Effect of Short and Long Term Exposure of HIV Patients to Highly Active Antiretroviral Therapy (HAART) on Lipid Profile

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Abstract

Aims
HIV infection and the use of highly active antiretroviral therapy (HAART) have been linked to alteration in lipid profile. The hyperlipidemia experienced during HAART appears to be dose and probably time dependent. The purpose of this study was therefore to estimate the lipid profile of South East Nigerian patients exposed to short and long term use of antiretroviral drugs.

Methods
Sixty HIV seropositive patients aged between 20-60 years were entered into this study; twenty (20) of which were on short term and twenty (20) on long term therapy; while another 20 were HAART naïve serving as positive control. Twenty (20) apparently healthy age-matched HIV negative individuals served as negative controls. The HIV patients were all attending HIV clinic of University Nigeria Teaching Hospital (UNTH) Ituku-Ozalla, Enugu. Blood samples were collected from these subjects with informed consent. Ethical clearance was obtained from the Hospital’s Ethics Committee. Estimation of the lipid profile was carried out using standard methods.

Results
The results obtained showed that HIV seropositive subjects on short term HAART had significantly higher mean levels of total cholesterol (7.52±0.78 mmol/L), LDL-c (4.70 mmol/L), TG (3.62±0.078 mmol/L) and significantly reduced HDL-c (0.55±0.10) (p<0.001); while those on long term HAART had significantly increased total cholesterol (5.68±0.35 mmol/L), LDL-c (4.14±0.45 mmol/L), TG (1.97±0.16 mmol/L) and significantly reduced HDL-c (0.75±0.14 mmol/L) when compared with HIV seronegative individuals (p<0.001). The HDL-c of patients on short and long term HAART showed no significant mean difference (p=0.018) while significant differences were seen between their TGs (p=0.0001). The mean value was higher in those on short term HAART. The mean differences of lipid profile short term HAART compared to HAART naïve subjects were significantly increased except the HDL-c, which was significantly reduced (p<0.001) but when the profile of HAART naïve subjects was compared with those on long term HAART only TC and LDL-c had significantly increased differences (p<0.001). The HDL-c did not show any significant difference between HAART naïve and long term HAART (p=0.570)

Conclusion
This study demonstrated that metabolic abnormalities associated with exposure to HAART may increase the risk of cardiovascular disease due to observed lipid profile alterations particularly with decreased HDL-c.

Key Words: HAART; Short Term; Long Term; Seropositive; Lipid Profile; South East Nigeria

Introduction
HIV is a lentivirus (a member of the family Retroviridae) which slowly weakens immune system by invading and destroying immune cells that defends the body against infections. Till date no definite drug has been developed to cure this disease since its discovery in early 80s. The advent of antiretroviral drugs ARV/HAART has been a promising means through which ameliorating of this life threatening disease is achieved [1,2].

ARV/HAART treatment is aimed towards prolonging survival of infected individuals while maintaining an acceptable quality of life; to restore and protect their immune functioning by allowing the CD4 cells to replenish their numbers, to ensure maximum and lasting control of the amounts of HIV in the body of infected individuals, and to reduce HIV related illnesses and deaths. Despite this good goal and achievements with ARV/HAART, a number of metabolic disturbances have been observed in the course of treatment.

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treatment with these drugs. Lipid metabolism has been observed as one of the major altered pathways in HIV infected and AIDS patients [3-7]. These disturbances are highly noticeable especially during ARV/HAART treatments. Domingo et al. [8] reported that HAART treatment results in lipid disturbances in which there were increases in ‘bad cholesterol’ LDL-c and decreases in good cholesterol HDL-c which is a hallmark of risk of cardiovascular diseases. This hyperlipidemia during HAART appears to be dose and probably time dependent.

