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Original Research Article

The Effects of Highly Active Antiretroviral Therapy on the Activities of Some Liver Enzymes and the Concentrations of Protein and Albumin in HIV Positive Patients in Nsukka South East Nigeria

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ABSTRACT

Some biological changes are observed during human immuno deficiency virus (HIV) infection. Once cluster of differentiation 4 ($CD4^+$) count decreased to 500 cells/mm^3 (highly active antiretroviral therapy) (HAART) is initiated. This work tried to elucidate the effect of HAART on some of the biochemical changes caused by HIV infection. 63 subjects comprising, 20 apparently healthy control subjects and 43 HIV positive subjects ready to be placed on HAART (these subjects attended HIV clinic in Bishop Shanahan Hospital Nsukka) were recruited for the study. A known volume of blood, 10ml was collected from each subject through venepuncture prior to the initiation of HAART (basal sample) then 4 and 8 months into the administration of HAART. The activities and concentrations of the following biochemical parameters: Aspartate amino transferase (AST), Alanine, amino transferase (ALT), total protein and albumin, were determined. $CD4^+$ count was also determined at each presentation. The results showed that $CD4^+$ count increased significantly from baseline to 8 months into treatment ($p < 0.05$), ALT and AST increased from baseline to 4 months into treatment, but decreased by the 8th month, (ALT: $p < 0.05$) (AST: $p > 0.05$).
Total protein and albumin increased significantly from baseline to 8 months into treatment ($p < 0.05$). Even though the studied parameters improved because of treatment they were still significantly different from the observations made for the healthy control subjects ($p < 0.05$). Hence treatment with HAART amounted to a positive prognosis for HIV/AIDS infection as it concerns liver enzymes and plasma protein and albumin.

Key words: HIV/AIDS, HAART, $CD4^+$, AST, ALT, Total Protein, Albumin.

INTRODUCTION

The HIV/AIDS (human immunodeficiency virus/ acquired immunodeficiency syndrome) pandemic has been terrorizing humanity over the past three decades. It has undermined the health of so many people, consequently affecting adversely, the work force and the economic stability of so many countries all over the world. World Health Organization (WHO) and United Nations Programme on AIDS (UNAIDS), [(1)] estimated that about 33.4 million people worldwide were living with AIDS, with 2.7 million new infections per year. Some biochemical abnormalities accompany infection with human immunodeficiency virus. These changes occur as a result of the complications of the disease itself, for example the body's normal response to infection depletes nutritional stores. Furthermore metabolic stress responses cause catabolism of protein

stores, consequently depleting them. [2,3] Studies have shown that the antioxidant system of the body is adversely affected in HIV infection, and changes in the activities of its components have been documented by several workers. [4] Other studies have also stated that ALT and AST activities usually increase in asymptomatic HIV sero-positive patients, signaling liver involvement in HIV infection. Patients especially at the final stage of AIDS may develop, HIV associated nephropathy (HIVAN) which leads to an increase in their serum creatinine levels. [5] There are also changes in protein concentration especially reflecting a decrease in albumin and an increase in C-reactive protein. [2,6] The current treatment for HIV infection consists of highly active anti retroviral therapy. These drugs which are classified into, Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non nucleoside reverse transcriptase inhibitors (NNRTI), Protease inhibitors (PT), and Fusion inhibitors (FI) were introduced in 1996 to improve the patients' quality of life, reduce HIV viraemia, and possibly prolong the life of the patient. They do not cure the patient of HIV or prevent the return once treatment is stopped. [2]

Since infection with HIV resulted in the deterioration of the general well being of its patients, giving rise to many adverse biochemical changes, it became pertinent that research be geared towards examining the biochemical effects of HAART (Highly active antiretroviral therapy) with a view to determining whether they exert positive or negative effects on the parameters or systems under study, with respect to the population under consideration. A closer look at the anabolism and some liver enzymes of these patients following treatment needed to be taken to appreciate the effects of these drugs as these parameters have been observed to be severely affected by the infection. Hence the aim of the work is to determine the effect of HAART on the some liver marker enzymes (AST and ALT), and plasma protein and albumin.

