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Research Article

Clinical Effect of Combined Antiretroviral Therapy (CART) on Lipid Profile and Some Atherogenic Indices of HIV Patients in Niger Delta Region

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Abstract

Background: The effect of Combined Antiretroviral Therapy (CART) on lipid profile and some atherogenic indices (including Castelli Risk) of HIV Patients attending Tertiary Health Facilities in Niger Delta Region, Nigeria were evaluated.

Research Design and Method: A cross sectional research design was explored to recruit a total of 199 HIV positive patients already on combined antiretroviral therapy (CART) for a period of 1- 16 years within the age range of 20 - 67 years for this study. Out of which 133 subjects were females and 66 were males respectively. Lipid parameters and some atherogenic indices were analysed using Randox Diagnostics kits, United Kingdom.

Results: The results obtained from this study when female HIV patients were considered, indicated significantly higher values in Triglyceride (TG) and Very Low Density Lipoprotein Cholesterol (VLDL) as the duration (in years) of therapy were increased. TG had values of 1.36 ± 0.26, 1.40 ± 0.47, 1.43 ± 0.36 and 2.24 ± 1.66 for different exposure of 1 - 4 years, 5 - 8 years, 9 - 12 years and 13 - 16 years respectively. Also, VLDL-C had values of 0.61 ± 0.12, 0.64 ± 0.21, 0.63 ± 0.16 and 1.02 ± 0.75 for different exposure of 1 - 4 years, 5 - 8 years, 9 - 12 years and 13 - 16 years respectively. In the analysis of variance for both TG and VLDL-C, significantly higher values were seen in TG of 13-16 years of exposure to CART compared with 1 - 4 years of exposure to CART. In addition, significantly higher values were seen in TG of 13 - 16 years of exposure to CART compared with 5 - 8 years as well as 9 - 12 years of exposure to CART. However, no significant differences were seen when duration of 5 - 8 years was compared with 9 - 12 years of exposure respectively. However, when male subjects were considered, no significant differences were seen in all the lipid parameters and atherogenic indices considered. Finally, when male and female subjects using CART were compared, no significant differences were seen in all the lipid parameters and atherogenic indices considered. The increased lipid fractions especially TG and VLDL could induce increased risk of cardiovascular disease through the formation of atherosclerotic plaques.

Conclusion: Therefore, it is strongly important that HIV patients on CART be monitored carefully especially in developing countries like Africa where access to complete or good health facility is of great challenge.

Keywords: CART; HIV-Patients; Lipid Profile; Atherogenic Indices; Risk Factors

Introduction

Metabolic disorders during the course of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) were seen long before the advent of anti-retroviral regimens [1]. Nevertheless, in the early phase of HIV infection, most patients exhibit varying clinical signs of immunosuppression such as fever, intestinal infections, malaria, weight loss and depletion of protein reserves [1]. The possible means of HIV infection inducing changes in lipid metabolism was already forecasted, as a result of the HIV viral particle in the plasma that may induce changes in the level of plasma concentrations of TC, HDL, TG and LDL [2].

Interestingly though, the primary aim of anti-retroviral therapy for human immunodeficiency virus (HIV) infection is to suppress viral replication, several clinical studies have indicated that the best way to achieve the suppression of HIV viral replication is by combination therapy with two or more anti-retroviral agents (which defines combined anti-retroviral therapy (CART)). Nonetheless, the use of CART takes into cognizance the patient's prior history of anti-retroviral use, the side effects of these agents and drug-drug interactions that occur among these agents and with other drugs as well [3]. The use of CART was shown to effectively suppress the replication of HIV viral particles and drastically reduce mortality and morbidity [4]. The different CART regimens, all consist of at least three different antiretroviral drugs, which are effective in reducing HIV viremia to undetectable levels [5]. CART regimes suppresses viral replication by acting at different stages of the replication with their different combinations of drugs actions, such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs),fusion inhibitors, entry inhibitors, and integrase strand transfer inhibitors (InSTIs) [6-11]. Besides the benefits that come with the use of various CART regimens, laboratory and clinical observations have indicated that CART induces adverse effects on metabolic complications. Metabolic complications such as diabetes, insulin resistance, altered fat distribution and endothelial dysfunction are common among HIV patients [12]. It has been reported that HIV infection, specifically alters lipid metabolic pattern negatively such as changes in high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), triglycerides (TG) and lipid peroxidation as a result of the critical role of cholesterol in the mechanism of HIV replication [12]. As a result of the changes in lipid metabolism, changes in some atherogenic indices such as Atherogenic index of Plasma (AIP), TC/HDL ratio, etc. which are more useful makers for dyslipidaemia and strong indicators for cardiovascular diseases have also been reported in HIV patients [13,14]. However, in this study, the effect of CART or HAART on Lipid profile and some atherogenic indices on HIV patients at varying duration of exposure from the onset of treatment in male and female subjects will be considered. It is firmly believed that data generated would help clinicians and other health givers on the appropriate ways and means of diagnosis and management of patients that needed urgent medical attention and also proffer solutions on how to reduce the accruable risk factors amongst patients in our communities

