*Original Article*

# Evaluation of Some Liver Enzymes in HIV/AIDS Patients on Antiretroviral Therapy in University of Abuja Teaching Hospital, Nigeria

*Abriba Simon Peter[1], Gambe Solomom Matthias[1], Chindo Ezekiel[1], Osadolor Humphrey Benedo[2]*

## Abstract

***Background:*** Hepatoxicity is a major complication and side effect of antiretroviral therapy (ART). Unfortunately, such studies in this area of evaluating the adverse drug reaction of ART on the liver hepatocytes are only few in number in Nigeria. ***Objective:*** To determine the levels of some liver enzymes in HIV/AIDS patients on antiretroviral therapy (ART) and as well evaluate their impact on liver hepatocytes. ***Methods:*** This is a hospital-based case-control study. A total of 153 subjects were recruited in the study, and they were divided into three groups: the control group (which consist of apparently healthy subjects), the study group 1 (consist of HIV positive subject not on ART), and study group 2 (consist of HIV/AIDS patients on ART). The liver enzymes Alanine amino Transferase (ALT), Asparate amino Transfarase (AST) and Alkaline Phosphatase (ALP) were determined using enzyme linked spectrophotometric assay methods, according to the manufacturer's specifications. ***Results:*** The mean standard deviation (SD) of ALT and AST activity of the study group 1 showed significant differences when compared with that of the control group $P<0.001$, but the ALP has no significant differences $P>0.05$. In Study group 2, (HIV/AIDS patients on ART) showed significant differences of $P<0.001$ in ALT, AST and ALP. ***Conclusion:*** Some liver enzymes were elevated in subjects on antiretroviral therapy; this elevation could be due to hepatotoxicity of the (ART) used by the HIV/AIDS patients on the liver hepatocytes.

***Keywords:*** HIV/AIDS, antiretroviral therapy, hepatotoxicity, liver enzymes

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## Introduction

Acquired Immunodeficiency Syndrome (AIDS), is a fatal illness caused by a retrovirus known as the human immunodeficiency virus (HIV) which breaks down the immune system, leaving the patient vulnerable to a host of life-threatening opportunistic infections, neurological disorder and unusual malignancies[1]. Antiretroviral Therapy (ART) has significantly reduced morbidity and mortality in persons living with HIV worldwide[2]. An estimated 19.5 million people globally had received ART by 2016[3]. With the introduction and implementation of ART, the life expectancy of individual patients infected with HIV is now said to be approaching that of the general population[4].

However, ART has some adverse effects, especially hepatic damage, which comes along with the treatment[5]; an earlier study showed that the prevalence of liver transaminase elevation among HIV-positive individuals on ART ranged from 14% to 20%[6]. Consistently, evidence has shown that the incidence of hepatic injury in ART-treated patients was increased[5]. However, quite a few other studies indicated that the approved

1. Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bingham University, Karu Nassarawa State, Nigeria.
2. Department of Medical Laboratory Science, College of Health Sciences, University of Benin, Nigeria.

**Correspondence to:** Dr. Abriba Simon Peter, Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bingham University, Karu Nassarawa State, Nigeria. Email: abribasimonpeter@yahoo.com

antiretroviral agents have low liver toxicity and generally are considered to be well tolerated[7,8].

Mechanisms of liver damage among HIV-1 infected patients are multiple, probably attributing to HIV infection itself[9] hepatitis viral co-infections, ART-related hepatotoxicity[10], AIDS related neoplasm[11], or experiencing age-related co-morbid conditions[12]. Hepatitis viral infections, either hepatitis B virus (HBV) or hepatitis C virus (HCV), have been reported to lead to hepatotoxicity[14]. Elevated hepatotoxicity was observed to be associated with ART in HIV/AIDS patients co-infected with HBV or HCV[13]. ART-related hepatotoxicity was also reported in quite a few previous studies[7,12,15].