MATERIALS AND METHODS

Materials

Subjects

Forty three (43) HIV/AIDS subjects, attending the AIDS clinic of Bishop Shanahan Hospital, Nsukka south east Nigeria and twenty (20) apparently healthy subjects who served as controls were recruited for the study. Informed consent was obtained from the participants and ethical clearance was sought for and obtained from Annunciation Hospital ethical clearance committee, Emene Enugu Nigeria.

Methods

Inclusion Criteria

HIV positive patients not yet on antiretroviral therapy but are due to be placed on it by virtue of their $CD4^+$ counts (patients with $CD4^+$ count 500/mm^3 of blood and below were placed on HAART).

Design of the Experiment

All subjects were tested at presentation (after being confirmed positive), 4 months after the initiation of the antiretroviral therapy (Combivir N is the HAART in use in Bishop Shanahan Hospital, it contains zidovudine, lamivudine and nevirapine) and 8 months after. Their $CD4^+$ counts were also estimated, at all the presentations. The subjects were divided into 4 groups as follows:

Group 1 (G1): HAART naïve subjects (forty three HIV positive individuals ripe for HAART initiation).
Group 2 (G2): The same HIV positive subjects four months into treatment with HAART.
Group 3 (G3): The same HIV positive subjects eight months into treatment
Group 4 (G4): Control (twenty apparently healthy individuals).

Specimen Collection, Processing and Storage

Venous blood, five mililitre (5 ml), was aseptically collected from each subject, three mililitre (3 ml) aliquot was allowed to clot and centrifuged at 3000 rpm for 5

minutes, to separate serum from erythrocytes. The serum was pipetted into a clean serum bottle and either analyzed immediately or stored at -4°C for a maximum of 48 hours. A two milliliters (2 ml) amount of the sample was emptied into a sodium EDTA container for $CD4^+$ count. Retroviral screening was done using the requisite methods. $CD4^+$ enumeration was done by the principle of flow cytometry using partec cyflow machine. The activities of AST and A LT and the concentrations of protein and albumin were all estimated by the requisite spectrophotometric methods.

Statistical Analysis

This was done using graph pad prism version 5.

The results were presented as mean ± standard deviation. Differences between the results of the control subjects, and those of HIV positive subjects, before the commencement of HAART, 4 Months and 8 months into treatment, were analyzed using Student's t test at 95% significance. Effects of HAART on the biochemical parameters of HIV positive patients' were analyzed using ANOVA also at 95% level of significance.

RESULTS

EFFECTS OF HAART ON THE ACTIVITIES OF SOME LIVER MARKER ENZYMES AND ON THE CONCENTRATIONS OF PLASMA PROTEIN AND ALBUMIN.

Table 1: shows that mean ± SD of protein and albumin and $CD4^+$ count of control subjects (group 4) 7.83g/dl (SD = 0.34), 5.01g/dl (SD = 0.760) and 1023 cells/ mm^3 (SD=203) were higher than those of groups 1, 2 and 3 who are HIV positive patients. But while the differences between groups 4 and 1 and between groups 4 and 2 were significant ($p < 0.05$) for protein and albumin the difference between groups 4 and 3 was not significant ($p < 0.05$) for both parameters. 0n the other hand for the $CD4^+$ the differences between groups 4 and 1, 4 and 2 and 4 and 3 were significant ($p < 0.05$). In the same table mean ± SD of protein and albumin concentrations and $CD4^+$ count of group 1 HIV positive subject; 6.98g/dl (SD = 0.72), 4.28g/dl (SD = 0.88), 247 cells/ mm^3 (SD = 71) were lower than those of groups 2 and 3 HIV positive subjects ($p < 0.05$). In addition, the table shows that the activities of AST and ALT for the control subjects (group 4): 13-95 IU/L (SD = 1.40), and 8.35 IU/L (SD = 4.20) were lower than those of groups 1, 2 and 3 made up of HIV positive subjects ($p < 0.05$). The activities of AST and ALT for group 1 HIV positive subjects, were higher than those of group 3 HIV positive subjects, but lower than those of group 2 HIV positive subjects, but while the difference was significant for (AST: $p < 0.05$) It was not significant for (ALT: $p < 0.05$).

