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Gender Comparison Of Alpha-Fetoprotein, CD4, Albumin and Some Liver Enzymes in Symptomatic HIV Subjects on Antiretroviral Therapy

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Abstract.

The emergence of Human Immunodeficiency Virus (HIV) has remained an issue of global discuss till date as it continues to invade and ravage the world's population despite the efforts been made globally at tackling the impact of the virus. This is a case controlled study designed to comparatively evaluate the alpha-fetoprotein, $CD4^+$ T-cell count, albumin and some liver enzymes activities in male and female symptomatic HIV subjects on antiretroviral therapy in NAUTH Nnewi, South Eastern Nigeria. A total of seventy one (71) participants who were aged between 18 and 60 years attending the voluntary counseling and testing unit (VCT) and antiretroviral therapy unit (ART) of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi as well as 25 control subjects were randomly recruited for the study. CD4 count, alpha fetoprotein (AFP), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase activities were estimated by standard laboratory methods. Results showed no significant differences in the mean values of AFP, CD4 count, albumin, ALT, AST and ALP compared between male and female symptomatic HIV infected individuals on ART and symptomatic HIV infected male and female subjects NOT on ART ($p>0.05$) respectively. Also, there was no significant difference in ALT and AST activities when compared between male and female HIV seronegative control ($p>0.05$) although ALP activity was significantly higher in female control subjects than in males ($p=0.01$). This revealed no gender specific differences in mean values of alpha fetoprotein, albumin, CD4 T-cell count, and liver enzyme activities between male and female HIV infected symptomatic individuals on antiretroviral therapy and symptomatic HIV infected persons NOT on antiretroviral therapy.

KEY WORDS: HIV, CD4 T-cell count, alpha fetoprotein, albumin, liver enzymes, symptomatic HIV infected male and female individuals.

Introduction

The emergence of Human Immunodeficiency Virus (HIV) in 1980 has remained an issue of global discuss till date. HIV continues to invade and ravage the world's population despite the efforts been made globally at tackling the impact of the virus. The World Health Organization (WHO) describes the Human Immunodeficiency Virus (HIV) as a retrovirus affecting the immune system and creating impairment and destruction of defense systems (WHO, 2017). HIV is known to cause acquired immunodeficiency syndrome (AIDS) over time if left untreated. It is transmitted via blood, unsterilized blood products, semen, cervical and vaginal secretions and breast milk (WHO, 2017). Regrettably, approximately 76 million people have become infected with HIV since the start of the epidemic (UNAIDS, 2020).Today, there are approximately 38 million people currently living with HIV, and tens of millions of people have died of AIDS-related causes since the beginning of the epidemic (UNAIDS, 2020). The pathogenesis of HIV infection is a function of the virus life cycle, host cellular environment, and quantity of viruses in the infected individual (Klatt, 2014). HIV pathogenesis is basically a competition between HIV replication and the immune responses of the subject or patient via the cell-mediated and immune-mediated reactions. Having established that the main target of HIV is activated CD4 T lymphocytes (Agosto *et al*., 2014; Ezeugwunne *et al*., 2018) through the depletion of the total host cell CD4+ T-cell pool, via interactions with CD4 and the chemokine co-receptors. This results in host immunodeficiency (Lane, 2010) thereby leaving them vulnerable to various infectious agents. Untreated HIV replication causes progressive $CD4^+$ T cell loss and a wide range of immunological abnormalities, leading to an increased risk of infectious and oncological complications (Deeks *et al*., 2015). On the other, although the introduction of antiretroviral drugs has lead to significant reductions in the development or progression of HIV to AIDS through viral suppression leading to immune recovery, it is not without its own risks and attendant issues. Notable, HIV has negative impacts on several organs and systems of the human body. Several authorities have shown the negative effect of HIV and/or antiretroviral drugs on the kidney, liver, prostate gland, reproductive system and even the cardiovascular system to mention a few (Ezeugwunne *et al*., 2019; Ezeugwunne *et al*., 2019; Danjuma *et al*., 2020). However, our primary interest in this study is to evaluate the impact of HIV and /or antiretroviral drugs on the integrity and synthetic function of the liver as well as on CD4 count with emphasis on the gender differences observed. Studies have shown depleted CD4 cells in HIV seropositive individuals not on ART (Ezeugwunne *et al*., 2018), alterations in liver enzymes and alpha-fetoprotein (Johnkennedy *et al*., 2020), and varying results in view of its impact

on serum albumin level (Ezeugwunne *et al*., 2021). Despite these reports, there are only few works on the gender comparison of alpha-fetoprotein, CD4, albumin and some liver enzymes in symptomatic HIV subjects on antiretroviral therapy, hence the study.

