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Effect of treatment switch from first line to second line anti-HIV regimens on cardiac function parameters,lipid profile compositionandbody weightin albino Wistar rats.

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Abstract

Aim and objectives: *Effect of treatment switch from first line to second line anti-HIV regimens oncardiac function parameters, lipid profile composition and body weightin albino Wistar rats was investigated.*

Materials and Methods: *Fifteen (15) male albino Wistar rats weighing between 220g and 250g were divided into three (3) groups (1, 2_A, 2_B,) with 5 rats in each group. Group 1 which served as control received normal rat pellet and clean water. Group 2_A received first line regimen for 30 days, then switched to second line regimen for 15 days (a total of 45 days) while Group 2_Breceived first line regimen for 30 days, then switched to second line regimen for another 30 days (a total of 60 days).*

Results: *Significant increase ($p<0.05$) in activities of serum LDH and CK were observed in both Groups (2_A and 2_B) when compared with the control. However, LDH activity in Group 2_B was significantly low ($p<0.05$) compared to Group 2_A. Histological examination of hearts tissue of animals in the control Group showed no pathological lesion. Observed in Groups 2_A and 2_Bwere cardiac muscle nuclei and fibres with extravasated hemorrhage in the left ventricle.Serum concentration of total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol in both Groups (2_A and 2_B) were not significant when compared with the control. High concentration of serum triacylglycerol (TAG) and very low density lipoprotein cholesterol (VLDL-c) were observed in Group 2_A,whereas these parameters were insignificant in Group 2_B when compared with control. There was significant increase ($p<0.05$) in body weight of rats treated for 60 days (Group 2_B) when compared with Group 2_A and the control Group; however, body weight of rats in Group 2_A was statistically insignificant ($p<0.05$) compared to control.*

Conclusion: *Treatment switch from first to second line anti-HIV regimens exerts toxic effect on cardiac function parameters and also alters body weight in albino Wistar rats.*

Keywords: *Cardiac Function Parameters, Lipid Profile Composition, Body weight, Anti-HIV regimens and Treatment switch.*

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I. Introduction

The heart is a muscular, fist-sized organ located in the mediastinum – a space between the two lungs. Internally, the heart is essentially hollow. It is divided vertically into two halves by a septum, and each side of the heart has two internal chambers – an atrium on top and a ventricle at the bottom. Venous blood enters the right side of the heart through the right atrium and is pumped by the right ventricle to the lungs, where carbon dioxide is released and oxygen acquired. Oxygen is vital to life as it provides fuel for all the body functions. The main role of the heart is to pump oxygen-rich blood to every cells of the body[27].

Cardiovascular disease (CVD) is a general term used to describe medical conditions that affect the heart and blood vessels [40]. Such conditions among others include coronary artery diseases (CAD) such as angina, myocardial infarction (commonly known as heart attack), high blood pressure, atherosclerosis (hardening of arteries), heart failure and strokes [31]. Levels of some cardiac biomarkers that are linked to the injury of the heart are measured to detect CVD. These include among others, the enzymes: creatine kinase (CK) and lactate dehydrogenase as well as lipid profile composition. Rise in one or more of these biomarkers are associated with heart injury [16].A prospective observational cohort study reported an increased incidence of myocardial infarction and angina in HIV-positive patients taking anti-HIV regimens. These findings suggest a combined effect of HIV infection and anti-HIV regimenson overall CVD risk[18].

Lipids and lipoproteins are risk factors for coronary heart disease (CHD). It has been demonstrated that high levels of serum total cholesterol (TC), triacylglycerol (TAG), LDL cholesterol, very-low-density lipoprotein (VLDL), low concentration of HDL cholesterol, and increased body mass index (BMI) are significantly associated with CHD. Dyslipidemia (abnormal level of blood lipids) is one of the top five major risk factors leading to cardiovascular disorders. Abnormal serum lipids have been noted since the beginning of the HIV epidemic. In the late 80s before the advent of antiretroviral drugs, patients commonly had hypercholesterolemia and hypertriglyceridemia as a function of their wasted hyper-catabolic state, combined with increased pro-inflammatory cytokines [13].

However, the era of antiretroviral drugs has been associated with a dyslipidemic profile consisting of high total and LDL cholesterols, elevated triacylglycerol, and low HDL cholesterol. Body fat abnormalities are common in patients receiving potent antiretroviral drugs [4]. Abnormalities of lipid metabolism are common complications of HIV-positive population treated with anti-HIV regimens[8]. The effect of antiretroviral drugs on serum lipids is most pronounced with Protease Inhibitors (PIs), followed by Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and then Nucleoside Reverse Transcriptase Inhibitors (NRTIs)[37,5]. Several studies have demonstrated that the degree of weight gain experienced by HIV-infected persons receiving treatment is associated with markers of antiretroviral drug efficacy: greater virological suppression, $CD4^+$ cell recovery and reduced resting energy expenditure [38,19].

