

Alterations of alpha fetoprotein and some liver enzymes, in HIV patients undergoing antiretroviral therapy at Federal Medical Centre, Owerri

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Abstract.

Aim: This study is therefore aimed at evaluating the serum level of alpha fetoprotein and liver enzymes in HIV patients undergoing antiretroviral therapy at Federal Medical Centre, Owerri. **Materials and method:** A total of one hundred and fifty subjects which comprised 50 HIV patients on antiretroviral therapy, 50 HIV patients not yet on antiretroviral therapy and 50 healthy subjects as control were used in the study. The liver enzymes and alpha fetoprotein serum levels were determined using colorimetric end-point method and ELISA technique, respectively. Statistical analysis was performed on Statistical Package for Social Science (SPSS) windows version 20.0. Test of significance was determined using the student's t-test and the statistical significance was set up at $p < 0.05$. **Results:** Results obtained showed a significant increase ($p < 0.05$) in alpha fetoprotein ($4.64 \pm 4.42 \text{ ng/ml}$), Aspartate aminotransferase ($13.3 \pm 8.10 \text{ iu/L}$), Alanine Aminotransferase ($7.58 \pm 3.56 \text{ iu/L}$) and alkaline phosphatase ($68.73 \pm 54.95 \text{ iu/L}$) of the HIV positive patients when compared with to their controls ($1.43 \pm 1.53 \text{ ng/ml}$), ($5.75 \pm 3.03 \text{ iu/L}$), ($3.85 \pm 2.33 \text{ iu/L}$) ($25.9 \pm 9.17 \text{ iu/L}$) respectively. There were no significant difference ($P > 0.05$) in the mean value of the alpha fetoprotein of those already in ART ($5.91 \pm 5.60 \text{ ng/ml}$) when compared with the mean value seen in those not on the therapy ($3.36 \pm 2.10 \text{ ng/ml}$). Also, when compared according to duration of therapy, a significant increase was seen at $P > 0.05$ in all the parameters. This study inferred that long time use of these antiretrovirals has a damaging effect on the liver but can't possibly cause hepatocellular carcinoma except in the presence of other risk factors. Thus, the intake of the drug should be strictly under the doctor's prescription and monitoring.

Key words: Alpha Fetoprotein, Liver Enzymes, HIV, Antiretroviral therapy

Introduction

Human Immunodeficiency Virus (HIV) is a blood-borne virus which is transmitted through direct contact with an infected mucosal membrane or bodily fluids such as blood and semen. It can also be transmitted through sexual intercourse, shared intravenous drug paraphernalia, and

mother-to-child transmission, which can occur during the birth process or during breastfeeding. Infection with the human immunodeficiency virus (HIV) causes Acquired Immunodeficiency Syndrome (AIDS), which affects the cells of the immune system, and destroys or impairs their function[1].

The virus belongs to a class of viruses called retroviruses and more specifically, a subgroup called lentiviruses, or viruses that cause disease slowly[2].

HIV cannot replicate on its own, so in order to make new copies of itself, it must infect cells of the human immune system, called CD4 cells[3]. CD4 cells are white blood cells that play a central role in responding to infections in the body. Over time, CD4 cells are killed by HIV and the body's ability to recognise and fight some types of infection begins to decline slowly losing its ability to fight other infections and diseases, and ultimately leading to "immune deficiency"[4]. Immunodeficient people are prone to opportunistic infections and cancers. There is no cure or vaccine currently available, but the availability of effective antiretroviral therapy has significantly decreased mortality and increased survival times of HIV-infected people in high-income countries[5]

Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV[6]. Different classes of antiretroviral drugs act at different stages of the HIV life cycle to stop HIV from replicating. Combination of several (typically three or four) antiretroviral drugs is known as Highly Active Anti-Retroviral Therapy (HAART) [3]. The life expectancy of a person who carries the HIV virus is now approaching that of a person that tests negative for the virus, as long as they adhere to the combination of medication[6].

The liver is the largest internal organ and is situated in the upper right-hand side of the abdomen, protected by the ribs[7].

Although a healthy liver is important to everybody, it is especially important to people with HIV, not least because the liver plays an important role in how the body processes anti-HIV drugs and other drugs (Graham *et al.*, 2007).

