±17.47			
TDF,FTC,NVP	6	22.33±10.69			
TDF,3TC,ALLUVIA	5	14.80±04.55			
TDF,3TC,NVP	12	25.08±20.61			
TDF,3TC,EFV	8	23.25±17.84			
Other	7	22.14±08.57			
ALP					
AZT,3TC,EFV	18	13.00±9.97	55.808	6	0.458
AZT,3TC,NVP	24	12.07±7.62			
TDF,FTC,NVP	6	11.00±5.90			
TDF,3TC,ALLUVIA	5	10.20±6.69			
TDF,3TC,NVP	12	15.58±8.02			
TDF,3TC,EFV	8	13.50±4.24			
Others	7	7.71±5.12			

AZT: Zidovudine, 3TC: Lamivudine, EFV: Efavirenz, NVP: Nevirapine, ALLUVIA: Alluvia-ritonavir boosted lopinavir, FTC: Emtricitabine

(patients not on antiretroviral therapy). In our study, plasma AST and ALT were raised beyond the expected normal limit of which if it were to be compared with controls, the result might be significant as reported in some studies[26,27]. The raised values of these enzymes as also presented in Table 3 was more among patients who had taken medication for less than 5 years. This is evidence to corroborate the occurrence of adverse drug effects of antiretroviral therapy coming more early in the course of the treatment[28]. Adverse drug effects that may be due to antiretroviral therapy may range from mild to life-threatening conditions[29]. They are usually experienced within the first 6-12 weeks of which metabolic toxicities come with prolonged use of antiretroviral therapy[30]. Severe hepatotoxicity is a life-threatening condition that could affect patients on HAART. This is one of the reasons why the slightly raised values in our study should not be overlooked. The degree of toxicity of different regimens of antiretroviral therapy should also be put into consideration in other to categorize patients appropriately. Although the study observed no statistically significant differences when patients of different combination therapy were compared as shown in Table 4.

Majority of patients recruited had only taken medications for less than 5 years. Recruiting patients who had taken antiretroviral drugs for greater number of years would probably have given more strength to the study. Also, determination of plasma Gamma-Glutamyl Transferase (GGT) would have added more values to the study especially in t he area of explaining our findings on ALP.

CONCLUSION

There were no statistically significant differences in plasma levels of AST, ALT and ALP in patients on antiretroviral therapy when linked to the duration of treatment. We recommend, however, that raised values of these enzymes that were observed in patients who had taken medication for less than five years should not be overlooked. It may be a pointer to close monitoring of patients in their early part of the treatment.

SIGNIFICANCE STATEMENT

This study discovered higher plasma values of AST and ALT in male subjects than female subjects. Although, not statistically significant, raised values of AST and ALT among patients who had taken medication for less than 5 years need further investigations. This may be an eye-opener to researchers in the evaluation of the pathogenesis of likely liver damage that may occur as a result of drug administration and its regeneration process.