MATERIALS AND METHODS

Study design

This is a case controlled study designed to comparatively evaluate alpha-fetoprotein, CD4, albumin and some liver enzymes in male and female symptomatic HIV subjects on antiretroviral therapy in NAUTH Nnewi, South Eastern Nigeria. A total of seventy one (71) participants who were aged between 18 and 60 years attending the voluntary counseling and testing unit (VCT) and antiretroviral therapy unit (ART) of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi alongside 25 control subjects were randomly recruited for the study and the participants were grouped into:

I) Group A: HIV positive symptomatic subjects on ART (males = 31; females = 14)
II) Group B: HIV positive symptomatic subjects NOT on ART (males = 16; females = 10).
III) Group C: HIV negative control (males = 16; females = 9).

Lamivudine (150 mg twice daily), Stavudine (40mg twice daily) and Nevirapine (200 mg twice daily) were administered to the symptomatic HIV stage 11 male and female subjects on ART.

Inclusion and Exclusion criteria

Male and female participants on triple combination of Stavudine, Lamivudine and Nevirapine based on WHO first line of ART, were included in this study. Only participants who were aged between 18 and 60 years and fulfilled WHO criteria for HIV staging were included in the study. Pregnant women, and subjects who has history of smoking, hypertension, tuberculosis, diabetes, heart and renal diseases and any other clinical condition apart from HIV infection were excluded from the study.

Sample collection

Six millilitres (6mls) of blood sample were collected from each of the participants in each group and dispensed into EDTA and plain containers in appropriate volumes for the determination of the said parameters. The serum samples were stored at -20°C until analyzed.

Laboratory Methods

The participants were screened for HIV infection using Immunoassay and Immunochromatographic method. Antibodies to HIV-1 and HIV-2 in human plasma were determined using Abbott determine TM HIV -1 andHIV-2 kit, which is an in-vitro visually read immunoassay (Abbott Japan Co.Ltd.Tokyo, Japan) and HIV-1 and 2 STAT-PAK Assay kit, which is an Immunochromatographic test for the quantitative detection of antibodies to HIV-1 and HIV-2 in Human plasma (CHEMBIO Diagnostic system, Inc, New York, USA). CD4+T cells counts was achieved by using Cyflow counting system described by Ezeugwunne *et al*., (2018). Serum albumin concentration was determined using the method of Doumas and Watson (1971). Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) activities were estimated according to the method of Reitman and Frankel, (1957). Alkaline phosphatase activity was assayed for using the method described by Bessey *et al.* (1946). Serum alpha feto protein was determined by enzyme linked immunosorbent assay (ELISA)**.**

Informed consent and Ethical Approval

Informed consent of participants was properly sort and obtained. Ethical approval for the research was obtained from Ethical Committee, Nnamdi Azikiwe University Nnewi, Anambra State, Nigeria.

Statistical analysis

Results were expressed as mean $\pm$ SD and the data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 software The data were presented as mean± SD and the mean values of the control and test group were compared by Students t-test. Confidence limit was chosen at 95% ($P<0.05$) and $P< 0.05$ was regarded as significant.

RESULTS

Group comparison between symptomatic male and female HIV infected subjects on ART, HIV infected subjects NOT on ART and HIV negative control showed that serum AFP (ng/ml), Albumin (g/dl) and CD4+ count values were not significantly different when observed ($p>0.05$). See table 1.

There were no significant differences in the mean values of ALT, AST and ALP activities when compared between male and female symptomatic HIV infected subjects on ART, and HIV infected subjects NOT on ART ($p>0.05$). However, ALP activity differed significantly when compared between the control groups ($p=0.01$). See table 2.

Table 1: Comparison of mean ±SD serum levels of AFP (ng/ml), Albumin (g/dl), and CD4 (cell/µl) between male A and female B symptomatic HIV/AIDS subjects on ART (A), Not on ART (B) and Control

Variables	AFP (ng/ml)	Albumin (g/l)	$CD4^+$ (cells/µl)
Symptomatic HIV infected subjects on ART Male (n=31) A Female (n=14) B AVs B: F(p value)	4.17±3.55 5.92±4.92 1.40(0.18)	37.68±5.49 39.13±3.73 0.03(0.37)	577.16±352.80 702.50±371.31 0.38(0.28)
Symptomatic HIV infected subjects NOT on ART Male (n=16) A Female (n=10) B AVs B: F(p value)	4.26±2.82 5.15±2.72 7.71(0.14)	33.75±6.48 33.69±5.81 0.00(0.98)	355.00±137.65 446.70±223.26 2.44(0.21)
HIV negative control Male (n=16) A Female (n=9) B AVs B: F(p value)	5.43±4.02 7.32±6.14 1.01(0.36)	38.77±3.59 40.34±3.92 0.01(0.32)	912.75±114.41 880.56±106.67 0.14(0.50)