The major lipids in human plasma include cholesterol, triglycerides and phospholipids which combine with apoproteins to form lipoproteins that are released into the blood where they play important roles in transport and metabolism of lipids like VLDL, IDL, LDL, and HDL [9]. High LDL and lower concentrations of functional HDL are strongly associated with cardiovascular diseases (CVDs) as these promote atheroma development in arteries. LDLS are therefore often called ‘bad cholesterol’ because of its association with atheroma formation. HDL particles are thought to transport cholesterol back to the liver for excretion or to other tissues that use cholesterol to synthesize hormones in a process known as reverse cholesterol transport [10]. Gordon et al. [11] reported that large number of large HDL particles correlates with better health outcomes whereas small number of HDL particles is reported to be independently associated with atheromaous disease progression within the arteries and therefore the term ‘good cholesterol’. Increased levels of TC, LDL-c and reduced HDL-c in patients on HAART, which are associated with increased risk of CVDs have been reported [12,13]. Hypertriglyceridemia has been found to be the most prevalent of dyslipidemia in HIV patients and this is found in nearly 3-4% of patients with HIV, and second most common is hypercholesterolemia [14-17]. Recent studies have suggested that genetic factors may also contribute to hyperlipidemia in HIV patients [18]; this view was also shared with Donald et al. [19] who reported that there was a substantial individual variation in the response to specific antiviral agents which is related to both genetic susceptibility and environmental factors. The information on lipid profile in Nigeria patients (precisely South East) receiving HAART is scanty, and especially its level following short and long term treatments. Domingo et al. [8] reported that HAART treatment results in lipid disturbances in which there were increases in ‘bad cholesterol’ LDL-c and decreases in good cholesterol HDL-c which is a hallmark of risk of cardiovascular diseases. This hyperlipidemia during HAART appears to be dose and probably time dependent.

Materials and Methods

Eighty (80) subjects, subdivided into four groups were entered into this study with informed consent. Ethical approval was given by the Ethics Committee of the Teaching Hospital. The first group (negative control) consisted of twenty (20) HIV seronegative subjects. The second group (positive control) consisted of twenty (20) HIV seropositive subjects who were not on HAART. The third group was made up of twenty (20) HIV seropositive subjects on short term HAART (0-6 months), and fourth group was of twenty (20) HIV seropositive subjects on long term HAART (>1 year). The blood samples analyzed were collected from these patients attending HIV clinic at UNTH Ituku-Ozalla, Enugu and non HIV positive individual voluntarily.

Inclusion criteria for enrollment of patients for the study specified that subjects must: have laboratory evidence of HIV infection (for second, third and fourth groups); and have laboratory evidence of not being HIV positive (for first group). Exclusion criteria specified that subjects must: not have previous history of ARV therapy (second group); and not have other complications or disease process.

Sample Collection

Fasting blood samples were collected from these patients by a clean venepuncture from the antecubital vein using a 5ml disposal syringe and needle under aseptic conditions. The blood samples were collected with minimum stasis. About 3ml of blood were collected into sterile plain tubes. The blood samples were allowed to clot and were centrifuged to obtain the sera. The sera were separated into sterile tubes and were used to assay for total cholesterol, triglyceride, HDL-c levels. Haemolysis of sample was carefully avoided. The separated samples were stored and the analyses were carried out within 3 days of sample collection.

Analyses of Collected Samples

Enzymatic-spectrophotometric estimation of serum cholesterol was done using cholesterol oxidase/peroxidase method [20]. The reagent kits were produced by Bio-system SA Barcelona, Spain. Enzymatic-Spectrophotometric estimation of serum triglyceride using glycerol phosphate oxidase/peroxidase method [21] was used; the reagent kits were products of Bio-system SA Barcelona, Spain.

HDL-cholesterol was estimated by precipitation/ enzymatic spectrophotometry using phosphor tungstate/Mg-cholesterol oxidase/peroxidase method. The reagent kits were also products of Bio-system SA Barcelona, Spain.

Low density lipoprotein cholesterol was determined based on the formula introduced by National Cholesterol Education Programme (1993) according to equation [22].

\[ \text{LDL (mmol/L)} = \frac{\text{Cholesterol-triglyceride}}{2.2} - \text{HDL} \]

Statistical Analysis

Statistical analysis was performed using SPSS version 17 software. Significance was determined using one way analysis of variance (ANOVA) followed by Scheffe posttest \( p < 0.001 \) was considered significant. Data are presented as mean ±SD

Results

The results obtained from the analyses are shown below.
The results obtained from the analyses are as shown in the figures below.

**Figure 1:** Mean ±SD (mmol/L) of lipid profile in seronegative (negative control) group compared with HIV seropositive patients on short and long term HAART.

**Figure 2:** Mean±SD (mmol/L) of lipid profile in HIV seropositive patients (HAART naïve) as compared to HIV seropositive patients on short and long term HAART.
Figure 3: Mean±SD (mmol/L) of lipid profile of HIV seropositive patients on short term HAART compared to those on long term HAART.

Figure 4: Mean±SD (mmol/L) of lipid profile HIV seropositive HAART naïve (positive control) compared to seronegative subjects (negative control).
Discussion

This study focused on the effect of HIV pathogenesis, short and long term use of HAART on lipid profiles. HAART has been the only means through which treatment and life span extension of those living with HIV is mediated as no definite cure has been discovered yet [23]. This success story has not been without side effects as a number of findings have shown that HAART treatment is associated with induction or alteration of lipid metabolic pathways that predisposes patients to a number cardiovascular risk factors [24,25].