Materials and Methods

Materials

Materials used include centrifuge, Sp-300 Optima spectrophotometer from Japan as well as cholesterol, triglyceride, high density lipoprotein reagent purchased from Randox Diagnostics, United Kingdom.

Study Area

The study was carried out in Port Harcourt local government area in the city of Port Harcourt. Port Harcourt is one of the major cities in Nigeria and the most industrialized and populous city in the Niger Delta mainly because of the presence of multi-national and local oil and gas companies, seaport and high levels of commercial activities making it the commercial centre in the Niger Delta. Port Harcourt is situated along the coastal plains of Nigeria near the Atlantic Ocean. University of Port Harcourt Teaching Hospital, Military Hospital and Braith Waite Memorial specialist Hospital are the major tertiary hospitals in Port Harcourt with functional HIV clinics

Subjects

A total of one hundred and ninety nine HIV positive patients of age ranging between 20 - 67 years were recruited for this study of which 133 were female and 66 were male, hence cross sectional research design was carefully explored. The patients were recruited after obtaining ethical clearance and patient's consent. The selected HIV patients were patients already on combined antiretroviral therapy (CART) for a period of 1 - 16 years.

Inclusion Criteria

Subjects selected for the study were HIV patients on combined anti-retroviral therapy for at least a year and above attending HIV clinic in any tertiary hospital in Port Harcourt with visible hospital cards were involved in the study. In addition, the selected subjects showed no indication of opportunistic infections as at the time of sample collection. Also they must be willing to participate was a strongly uncompromising criteria

Exclusion Criteria

Subjects not selected for the study were HIV patients on combined anti-retroviral therapy not up to a year whether or not attending HIV clinic in any tertiary hospital in Port Harcourt with visible hospital cards. In addition, they were subjects with signs or indication of opportunistic infections as at the time of sample collection, even as those who did not express clear cut willingness to participate were also removed from the study.

Specimen Collection and Analysis

5 mls of whole blood samples were collected into lithium heparin bottle. The whole blood was spun at 3500 rpm for 10 minutes to obtain plasma for the analysis of total cholesterol (TC), triglyceride (TG) and High Density Lipoprotein (HDL). The method of analysis for TC and TG were based modified enzymatic methods as described by Flegg HM [15] and Stavropoulous WS and Crouch RD [16] respectively. Similarly, HDL-C was analysed using two steps which involved precipitation of the lipoprotein fractions of VLDL and LDL using phosphotungstic acid and magnesium ions, with HDL remaining in the supernatant. The second step involves the quantitation of HDL cholesterol fractions contained in the supernatant based on modified enzymatic methods as seen in cholesterol reagents as described by Flegg HM [15]. Low Density Lipoprotein (LDL) was calculated as described by Friedewald WT., *et al.* [17] using the Friedwald equation: LDL - cholesterol concentration (mmol/l) = TC - (TG/2.2 + HDL). Atherogenic indices were also calculated as ratio of TC/HDL, TG/HDL, LDL/HDL and AIP = Log (TG/HDL).

Statistical Analysis

Graphpad prism 5.03 was the statistical software used. Mean, standard deviation and inferential statistics using the students' statistical t-test were the statistical parameters used with statistical significance set at $p<0.05$. Data obtained were arranged in tables as seen in result session.