**For statistically significant result, p<0.05*

Table 2: Comparison of mean ±SD serum activities of AST (IU/L), ALT (IU/L), and ALP (IU/L) between symptomatic HIV/AIDS subjects on ART (A), NOT on ART (B) and Control (C)

Variables	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Symptomatic HIV infected subjects on ART Male (n=31) A Female (n=14) B AVs B: F(p value)	8.06±5.06 12.18±8.79 6.27(0.05)	5.12±4.45 7.37±5.36 0.70(0.15)	39.75±15.37 42.16±11.29 1.03(0.60)
Symptomatic HIV infected subjects NOT on ART Male (n=16) A Female (n=10) B AVs B: F(p value)	9.33±8.15 11.22±6.12 0.11(0.54)	6.39±5.19 9.52±5.13 0.51(0.15)	33.75±6.48 43.02±11.54 2.50(0.90)
HIV negative control Male (n=16) A Female (n=9) B AVs B: F(p value)	4.93±2.09 9.37±13.09 6.03(0.19)	2.21±2.29 2.63±2.90 0.01(0.69)	32.43±6.27 45.57±14.92 9.19(0.01)*

**For statistically significant result, p<0.05*

DISCUSSION

HIV infection has been an issue of public discuss among scholars globally as a result of its negative impact on various organs and system of the human body. More so, the accessibility of antiretroviral drugs tends to pose a threat towards the eradication of HIV infection especially in low income and developing countries of Africa such as Nigeria.

In this study, there were no significant differences in the mean values of alpha fetoprotein; albumin and CD4 in symptomatic HIV infected males on ART, infected HIV males NOT on drug and control subjects AST when compared with the values observed in the female counterpart respectively. AFP is an important tumor biomarker in diagnosis of liver, breast, gastric, rectal, prostate and ovarian cancer with more than 70% of liver cancer patients showing elevated level of serum AFP (Naz *et al*., 2018). Elevated level of Alpha-Fetoprotein (AFP) is useful in diagnosis of hepatocellular carcinoma which is gradually becoming common among the HIV infected population. In hepatocellular carcinoma patients AFP serum concentrations of 400-500 ng/ml are determined to be diagnostic (Naz *et al*., 2018). Usually, after delivery, blood level of AFP decreases to 0.1 mg/ml and in normal adults it may be found only at very low concentrations (5–10 ng/ml) (Ruoslahti and Seppala, 1972). In this study we found mean values of AFP among the male and female symptomatic HIV infected subjects on ART, HIV infected subjects NOT on ART as well as the HIV seronegative control group of <8 ng/ml which falls within normal reference range and hence may be suggestive of the absence of hepatocellular carcinoma among the studied groups. Alpha-fetoprotein represents the most prominent oncobiomarker used for the early diagnosis of HCC and monitoring of the tumor progression and metastasis, assessment of the cancer prognosis and successfulness of antitumor therapeutic measures (Terentiev and Moldogazieva, 2013).

Serum albumin is an important marker for the assessment of the synthetic functionality of the liver. In this study, despite the fact that the mean values of serum albumin did not differ significantly when compared between the male and female symptomatic HIV infected participants on ART, their mean values (37.4 – 39.1 g/l) fell within normal values in preference to those NOT on ART characterized by hypoalbuminemia. It follows therefore that the male and female subjects on ART experienced an immune recovery whereas in the case of those NOT on ART, there was a further worsening or progression of the disease. This finding corroborates well with previous report (Ezeugwunne *et al*., 2021). This finding is further strengthened by the documented values of CD4 T cell among the subjects in the present work. The $CD4^+$ T cell counts are the primary target of HIV infection because of the affinity of the virus to the CD4 surface marker. Infection with HIV leads to a progressive impairment of cellular functions,

which is characterized by a gradual decline in peripheral blood CD4+ T cell counts levels (Ezeugwunne *et al*., 2018).

The present study showed that the mean activities of ALT, AST and ALP did not differ significantly when compared between male and female symptomatic HIV infected individuals on ART, and between male and female symptomatic HIV infected persons NOT on ART, although the values of these enzymes as observed among the studied participants were normal. This is in contrast with the previous report of Atiba and colleagues who documented significant differences in mean enzyme activities of ALT and AST compared between male and female HIV infected subjects (Atiba *et al*., 2021). Furthermore, comparison between male and female HIV seronegative control showed no significant alterations in ALT and AST activities but revealed significant higher mean value of ALP activity in female control than in the male control subjects.

CONCLUSION

This study has shown no gender specific differences in mean values of alpha fetoprotein, albumin, CD4 T-cell count, and liver enzyme activities between male and female HIV infected symptomatic individuals on antiretroviral therapy and symptomatic HIV infected persons NOT on antiretroviral therapy.

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