Although there are many studies focusing on relationship of ART and liver function among HIV-1 infected patients, after extended exposure to antiretroviral therapy, whether the association between ART and hepatic dysfunction remains true is unclear. Moreover, even though most of the previous studies were controlled for baseline liver enzymes level[6,8,10], there were still some studies which had no initial liver function[16] or co-infection with viral hepatitis[5,7,13] reported.

Since ART generally lasts for many years and even for lifetime, the effect of long-term ART on liver function needs to be elucidated; it is crucial to ascertain whether the risks of hepatotoxicity or hepatic impairment are self-limiting, and to help to make adequate and better clinical decision, management and monitoring with better patients' outcome.

## Methods

This hospital-based case-control study was carried out between October 2022 and March 2023. A total of one hundred and fifty-three subjects were involved in the study, Subject below 18 years and above 65 years were excluded from the study, i.e., those between the ages 18-65 years were included in the study. Those who are HIV/AIDS subjects on Antiretroviral therapy (ART) were included and served as study group 2, those who were HIV positive but not on ART, serves as study group 1 while those who are not on any drug and HIV negative were used as control group (apparently healthy). Consent forms were given to the participants and the content or purpose of the study was explained to them and those who were interested signed the form, and as well were recruited for the study. 5 milliliters of blood samples were drawn from each of the subject, the samples were refrigerated at the temperature of 4$^{O}$C until analysis. Prior to specimen collection, demographic information of the participants was obtained through administration of prepared questionnaires. Interpreter was provided for translation where it was necessary. Each questionnaire had a unique participant identification number (PIDN). The first part of the questionnaires contained the bio data of the patients e.g. sex, age etc. The second part consists of duration of the condition and therapy. For reason of privacy, all data were kept confidential in accordance with Declaration of Helsinki. For each participant, only the PIDN was recorded on the laboratory forms (no names). All the filled questionnaires were destroyed after data entry had been completed.

Statistical data analysis was conducted using IBM SPSS Version 25 by one-way analysis of variance (ANOVA), while Student 't' test was used to compare the variables, statistical significance is defined as $p<0.05$.

## Results

In this study, a total of 153 subjects participated in the study, and they are within the Ages of 18-65 years. It was observed that 28.9% i.e. 15 participants in the study groups 1 who are HIV patients not on antiretroviral therapy (ART) fall within the age bracket (36-40yrs), it is then followed by ages (23-30 years) which made up of 25% i.e. 13. In study group 2, who are HIV/AIDS subjects on (ART), it is observed that 33% are within age (26-30 years), 17 in number, followed by age (36-40 years), which is 23.5% and 12 in number. It is observed that age 26-40 years is the highest hit with HIV diseases. The age distribution of participants in the control and study groups is represented in table 1. The study consists of male and female in both the control and the study groups; in the control groups 46% are made up of the male i.e. 23 in number, while 54% are made up of females-27 in number. In study group 1, those who are HIV positive but not on ART, 54.9% are male; there are 28 in number, while the female is made up of 46.2% that is 23 in number. In study group 2, 53.8% are males i.e. 28 in number, while 46.2% are female i.e. 24 in number (Table 2). The values of Alanine amino transferase (ALT) in the control group is 13.68±3.13 U/L while that of the study groups l is