Importantly, use of anti-HIV regimensby HIV-infected individuals have markedly improved the quality of life and prognosis of the affected patients, however, studies have shown that consistent use of these regimen can induce heart disease [17]. Once antiretroviral regimen is initiated, patients generally remain on medications indefinitely. A switch in regimen is often necessary because of both acute and chronic toxicities, concomitant clinical conditions, and development of virologic failure. However, there is existing fear that switching from initial regimen to next line of treatment with heavy drug burden can cause drugs-induced cardio-toxicity resulting in clinically significant myocardial dysfunction [10,28]. It is on this premise that this study was designed to investigate the effect of treatment switch from first line to second line anti-HIV regimens on cardiac function parameters, lipid profile composition and body weightin albino Wistar rats.

II. Materials and Methods

2.1. Drugs

Drugs used in thisstudy were obtained from University of Uyo Teaching Hospital (UUTH),Uyo, AkwaIbom State; and manufactured by Mylan Laboratories Limited, India.Thedrugs includedSymfi®(1200mg), recommended as first line anti-HIV regimen; and Combivir®(450mg)/Kaletra®(250mg) recommended as second line anti-HIV regimen.

2.2. Experimental Animals

Male albino rats of Wistarstrain wereused for this study. The animals were purchased from the Animal House, Faculty of Basic Medical Sciences, University of Uyo, AkwaIbom State, Nigeria. They were fed with rat chow and clean water *ad libitum*.The animals were kept in standard plastic cages and housed in a room with favourable temperature. The rats got acclimatised to the environment two weeks before the commencement of the experiment.Ethical committee of the Faculty of Basic Medical Sciences, University of Uyo, duly approved this study.

2.3. Preparation of Drug

All drugs were presented in tablets form. Therapeutic dosage of the drugs for human adult weighing seventy (70) kg were 1200 mg of Symfi®; 450mg of Combivir®and 250 mg of Kaletra® respectively. To obtain the corresponding therapeutic dosage for the rat models, one tablet each of Symfi®and Combivir® were crushed with pestle and mortar, dissolved in 100ml of distilled water to obtain stock solution of concentration of 12mg/ml and 4.5mg/ml respectively. Equally, two tablets of Kaletra®were crushed and dissolved in 100ml of distilled water to give a concentration of 5.0mg/ml. Required dosage for each of the rats were calculated based on the body weight, then measured as aliquot and administered to the animals through oral intubation.

2.4. Grouping of Animals

Fifteen (15) male albino Wistar rats weighing between two hundred and twenty (220) to two hundred and fifty (250) grams were used in the study. The rats were divided into three Groups (1, 2_A and 2_B) with five (5) rats per Group.All cages were labeled accordingly ready for drug administration.

2.5. Drug Administration

Group 1: Normal animal fed with rat chow and distilled water, received no treatment.

Group 2_A: Received 17.14mg/kg/bwt of Symfi® twenty four hourly as first line anti-HIV regimen for thirty days (30) days then switched to6.43mg/kgbwt of Combivir® + 3.57mg/kgbwt of Kaletra® twelve hourly for fifteen days (a total of 45 days).

Group 2_B: Received 17.14mg/kg/bwt of Symfi® twenty four hourly as first line anti-HIV regimen for thirty days (30) days then switched to6.43mg/kgbwt of Combivir® + 3.57mg/kgbwt of Kaletra® twelve hourly for another thirty days (a total of 60 days).

2.6. Collection of Sample for Analysis

On completion of drug administration (45 and 60 days respectively), the experimental animals were fasted overnight and sacrificed painlessly under chloroform anesthesia. Blood sample was collected from each animal by cardiac puncture using sterile needles and syringes. The blood samplewas allowed to clot for 30 min before it was centrifuged for 10 min at 3000 rpm to obtain sera for biochemical analyses. The heart tissues were excised, routinely processed and stained using haematoxylin and eosin (H&E) method. With the help of light microscope, it was viewed to observe histopathological changes.