Even though HIV drugs are intended to do our health good, the liver recognizes them as toxic compounds[8]. Working with the kidneys and other organs, the liver processes these drugs to render them safer. In the process, the liver can become "overworked," which can lead to liver damage. Antiretrovirals may then raise liver enzyme levels; Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) and Alkaline Phosphatase (ALP). These liver enzymes are secreted into the body fluids on elevation and are therefore used in the assessment of the liver function [9]

Alpha-fetoprotein (AFP) is a plasma protein produced by the embryonic yolk sac and the fetal liver. AFP content in fetal serum is high and gradually decreases to the level of adults after birth [10]. An elevated serum alpha fetoprotein level serves as a tumor marker in identification of cancers[11].

With the availability of highly active antiretroviral treatment (HAART) in 1996, a remarkable decrease in HIV-related morbidity and mortality has been observed. This decline has been associated with a relative significant increase in morbidity and mortality related to many different non-HIV-related diseases, such as chronic liver diseases. Also HIV-infected patients are at enhanced risk of several cancers compared to the general population[12].

Though HIV has become a chronic condition in which progression to AIDS is increasingly rare since the availability of antiretroviral therapy (ART) yet non-AIDS-related causes of morbidity and mortality are becoming increasingly prevalent in HIV-infected patients on ART[13]. There is therefore the need to establish the relationship between the use of these antiretrovirals and alpha feto protein as well as liver enzymes. However, the relationship of antiretroviral drugs to alpha feto protein and liver enzymes is not clear.

Hence, it is of great importance to determine the status of some alpha feto protein as well as liver enzymes among HIV positive subjects

MATERIALS AND METHODS

Experimental Design

The subjects were grouped into 50 HIV patients who have not started receiving antiretroviral therapy. 50 HIV positive patients on antiretroviral therapy and 50 apparently healthy individuals without any evidence of HIV and thus served as control.

Sample Collection

Five (5) milliliters of blood sample was collected by standard venopuncture method[15] from each participant and was dispensed into dry bottle. This was centrifuged to get the serum for the analysis alpha feto protein and liver enzymes

The Serum alpha feto protein was determined by enzyme linked immunoabsorbent assay (ELISA). While Determination of Serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were by Colorimetric end point reaction Method [15]. Determination of Serum Alkaline Phosphatase (ALP) by Colorimetric end point method [16]

Statistical Analysis

The values were expressed as mean \pm standard deviation. The significant difference between the mean value of control and experimental group was determined by one way analysis of variance (ANOVA) with post hoc t-test. $P < 0.05$ was considered as statistically significant.

RESULTS

The results and analysis are shown in the tables below:

Table 4.1: The serum levels of AFP, AST, ALT and ALP in HIV patients and controls.

Parameters	HIV patients (n=40)	Controls (n=20)	t-value	P-value
AFP (ng/ml)	4.64±4.42	1.43±1.53	3.097	0.003
AST (iu/L)	13.3±8.10	5.75±3.03	4.179	0.0002
ALT (iu/L)	7.58±3.56	3.85±2.33	3.963	0.0001
ALP (iu/L)	68.73±54.95	25.9±9.17	3.403	0.001

P < 0.05 = Statistically Significant

Table 4.2: The serum levels of AFP, AST, ALT and ALP in HIV patients on ART and those not on ART.

Parameters	HIV patients on ART (n=20)	HIV patients not on ART (n=20)	t-value	P-value
AFP (ng/ml)	5.91±5.60	3.36±2.10	1.858	0.07
AST (iu/L)	16.2±8.93	10.4±5.88	2.365	0.02
ALT (iu/L)	8.8±4.13	6.35±2.29	2.262	0.03
ALP (iu/L)	96.4±57.56	41.05±34.55	3.590	0.0009

P < 0.05 = Statistically Significant

Table 4.3: The serum levels of AFP, AST, ALT and ALP in HIV patients on ART according to the duration of therapy.