EFFECT OF HAART ON SOME LIVER MARKER ENZYMES AND PLASMA PROTEIN AND ALBUMIN CONCENTRATIONS OFHIV POSITIVE SUBJECTS.

Table 1: Mean ± SEM OF AST, ALT, PLASMA Protein and Albumin

Groups	$CD4^+$ cells/mm^3	AST(IU/L)	ALT(IU/L)	Plasma protein (g/dl)	Albumin (g/dl)
G1 (43)	247± 71	37.2±15.20	20.21±8.70	6.98±0.72	4.28±0.88
G2(43)	310±107	44.6±24.7	27.162±6.10	7.31±0.47	4.58±0.78
G3(43)	319±139	25.6±4.20	16.14±5.24	7.69±0.71	5.00±0.36
G4(20)	1023±203	13.95±1.40	8.35±4.20	7.83±0.34	5.01±0.76
F(p) value	198.96(0.000)	20.30(0.000)	4.50(0.005)	14.43(0.000)	9.01(0.000)
G1vsG2	0.02*	0.037*	0.113	0.015*	0.055
G1vsG3	0.008*	0.001*	0.352	0.000*	0.000*
G2vsG3	0.740	0.000*	0.013*	0.004*	0.007
G1vsG4	0.000*	0.000*	0.032*	0.000*	0.000*
G2vsG4	0.000*	0.000*	0.001*	0.002*	0.030*
G3vsG4	0.000*	0.009*	0.157	0.401	0.988

*: *Significantly different results.*

DISCUSSION

The results of the work showed that the use of highly active antiretroviral therapy (HAART) led to a steady increase in CD_4^+ count from the HAART naïve stage to eight months into treatment this is supported by the work of Ibe *et al* [(7)] which found out that the use of HAART reduces the replication of HIV, leading to the improvement of $CD4^+$ count.

The liver function markers: alanine amino transferase (ALT) and aspartate amino transferase, (AST) both showed increases from baseline stage to the 4 month of HAART administration, but decreased to below the activities seen in the basal stage after 8 months. However, it is important to state that while these changes were appreciable for ALT, they were not significant for AST. This effect was supported by the works of Drain *et al* [(2)] and Sundaram *et al.* [(8)] which stated that drug metabolism results in increased release of reactive oxygen species which are damaging to tissue and can increase enzymatic activities.

Total protein and albumin concentrations showed steady increases from the HAART naïve stage to the 8 month of the use of HAART. This finding agrees with the work of Chanham *et al* [(9)] which found increased protein and albumin concentration after the initiation HAART in an Indian population.

A possible explanation of the effect seen on these enzymatic activities after the first few months of introduction to HAART is the fact that drug metabolism results in increased release of reactive oxygen species which are damaging to tissues. [(2,8)] The body of the subjects then adjusted to the condition by the eighth month, leading to a seeming recovery stage, this supports a favorable prognosis with the use of HAART.

The concentrations of total protein and albumin increased steadily from HAART naïve stage, through the fourth month, to the eight month of the use of HAART, showing a positive influence of HAART on total protein and albumin concentrations. This agrees with the work of Chanham *et al* [(9)] which showed that in an Indian population, protein and albumin concentrations, increased after initiation of HAART.

It is noteworthy that AST and ALT, showed higher baseline levels and activities for HIV positive subjects than was found in their apparently healthy counterparts. This can be attributed to the fact that the presence of the virus itself and its destructive activities can lead to damages in a crucial organ like the liver leading to increases in the activities of liver function enzymes studied, prior to the use of HAART. This agrees with the work of Maduka, [(10)] which showed that even in asymptomatic HIV positive subjects, the liver already got adversely affected. It also agrees with the work of Mata-Marin *et al*, [(11)] which revealed that increased viral load leads to a direct damage of hepatic cells (direct inflammation or apoptosis) which will invariably increase the activities of AST and ALT.

CONCLUSION

The commencement of HAART for the study population led to an increase in their CD_4^+ count, total protein and albumin. Also the activities of the liver enzymes (AST and ALT) which were already high increased further, by the fourth month, but dropped to below the baseline by the eight month showing a picture of an initial derangement but an attempt towards recovery by the system. All these are indicative of a positive prognosis with regard to HIV/AIDS infection which resulted from the initiation of HAART.

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