Results

The results obtained from this study when female HIV patients were considered, indicated significantly higher values in Triglyceride (TG) (mmol/L) and Very Low Density Lipoprotein Cholesterol (VLDL) (mmol/L) as the duration (in years) of therapy were increased. TG had values of 1.36 ± 0.26, 1.40 ± 0.47, 1.43 ± 0.36 and 2.24 ± 1.66 for different exposure of 1 - 4 years, 5 - 8 years, 9 - 12 years and 13 - 16 years respectively. Also, VLDL-C (mmol/L) had values of 0.61 ± 0.12, 0.64 ± 0.21, 0.63 ± 0.16 and 1.02 ± 0.75 for different exposure of 1 - 4 years, 5 - 8 years, 9 - 12 years and 13 - 16 years respectively. In the analysis of variance for both TG (mmol/L) and VLDL-C (mmol/L), significantly higher values were seen in TG of 13 - 16 years of exposure to CART compared with 1 - 4 years of exposure to CART. In addition, significantly higher values were seen in TG (mmol/L) of 13 - 16 years of exposure to CART compared with 5 - 8 years as well as 9 - 12 years of exposure to CART. However, no significant differences were seen in duration of 5 - 8 years when compared with 9 - 12 years of exposure (Table 1). However, when male subjects were considered, no significant differences were seen in all the lipid parameters and atherogenic indices considered (Table 2). Finally, when male and female subjects using CART were compared, no significant differences were seen in all the lipid parameters and atherogenic indices considered (Table 3).

Parameters	1 - 4 yrs	5 - 8 yrs	9 - 12 yrs	13 - 16 yrs	p-value	F-value	Remark
TC (mmol/L)	3.76 ± 0.78^{a}	3.91 ± 1.24^{ab}	4.190 ± 1.01^{abc}	3.60 ± 1.05^{abc}	0.4394	0.9076	NS
TG (mmol/L)	1.36 ± 0.26^{a}	1.40 ± 0.47^{ac}	1.43 ± 0.36^{ace}	2.24 ± 1.66^{bdf}	0.0026	5.012	S
HDL-C (mmol/L)	3.74 ± 0.85^{a}	3.98 ± 0.57^{ab}	3.76 ± 0.73^{abc}	3.88 ± 0.62^{abc}	0.3341	1.144	NS
LDL-C (mmol/L)	0.60 ± 0.20^{a}	0.70 ± 0.17^{ab}	0.2160 ± 0.20^{abc}	1.30 ± 0.74^{abc}	0.3006	1.233	NS
TC/HDL	1.13 ± 0.64^{a}	1.02 ± 0.45^{ab}	1.18 ± 0.42^{abc}	0.95 ± 0.35^{abc}	0.5361	0.7297	NS
TG/HDL	0.40 ± 0.20^{a}	0.37 ± 0.17^{ab}	0.42 ± 0.24^{abc}	0.62 ± 0.54^{abc}	0.0850	2.257	NS
LDL/HDL	0.05 ± 0.57^{a}	0.15 ± 0.40^{ab}	0.02 ± 0.34^{abc}	0.33 ± 0.17^{abc}	0.3899	1.012	NS
VLDL-C (mmol/L)	0.61 ± 0.12^{a}	0.64 ± 0.21^{ac}	0.63 ± 0.16^{ace}	1.02 ± 0.75^{bdf}	0.0026	5.012	S
AIP	-0.43 ± 0.16^{a}	-0.46 ± 0.14^{ab}	-0.42 ± 0.20^{abc}	-0.30 ± 0.29^{abc}	0.1809	1.651	NS

Table 1: Analysis of variance (ANOVA) on female subjects on CART at different duration of exposure.

Values in each column with different superscript letter (a, b) differ significantly ($p < 0.05$) when comparing 1 - 4 yrs with others. Values in each column with different superscript letter (c, d) differ significantly ($p < 0.05$) when comparing 5 - 8 yrs with others. Values in each column with different superscript letter (e, f) differ significantly ($p < 0.05$) when comparing 9 - 12 yrs with others.