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REFERENCES

1. Adewole, O.O., S. Eze, Y.E. Betiku, E. Anteyi, I. Wada, Z. Ajuwon, G. Erhabor, 2010. Lipid profile in HIV/AIDS patients in Nigeria. Afr. Health Sci., 10: 144-149.
2. Calza, L., V. Colangeli, R. Manfredi, I. Bon, M.C. Re and P. Viale, 2016. Clinical management of dyslipidaemia associated with combination antiretroviral therapy in HIV-infected patients. J. Antimicrob. Chemother., 71: 1451-1465.
3. Ndashimye, E. and E.J. Arts, 2019. The urgent need for more potent antiretroviral therapy in low-income countries to achieve UNAIDS 90-90-90 and complete eradication of AIDS by 2030. Infect. Dis. Poverty, Vol. 8. 10.1186/s40249-019-0573-1.
4. Heestermans, T., J.L. Browne, S.C. Aitken, S.C. Vervoort and K. Klipstein-Grobusch, 2016. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: A systematic review. BMJ Glob. Health, Vol. 1. 10.1136/bmjgh-2016-000125.
5. da Cunha, J., L.M.F. Maselli, A.C.B. Stern, C. Spada and S.P. Bydlowski, 2015. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. World J. Virol., 4: 56-77.
6. Tesfa, E., D. Siefu, Y. Belayneh and Z. Mekonnen, 2019. Liver enzyme elevation in patients taking HAART compared with treatment naïve controls at Debre Berhan Referral Hospital: A comparative cross-sectional study, Northeast Ethiopia. BMC Res. Notes, Vol. 12. 10.1186/s13104-019-4748-4.
7. Price, J.C. and C.L. Thio, 2010. Liver disease in the HIV-infected individual. Clin. Gastroenterol. Hepatol., 8: 1002-1012.
8. Osakunor, D.N.M., C. Obirikorang, V. Fianu, I. Asare and M. Dakorah, 2015. Hepatic enzyme alterations in HIV patients on antiretroviral therapy: A case-control study in a hospital setting in Ghana. PLoS ONE, Vol. 10. 10.1371/journal.pone. 0134449.
9. Shiferaw, M.B., K.T. Tulu, A.M. Zegeye and A.A. Wubante, 2016. 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 Res. Treat., Vol. 2016. 10.1155/2016/1985452.
10. Fagbamigbe, A.F., S.B. Adebayo and E. Idemudia, 2016. Marital status and HIV prevalence among womenin Nigeria: Ingredients for evidence-based programming. Int. J. Infect. Dis., 48: 57-63.
11. Mabaso, M., Z. Sokhela, N. Mohlabane, B. Chibi, K. Zuma and L. Simbayi, 2018. Determinants of HIV infection among adolescent girls and young women aged 15-24 years in South Africa: A 2012 population-based national household survey. BMC Public Health, Vol. 18. 10.1186/s12889-018-5051-3.
12. Freeman, E. and P. Anglewicz, 2012. HIV prevalence and sexual behaviour at older ages in rural Malawi. Int. J. STD AIDS, 23: 490-496.
13. Badru, T., J. Mwaisaka, H. Khamofu, C. Agbakwuru and O. Adedokun *et al*., 2020. HIV comprehensive knowledge and prevalence among young adolescents in Nigeria: evidence from Akwa Ibom AIDS indicator survey, 2017. BMC Public Health, Vol. 20. 10.1186/s12889-019-7890-y.
14. Kharsany, A.B.M. and Q.A. Karim, 2016. HIV infection and AIDS in sub-saharan Africa: Current status, challenges and opportunities. Open AIDS J., 10: 34-48.
15. Dalhatu, I., D. Onotu, S. Odafe, O. Abiri and H. Debem *et al*., 2017. Outcomes of Nigeria's HIV/AIDS treatment program for patients initiated on antiretroviral treatment between 2004-2012. PLoS ONE, Vol. 12. 10.1371/journal.pone.0170912.
16. Kasia, B.E., E.E. Efemena and P. Prophet, 2020. Assessment of alanine amino transferase (ALT) and alkaline phosphatase (ALP) level amongst apparently healthy students of Niger Delta University. Nig. Del. Med J., 4: 19-26.
17. Neuman, M.G., M. Schneider, R.M. Nanau and C. Parry, 2012. HIV-antiretroviral therapy induced liver, gastrointestinal and pancreatic injury. Int. J. Hepatol., Vol. 2012. 10.1155/2012 /760706.
18. Neff, G.W., J. Dushyantha and K.E. Sherman, 2006. Drug-induced liver injury in HIV patients. Gastroenterol. Hepatol., 2: 430-437.
19. Masuda, M., K. Okuda, D.D. Ikeda, H. Hishigaki and T. Fujiwara, 2015. Interaction of genetic markers associated with serum alkaline phosphatase levels in the Japanese population. Hum. Genome Var., Vol. 2. 10.1038/hgv.2015.19.
20. Turan, S., B. Topcu, İ.Gökce, T. Güran and Z. Atay *et al*., 2011. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. J. Clin. Res. Pediatr. Endocrinol., 3: 7-11.
21. McMillan, J.M., D.A. Cobb, Z. Lin, M.G. Banoub and R.S. Dagur *et al*., 2018. Antiretroviral drug metabolism in humanized PXR-CAR-CYP3A-NOG mice. J. Pharmacol. Exp. Ther., 365: 272-280.
22. Tseng, A., C.A. Hughes, J. Wu, J. Seet and E.J. Phillips, 2017. Cobicistat versus ritonavir: Similar pharmacokinetic enhancers but some important differences. Ann. Pharmacother., 51: 1008-1022.

23. Malakouti, M., A. Kataria, S.K. Ali and S. Schenker, 2017. Elevated liver enzymes in asymptomatic patients-what should I do? J. Clin. Transl. Hepatol., 5: 394-403.
24. Giannini, E.G., R. Testa and V. Savarino, 2005. Liver enzyme alteration: A guide for clinicians. Can. Med. Assoc. J., 172: 367-379.
25. Abubakar, M.G., M. Abduljalil and Y.I. Nasiru, 2014. Changes in liver function enzymes of HIV/AIDS patients treated with antiretroviral drugs (ARVS) in specialist hospital, Sokoto, Nigeria. Niger. J. Basic Appl. Sci., 22: 85-89.
26. Lucien, K., A. Clement, N. Fon, P. Weledji and C. Ndikvu, 2011. 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: 174-178.
27. Ngala, R.A., D. Opoku and G. Asare, 2015. Effects of HIV infection and highly active antiretroviral therapy (HAART) on the liver of HIV patients. Trends Med. Res., 10: 1-11.
28. Mataranyika, P.A., D. Kibuule, F. Kalemeera, H. Kaura, B. Godman and T.W. Rennie, 2018. Liver enzyme elevations in a cohort of HIV/AIDS patients on first-line antiretroviral therapy in Namibia: Findings and implications. Alexandria J. Med., 54: 49-56.
29. Eluwa, G.I., T. Badru and K.J. Akpoigbe, 2012. Adverse drug reactions to antiretroviral therapy (ARVs): Incidence, type and risk factors in Nigeria. BMC Pharmacol. Toxicol., Vol. 12. 10.1186/1472-6904-12-7.
30. Chawla, A., C. Wang, C. Patton, M. Murray, Y. Punekar, A. de Ruiter and C. Steinhart, 2018. A review of long-term toxicity of antiretroviral treatment regimens and implications for an aging population. Infect. Dis. Ther., 7: 183-195.