20.19±7.01 U/L when the two mean values were compared, it is observed that there is a significant difference between the two groups, with P value of <0.001. The value of Aspartate amino transferase (AST) in the control groups is 13.82±2.26 U/L, while that of the study group l is 20.11±6.76 U/L. It is observed that there is a significant difference between the two groups (p<0.001). The value of Alkaline phosphatase (ALP) of the control groups is 88.94±14.54 U/L. While that of the study group 1 is 92.03±20.6l U/L, when the values were compared, there was no significant difference between the two groups (p>0.05) (Table 3). The values of Alanine amino transferase (ALT) in the study group 2 is 63.28±39.20 U/L, when it was compared with that of the control group show significant differences of P value <0.001. The value of Aspartate amino transferase (AST) in the study group 2 is 59.26±32.62 U/L, when its value was compared with that of the control group, show significant difference (p<0.001). The value of Alkaline phosphatase (ALP) in the study group 2 is 115.59±31.17U/L, when compared with that of the control group show significant difference between the two groups (p<0.001) (Table 4). To compare the liver enzymes in study 1 (no ART) and study 2 (on ART), we have found that the values of alanine amino transferase (ALT) in the groups show significant difference between the two groups, (p<0.001). The value of aspartate amino transferase (AST) in the two groups show significant differences between the two groups (p<0.001). The value of alkaline phosphatase (ALP) in the two groups shows significant difference between the two groups (p<0.001). It is observed that the enzymes ALT and AST are significantly higher in HIVIAIDS who are on ART, when compared with that of HIV patients not on ART. The values were 3- to 5-folds above upper limit of normal values (Table 5).

**Table 1:** Age distribution of the study participants

| Age groups (years) | Control group | Study group 1 | Study group 2 |
|---|---|---|---|
| 20-25 | 2(4%) | 4(8%) | 5(10%) |
| 26-30 | 12(24%) | 13(25%) | 17(33%) |
| 31-35 | 5(10%) | 7(13%) | 10(20%) |
| 36-40 | 13(26%) | 15(28.9%) | 12(23.5%) |
| 41-45 | 4(8%) | 9(17%) | 4(8%) |
| 46-50 | 5(10%) | 3(6%) | 1(2%) |
| 51-55 | 3(6%) | 1(2%) | 1(2%) |
| 56-60 | 6(12%) | 0(0%) | 1(2%) |
| >60 | 0(0%) | 0(0%) | 0(0%) |
| Total | 50(100%) | 51(100%) | 52(100%) |

% = Percentage

**Table 2:** Sex distribution in the control and study groups

| Sex | Control group | Study group 1 | Study group 2 |
|---|---|---|---|
| Male | 23(46%) | 28(54.9%) | 28(53.8%) |
| Female | 27(54%) | 23(45.1%) | 24(46.2%) |
| Total | 50(100%) | 51(100%) | 52(100%) |

% =Percentage.

**Table 3:** Liver enzymes in the control and study 1 (HIV/AIDS no ART)

| Parameters (U/L) | Control group (n = 50) | Study group 1 (n=51) | z-score | P-value |
|---|---|---|---|---|
| ALT | 13.68±3.12 | 20.19±7.01 | 6.0 | <0.001 |
| AST | 13.82± 14.54 | 20.11±20.61 | 6.24 | <0.001 |
| ALP | 88.94 ± 14.54 | 92.03 ± 20.61 | 0.87 | >0.05 |

U= Unit, L= Liter

**Table 4:** Liver enzymes in the control and study 2 (HIV/AIDS on ART).

| Parameters | Control | Study 2 z-score | P-value | |
|---|---|---|---|---|
| (U/L) | (n=50) | (n=52) | | |
| ALT | 13.68±3.12 | 63.28±39.20 | 7.05 | <0.001 |
| AST | 13.82±2.26 | 59.26±32.62 | 7.52 | <0.001 |
| ALP | 88.94± 14.54 | 115.59±31.17 | 5.49 | <0.001 |

**ALT=** Alanine amino Transferase, **AST**= Aspartate amino Transferase, **ALP**= Alkaline phosphatase, **U**= Unit, **L**= Liter.

**Table 5:** Liver enzymes in study 1 (no ART) and study 2 (on ART)

| Parameter U/L | Study 1 (n=51) | Study 2 (n=52) | z-score | P-value |
|---|---|---|---|---|
| ALT | 20.19 ± 7.01 | 63.28 ± 39.20 | 6.1 | <0.001 |
| AST | 20.11 ± 6.76 | 59.26± 32.62 | 6.4 | <0.001 |
| ALP | 92.03±20.61 | 115.59±31.17 | 4.5 | <0.001 |

U= Unit, L= Liter, ALT= Alanine amino Transferase, AST= Aspartate amino Transferase, ALP= Alkaline phosphatase.