The results obtained from this study showed a significant increase in total cholesterol (TC) (7.52±0.78 mmol/L), low density lipoprotein cholesterol (LDL-c) (4.70±0.55 mmol/L), triglyceride (TG) 3.62±0.78, very low density lipoprotein cholesterol (VLDL-c) (1.65±0.35 mmol/L), and significant decrease in high density lipoprotein cholesterol HDL-c (0.75±0.94 mmol/L) in HIV seropositive subjects on short term therapy. Seropositive patients on long term therapy also showed a significant increase in TC (5.69±0.35 mmol/L), TG (1.97±0.16 mmol/L), VLDL-c (0.90±0.07 mmol/L) and significant decrease in HDL-c (0.75±0.14 mmol/L). All the mean differences were more remarkable in group on short term HAART than those on long term HAART. These results are consistent with that of Montes et al. [26] who reports that HIV patients on short term HAART had elevated TC, LDL-c, TG, VLDL-c and reduced HDL-c which are associated with increased cardiovascular disease. Our study also showed a significant increase in TC in HIV positive subjects both in short and long term HAART compared to the negative control.

When the lipid profile between HIV seropositive subjects on short term HAART were compared with those of HIV positive HAART naïve subjects, there were significant increases in TC, LDL-c, TG, VLDL-c and significant decrease in HDL-c (p<0.001). This implies that starting ART/HAART treatment for HIV positive patients could lead to rapid alterations in lipid profile. The comparison of results of lipid profile between HIV seropositive subjects on long term and HIV naïve subjects showed significant increases in TC and LDL-c (p<0.001). There were no significant differences in TG (p=0.956); VLDL-c (p=0.953) and HDL-c (p=0.570) when the mean differences between the HAART naïve and patients on long term HAART were compared. It seems that severity of HAART induction of dyslipidemia decrease in prolonged administration. This finding is consistent with that of Silva et al. [27] who reported an increase in HDL-c in patients on prolonged HAART.

Comparison between HIV positive HAART naïve subjects and HIV seronegative subjects showed that there were significantly reduced mean differences in VLDL-c, TG and HDL-c (p<0.001). Calza et al. [28] reported that lipid abnormalities in HIV patients before drug therapy could result in metabolic complications which include hypertriglyceridemia, hypercholesterolemia, insulin resistance syndrome, diabetes mellitus and truncated adiposity and may similarly predispose HIV infected subjects to accelerated coronary illness. The reduction in HDL-c level in HIV seropositive HAART naïve patients compared to seronegative individuals is consistent with Falutz, [29], who reported a significant decrease in HDL-c of HIV HAART naïve when compared with seronegative individuals.

Comparison of lipid profile of HIV HAART naïve patients and seronegative subjects showed TC (p=0.009) and LDL-c (p=0.963) indicating no significant differences between them. This could be as a result of the cross sectional nature of this study in which age and sex were not differentiated; but HDL-c, VLDL-c and TG showed significant differences between HAART naïve and seronegative individuals, this is in line with the work of Estrada et al.[30] that reported high prevalence of metabolic syndrome in AIDS patients than HIV negative individuals. Also HIV infection has been found to induce a progressive increase in TG and also a progressive reduction in HDL-c, TC and LDL-c [7].

Genetic make-up has been reported to be responsible for some variation in tolerance of HAART [18,19] but our findings did not deviate from many other findings indicating that patients on HAART in the South East Nigeria conforms to general response to HAART.

Our findings support the fact that HAART induces metabolic abnormalities as observed in lipid profile alterations in this study, similar findings have been reported [31,32] who showed that patients receiving HAART had alterations in lipid profile, mainly with high triglycerides. The use of HAART leads to decrease in HIV morbidity and mortality but the resulting abnormal lipid profile that accompanies it should as well be managed appropriately to prevent development and progression of cardiovascular diseases. Monitoring of lipid profile in HIV patients on drug therapy (HAART) therefore becomes very important. Our results did not present any significant difference from other documented evidences that have reported alterations in lipid metabolism in HIV patients on HAART and seropositive HAART naïve patients indicating that genetic variations and environmental factor may not be important in HAART treatment. Metabolic adjustments/adaptation following long term treatment may also be responsible for the lipid profile of long term HAART patients.

References