Parameters	1 - 4 yrs	5 - 8 yrs	9 - 12 yrs	13 - 16 yrs	p-value	F-value	Remark
TC (mmol/L)	3.63 ± 1.04^{a}	3.81 ± 0.84^{ab}	4.07 ± 0.84^{abc}	3.55 ± 0.78^{abc}	0.6733	0.5152	NS
TG (mmol/L)	1.31 ± 0.26^{a}	1.56 ± 0.80^{ab}	1.27 ± 0.44^{abc}	1.40 ± 0.14^{abc}	0.3545	1.1030	NS
HDL-C (mmol/L)	3.80 ± 0.56^{a}	3.82 ± 0.70^{ab}	4.0 ± 0.23^{abc}	4.0 ± 0.28^{abc}	0.8692	0.2385	NS
LDL-C (mmol/L)	0.76 ± 1.21^{a}	0.72 ± 1.12^{ab}	0.49 ± 0.87^{abc}	1.09 ± 0.99^{abc}	0.9122	0.1761	NS
TC/HDL	1.0 ± 0.47^{a}	1.05 ± 0.43^{ab}	1.02 ± 0.20^{abc}	0.90 ± 0.26^{abc}	0.9486	0.1191	NS
TG/HDL	0.36 ± 0.10^{a}	0.44 ± 0.28^{ab}	0.32 ± 0.10^{abc}	0.35 ± 0.06^{abc}	0.3462	0.1191	NS
LDL/HDL	0.16 ± 0.44^{a}	0.15 ± 0.39^{ab}	0.12 ± 0.22^{abc}	0.26 ± 0.23^{abc}	0.9757	0.0701	NS
VLDL-C (mmol/L)	0.60 ± 0.12^{a}	0.71 ± 0.36^{ab}	0.58 ± 0.20^{abc}	0.64 ± 0.06^{abc}	0.3545	1.103	NS
AIP	-0.46 ± 0.11^{a}	-0.41 ± 0.20^{ab}	-0.52 ± 0.18^{abc}	-0.45 ± 0.07^{abc}	0.3520	1.109	NS

Table 2: Analysis of variance (ANOVA) of male subjects on CART at different duration of exposure.

Values in each column with same superscript letter (a) do not differ significantly ($p < 0.05$) when comparing 1 - 4 yrs with others.
Values in each column with same superscript letter (b) do not differ significantly ($p < 0.05$) when comparing 5 - 8 yrs with others.
Values in each column with same superscript letter (c) do not differ significantly ($p < 0.05$) when comparing 9 - 12 yrs with others.

Parameters	Male	Female	p-value	t-value	Remark
TC (mmol/L)	3.751 ± 0.92	3.893 ± 1.07	0.3541	0.9288	NS
TG (mmol/L)	1.421 ± 0.58	1.424 ± 0.51	0.9694	0.0384	NS
HDL-C (mmol/L)	3.832 ± 0.60	3.860 ± 0.70	0.7792	0.2807	NS
LDL-C (mmol/L)	0.73 ± 1.12	0.61 ± 1.30	0.5446	0.6069	NS
TC/HDL	1.02 ± 0.42	1.08 ± 0.51	0.4408	0.7724	NS
TG/HDL	0.39 ± 0.20	0.40 ± 0.22	0.7855	0.2726	NS
LDL/HDL	0.1558 ± 0.39	0.1040 ± 0.45	0.4236	0.8019	NS
VLDL-C (mmol/L)	0.6457 ± 0.27	0.6471 ± 0.23	0.9694	0.0385	NS
AIP	-0.45 ± 0.16	-0.44 ± 0.17	0.8027	0.2502	NS

Table 3: Comparative analysis of male and female patients on CART.

Yrs: Years; NS: Not Significant; S : Significant; TC: Cholesterol (mmol/L); TG: Triglycerides (mmol/L); HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol (mmol/L); VLDL-C : Very Low Density Lipoprotein Cholesterol (mmol/L); AIP: Atherogenic Index of Plasma

Discussion

Though CART has shown to have enormous therapeutic benefits from its use among HIV patients, however, laboratory and clinical results have also indicated that CART induces adverse effects on metabolic complications [18,19]. However, from the results obtained when HIV positive females on CART were considered, changes were seen in lipid metabolism characterized by statistically significantly higher values in Triglyceride (TG) and Very Low Density Lipoprotein (VLDL) as the duration of exposure to CART increased from the interval of 1 - 4 years to 13 - 16 years. The VLDL although, appeared normal in all the groups notwithstanding the duration of exposure to CART. By implication, this statistical significant variation observed in VLDL in relation to the level of exposure to CART did not placed the subjects on clinically abnormal scale due to the fact that; the high mean VLDL value reported in age 13-16 years remained within the normal reference range (≤ 3.2 mmol/L). Nevertheless, no significant differences were seen in the other lipid parameters and atherogenic indices considered (AIP, CR-1, CR-2 and TG/HDL) (Table 1). The results of TG and VLDL obtained in this study concur with the findings of Wohl DA., *et al.* [18] and Sprinz E., *et al* [19]. They reported increased levels of lipid fractions among HIV patients using CART. However, contrary to these findings [20] reported that hypertriglyceridaemia is not common amongst the Black HIV patients on CART.