## Discussion

This study showed that some liver enzymes were altered in HIV/AIDS subjects on antiretroviral therapy (ART). The alterations in the liver enzymes suggest the adverse effects of ART on patients or subjects placed on antiretroviral therapy (ART). Since ART preparations are made to inhibit some of the HIV transcription process; it could have produced some adverse drug reactions leading to the elevations of the liver enzymes. Liver enzymes e.g., alanine amino transferase, aspartate amino transferase in the study group 2, that is patients on ART were significantly elevated, this finding is in tandem with some authors who had earlier investigated liver enzymes in HIV/AIDS patients on ART and also suggested a novel mechanism for ART administration to reduce or minimize hepatotoxicity[17].

The liver as a drug metabolizing and detoxifying organs in the body is subject to potential damage from an enormous array of pharmaceuticals and environmental chemicals, which suggested that injury may result from direct toxicity, by hepatic conversion of a xenobiotic to an active toxin or through immune mechanisms, usually by a drug or a metabolite acting as a hapten[18]. Predictable drug reaction may occur in anyone who accumulates a sufficient dose[18]. This may be responsible for the increase in the liver enzymes in infected HIV/AIDS patients on ART in this study. Changes in the mentioned liver enzymes should not be surprising since it is likely that an intact immune response to trail replication is necessary to produce the hepatocellular necrosis and inflammation seen in active hepatitis due to HIV infections and AIDS[19].

The liver enzymes Alanine amino transferase (ALT), Aspartate amino transferase (AST) and Alkaline phosphatase (ALP) of the control group and the study group 1, that is HIV subjects who are not on ART were compared, a significant difference was observed in ALT and AST, while there was no significant difference in the values of ALP; the liver enzymes in study group 2 subject also shows a high significant differences when compared with the control group and study group 1. These findings is in tandem and consistent with other investigators, who found out that liver enzymes of patients on Anti-retroviral therapy, were 3 to 5 fold higher than the normal subjects. However, we suggest that Liver enzymes abnormalities should be interpreted with care; some ART has been found to increase the levels of some liver enzymes[20]. These findings are consistent with previous studies on liver toxicity caused by various antiretroviral drugs such as Nevirapine (NVP), Efavirenz (EFV), and Tenofovir, studies also observed a strong association between drugs and the development of (liver enzyme elevation) emerging within the first 2 years after drug initiation[20,21].

This study did not categorize the subjects on ART into regimen of the drugs they were placed on and as such could not determine which of the ARTs produces the most server adverse effects or drug reaction on the liver hepatocytes; this serves as a limitation in our study.

## Conclusion

Our data suggest that alanine amino transferase, aspartate amino transferase and alkaline phosphatase were elevated in the subjects on ART. Elevation of liver enzymes activities in study group 2 was observed, which suggest hepatotoxicity effects of ART on liver hepatocytes; therefore, we suggest that a novel mechanism of ART administration be followed in order to achieve less hepatotoxicity of the liver hepatocytes and to avoid hepatic damage risk.

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**Author's contribution:** ASP The principal investigator: responsible for research concept and selection of research title, wrote the research protocol and proposal; analyzed and collated the research data; also carried out the statistical analysis of the data along with the second author, documented and interpreted the data, and wrote the manuscript.; SMG Responsible for collation of data and involved in statistical analysis; CE Involved in the sample processing and data collation; OHB Involved in the selection of the research title and supervision of the research work and carried out statistical analysis of data. All the authors read and approved the final draft of this manuscript.