Parameters	4-8 weeks (n=6)	9-12 weeks (n=6)	>12 weeks (n=8)	P-value
AFP (ng/ml)	0.72±1.00	2.88±1.97	12.08±3.11	0.00
AST (iu/L)	6.0±3.92	14.83±4.74	24.88±4.04	0.000003
ALT (iu/L)	4.33±2.56	8.33±1.37	12.5±2.74	0.00007
ALP (iu/L)	36.17±7.58	73.33±22.39	158.88±29.02	0.000

P < 0.05 = Statistically Significant

Discussion

HIV infection affects approximately 35 million persons worldwide. Progression to advanced liver disease remains a leading cause of death among HIV-infected persons. Though mortality from HIV complications has been dramatically reduced wherever effective combination antiretroviral therapy is utilized, there has been little impact on liver related mortality. Liver disease still remains an important contributor to morbidity and mortality among those with HIV infection [17]

This study has shown that there was a significant increase ($p < 0.05$) in the serum level of liver enzymes in HIV patients when compared with apparently healthy subjects (control). Further investigation reveals that the elevation in the liver enzymes was higher in HIV patients already in antiretroviral therapy. This agrees with the work of Campell [18], which reported that liver enzymes elevations are frequently in HIV- infected patients, especially those treated with HAART. This significant increase seen in HIV patients treated with HAART could be linked to mitochondrial toxicity which is caused by the drug [19]. Mitochondrial toxicity, causes damage and a significant decrease to the mitochondria of the body cells because the drugs interfere with the enzyme needed in the production of mitochondria which could manifest as lactic acidosis, in which there is a build-up of lactic acid in the tissues of the body leading to loss of energy, organ failure, and eventually death [20].

Some increases in liver enzymes were also observed in some HIV patients not yet on ART which is in agreement with other works [21]. This may be due to direct inflammation induced by the HIV virus on the liver cell. It may also be due to gall bladder disease, alcohol and infection with bacterial or other opportunistic agents since viral hepatitis coinfecting patients were excluded.

Alpha fetoprotein is a sensitive marker employed in the diagnosis of hepatocellular carcinoma. It is usually produced whenever liver cells are regenerating with values between 100-350 ng/ml suggesting hepatocellular carcinoma. Hepatocellular carcinoma (HCC) is a concern among individuals with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). It was observed from this study that there were slight increases in the level of AFP in HIV patients on ART, but wasn't significant when compared with those not on ART. This agrees with the work of Abelev [23] which states that Serum AFP levels may also be raised in chronic liver disease with high levels of hepatocyte regeneration but remain low in the majority of patients with cirrhosis in the absence of HCC, thus, AFP levels could still be low even when the liver enzymes are elevated.

The insignificant rise in AFP of HIV patients on ART when compared with those not yet on ART proves that the use of antiretrovirals could reduce the risk of AIDS-defining cancers (ADC). HIV infection leads to a weakened immune system and a lower number, or count, of CD4+ T cells that help fight infection. This makes it more likely that people living with HIV will be infected with cancer-causing viruses, such as human papillomavirus and Kaposi sarcoma herpesvirus. Treatment with combination antiretroviral treatment (cART), which means using more than 1 drug to fight HIV infection and maintain the immune system, leads to reduced risk

of infections and HIV-associated cancers such as Kaposi sarcoma and non-Hodgkin lymphoma [24]. They suggested from their study that antiretrovirals may confer additional anti-cancer benefits other than maintaining immune function and went further to state that protease inhibitor (PI) agents have been shown to confer a broad-spectrum of anti-cancer properties.

The risk of some non-AIDS defining malignancies (NADM) which may likely occur in HIV positive persons could be unrelated to ART use and rather attributed to coinfection with hepatitis virus, as this poses a higher risk of developing liver cancer. Also smoking, alcoholism and tobacco use could as well be causative factors.

In Conclusion this study shows that long time administration of antiretroviral drugs could be deleterious to the basic functions of the liver as there is a significant increase in the level of the alkaline phosphatase and transaminases which indicates liver damage. This effect is of course expected to be higher in HIV positive patients who already have liver damage from other sources before commencing the therapy. Also this antiretroviral drugs tend to reduce the risk of AIDS-defining cancers (ADC) expected in HIV positive patients, by boosting the immune system, and this could be helpful if the therapy in commenced early enough. The basic claim of high risk of cancers, mostly NADMs, could be attributed to other factors mostly, co infection with hepatitis virus.

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