Furthermore also, when HIV positive males on CART were considered, no significant differences were seen in all the parameters considered (Table 2) respectively. The result obtained was in line with the reports of Sumner., *et al*. 2010. They reported that dyslipidaemia is not very common among black HIV patients on CART. In addition, when HIV positive males and females on CART at different interval of exposure were compared, no significant differences were seen as well (Table 3). This also strongly suggests that the use of CART by HIV patients has no link with the sex of the patient regarding to cardiovascular risks except, if there are predisposing confounding factors already in place. In other words, sex of the HIV patients using CART does not pose a risk on the individual especially if there are no predisposing factors that will induce such immunosuppression outcomes.

Nevertheless, the statistically significant increases seen in TG and VLDL could be as a result of prolonged effect of protease inhibitors (PI) in CART which stimulate hepatic triglyceride (TG) and Very Low Density Lipoprotein (VLDL) synthesis while suppressing Cholesterol (TC), LDL-C and HDL-C synthesis. The increase especially in TG could also be due to the presence of inflammation, resulting in elevation of interferon-α which interferes with free fatty acid metabolism, lipid peroxidation and TG clearance thereby contributing to lipid dysfunction especially hypertriglyceridaemia. This finding is in line with the reports of Haugaard SB., *et al* [21]. The increase in lipid fractions especially TG and VLDL could induce increased risk of cardiovascular disease through the formation of atherosclerotic plaques. Cardiovascular disease or complications of cardiovascular diseases among HIV patients have been a major cause of death due to poor or inadequate health access by these classes of patients. In developing countries especially in Africa (e.g. Nigeria), complications of poor HIV patients management viz-a-viz complications of metabolic disorders have also led to economic and social burdens in the society at large.

The observed dyslipidemia characterized by hypertriglyceridemia and increased VLDL could also be as a result of CART affecting the hydrolysis of triglyceride-rich lipoproteins and tissue lipase, disrupts normal post-prandial free fatty acid and lipoprotein catabolism and interferes with peripheral fatty acid trapping [20]. Though dyslipidaemia occurs in NNRTI-based CART such as zidovudine, stavudine or lamivudine, but lipid metabolism disorders are most seen in patients using PI-based regimen [22,23]. As reported by Zaera MG., *et al*. [24], the most obvious mechanisms involved in CART-induced lipid disorders are that of mitochondrial changes which promotes metabolic disorders in adipocytes and increased lipidaemia.

However, other factors, such as virological adaptation, genetic composition and individual immunological features, may be involved in the metabolic and lipid alterations observed because not all of the patients especially the male patients exposed to the same CART regimens were affected [1]. There are also significant proves in the literatures showing that the PIs are associated with increased hepatic triglycerides-synthesis, VLDL, and to a lesser extent, total cholesterol (TC) [14,18]. Moreover, it was observed that these drugs impair the hydrolysis of triglyceride-rich lipoproteins by lipase, which reduces the storage of free fatty acids and interferes with the normal postprandial metabolism of free fatty acids [25]. The relatively normal TG in the male patients could be due to the fact that they had a fair immune status. This is because increased TG tends to occur with profound immunosuppression. Nonetheless, hypertriglyceridemia is also known to be quite rare in the black race even in the presence of insulin resistance, type 2 diabetes mellitus and cardiovascular disease [18]. Atherogenic indices obtained in this study were all suggestive of low risk with high levels of statistical similarities between groups of gender and exposure durations for the studied subjects. The output of these atherogenic indices reflects the traditional lipid indices with some degrees of similarities pointing to low risk. Though atherogenic indices such as AIP, TC/HDL ratio, LDL/HDL ratios, TG/HDL and so on are more useful indices of atherogenicity and cardiovascular risk, however, recent meta-analyses of prospective studies indicated that elevated triglycerides (TGs) are also an independent risk factor for coronary heart disease (CHD) [26]. Nonetheless, there is urgent need for continuous, prompt and increasing monitoring and evaluation of the risk factors amongst patients and apparently healthy subjects especially in developing communities where their seems to be probably increasing visibility of lack and decay of health infrastructure in the region [27,28]. The importance of training and re-training of staff.in the health sector cannot be under-scored in the region, thus, this would in no doubt help to empower them with new modern skills of case management and diagnosis outcome.

Conclusion and Recommendation

The use of CART on HIV patients over a long period of time could induce hyperlidaemic complications especially that of hypertriglyceridaemia and VLDL. These complications can in turn accelerate the incidence of cardiovascular diseases such as coronary heart disease and other forms of cardiovascular disorders. Therefore, it is important that HIV patients on CART should be monitored carefully and regularly especially in developing countries like Africa where access to complete or good health care facility is of great challenge.

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