## References


1. Grunfeld C, Kotler DP, Shigenaga JK, Doerrler W, Tierney A, Wang J, Pierson RN Jr, Feingold KR. Circulating interferon-alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med. 1991;90(2):154-62.
2. Wada N, Jacobson LR., Cohen M. Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome- negative individuals followed simultaneously in long-term cohort studies 1984-2008. Am J Epidemiol. 2013;177:116-25.
3. UNAIDS. Global AIDS. 2017.
4. Bern **JS,** Kasbekar N. Highly active antiretroviral therapy and the kidney: an update on antiretroviral medications for Nephrologist. Clin J Am Soc Nephrol 2006;1:117-29.
5. Neukam K, Mira JA, Collado A. Liver Toxicity of Current Antiretroviral Regimens in HIV-infected Patients withChronic Viral Hepatitis in a real-life setting: The HEPAVIR SEG-HEP Cohort. PLoS One. 2916;11:e0148104.
6. Rodriguez-Rosado R, Garcia-Samaniego J, Soviano V. Hepatotoxicity after introduction of highly active antiretroviral therapy. AIDS. 1998;12:1256.
7. Vispo E, Fernandez-Montero JV, Labarga P. Low risk of liver toxicity using the most recently approved antiretroviral agents but still increased in HIV- hepatitis C virus coinfected patients. AIDS. 2013;27:1187-8.
8. Palacios R, Vergara S, Rivero A. Low incidence of severe liver events in HIV patients with and without hepatitis C or B co-infection receiving Lopinavir/ Ritonavir. HIV Clin Trial. 2006;7:319-23.
9. Towner WJ, Xu L, Leyden WA. The effect of HIV infection, immunodeficiency, and antiretroviral therapy on the risk of hepatic dysfunction. J Acquir Defic Syndr. 2012;60:321-7.
10. Moodie EE, Pant Pai N, Klein MB. Is antiretroviral therapy causing long-term liver damage? A comparative analysis of HIV-mono-infected and HIV/Hepatitis C Cohort. PLoS One. 2009;4:e4517.
11. Lefkowitch JH. Pathology of AIDS-Related liver disease. Dig Dis. 1994;12:321-30.
12. Deek SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med. 2011;62:141-55.
13. Heil EL, Townsent ML, Shipp K. Incidence of severe Hepatotoxicity Related to Antiretroviral therapy in HIV/HCV coinfected patients. AIDS Res Treat. 2010;2010:1-4.
14. Kalyesubula R, Kagimu M, Opio KC. Hepatotoxicity from a first line antiretroviral therapy: an experience from a resource limited setting. Afr Health Sci. 2011;11:16-23.
15. Logan S., Rodger A., Maynard-Smith L. Prevalence of significant liver disease in human immunodeficiency virus-infected patients exposed to Didanosine: a cross sectional study. World J Hepatol. 2016;8:1623-8.
16. Dusingize JC, Hoover DR, Shi Q, Mutimura E, Rudakemwa E, Ndacyayisenga V, et al. Association of Abnormal Liver Function Parameters with HIV Serostatus and CD4 Count in Antiretroviral-Naive Rwandan Women. AIDS Res Hum Retroviruses. 2015;31(7):723-30.
17. Nu Núñez MJ, Martín-Carbonero L, Moreno V, Valencia E, Garcia-Samaniego J, Castillo JG, et al. Impact of antiretroviral treatment-related toxicities on hospital admissions in HIV-infected patients. AIDS Res Hum Retroviruses. 2006;22(9):825-9.
18. Lee WM. Acute liver failure. N Engl J Med. 1993;329(25):1862-72.
19. Lee WM. Review article: drug-induced hepatotoxicity. Aliment Pharmacol Ther. 1993;7(5):477-85.
20. Gisolf EH, Dreezen C, Danner SA, Weel JL, Weverling GJ; Prometheus Study Group. Risk factors for hepatotoxicity in HIV-1-infected patients receiving ritonavir and saquinavir with or without stavudine. Prometheus Study Group. Clin Infect Dis. 2000;31(5):1234-9.
21. Kovari H, Sabin CA, Ledergerber B, Ryom L, Reiss P, Law M, et al. Antiretroviral Drugs and Risk of Chronic Alanine Aminotransferase Elevation in Human Immunodeficiency Virus (HIV)-Monoinfected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study. Open Forum Infect Dis. 2016;3(1):ofw009.