2.7. Evaluation of Serum Cardiac Function Parameters

Lactate Dehydrogenase (LDH) was determined based on the method described by Wacker[39]. Serum Creatine Kinase (CK) was assayed using Rosalki[36] technique. Serum Total Cholesterol was determined based on the method developed by Roeschlau*et al.,* [35]. The method used in determining triacylglycerol was described by Fossati*et al.,* [9] and McGowan *et al.,* [24]. High Density Lipoprotein Cholesterol (HDL-c) was assayed using Pisani[32] method. Low Density Lipoprotein Cholesterol (LDL-c) and Very Low Density Lipoprotein Cholesterol (VLDL-c): LDL-cholesterol was calculated from measured values of total cholesterol, triacylglycerol and HDL-c according to Friedewald[10]formula in the relationship: [LDL-c] = [T-Chol] - [HDL-c] - [TAG]/5, where [TAG]/5 is an estimate of VLDL-c. All values were expressed in mg/dL.

2.8. Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0 and results expressed as mean ± standard error of mean (SEM). Analysis of Variance (ANOVA) and Least Significant Difference (LSD) multiple post hoc comparison tests were carried out on the data and Mean difference between groups were considered statistically significant at $p<0.05$.

III. Result

3.1. Biochemical parameters and body weight

Observed from the result in Table 1 was statistically significant ($P<0.05$) increase in serum LDH in both Groups (2_A and 2_B) in comparison with the control Group. Same was observed in the enzyme activity in Groups 2_B when compared with Group 2_A. Equally, serum activity of CK showed significant ($P<0.05$) increase with high activity in both Groups compared to Group 1 (control). From Table 2, the result showed significant ($P<0.05$) increase in serum TAG and VLDL-c in Group 2_A (rats treated with first line regimen for 30 days then switched second line regimen for 15 days) compared with the control Group. However, these parameters were non-significant ($P<0.05$) in Group 2_B compared also to control. No significant difference ($P>0.05$) was observed in all the markers of lipid profile in Group 2_B when compared with control Group. From the result in Table 3, there was no significant ($P<0.05$) increase in body weight in Group 2_A, whereas statistically significant ($P<0.05$) increase in body weight was observed in rats in Group 2_B(rats treated with first line regimen for 30 days then switched second line regimen for another30 days)when compared with Group 2_A as well as control Group.

Table 1: Effect of treatment switch from first line to second line anti-HIV regimens on cardiac enzymes in male albino Wistar rats.

GROUPS (n=5)	LDH (U/L)	CK (U/L)
1 (Control)	202.67 ± 13.54	9.57 ± 0.93
2_A (1st line for 30days + 2nd line for 15 days) = 45 days	309.67 ± 31.94[a]	22.99 ± 2.02[a]
2_B (1st line for 30 days + 2nd line for another 30 days) = 60 days	294.67 ± 22.81[ab]	26.23 ± 2.57[a]

Values are presented as Mean ± Standard Error of Mean (SEM)

Legends: LDH = Lactate Dehydrogenase; CK = Creatine Kinase; [a] = significantly different when compared to Group 1 ($p<0.05$); [b] = significantly different when compared to Group 2_A ($p<0.05$); n = number of animals per group.

Table 2: Effect of treatment switch from first line to second line anti-HIV regimens on markers of lipid profile in male albino Wistar rats.

GROUPS (n=5)	TC (mmol/L)	TAG (mmol/L)	HDL-c (mmol/L)	LDL-c (mmol/L)	VLDL-c (mm0l/L)
1 (Control)	3.02 ± 0.35	0.83 ± 0.07	0.74 ± 0.04	1.90 ± 0.41	0.38 ± 0.03
2_A (1st line for 30days + 2nd line for 15 days) = 45 days	2.64 ± 0.21	1.21±0.13[a]	0.76 ± 0.07	1.33 ± 0.17	0.55 ± 0.06[a]
2_B (1_{st} line for 30 days + 2nd line for another 30 days) = 60 days	2.73 ± 0.15	1.11 ± 0.09	0.70 ± 0.10	1.53 ± 0.18	0.50 ± 0.04

Values are presented as Mean ± Standard Error of Mean (SEM)

Legends: TC = Total Cholesterol; TAG = Triacylglycerol; HDL-c = High Density Lipoprotein Cholesterol; LDL-c = Low Density Lipoprotein Cholesterol; VLDL-c = Very Low Density Lipoprotein Cholesterol. [a] = significantly different when compared to Group 1 ($p<0.05$); [b] = significantly different when compared to Group 2_A ($p<0.05$); n = number of animals per group.

Table 3: Effect of treatment switch from first line to second line anti-HIV regimens on body weight in male albino Wistar rats.

GROUPS (n=5)	Initial bwt (g)	Final bwt (g)	Absolute difference (g)	Percentage increase (%)
1 (Control)	208.25 ± 2.14	254.00 ± 5.28	43.25 ± 2.78	20.77 ± 1.25
2_A (1st line for 30days + 2nd line for 15 days) = 45 days	244.00 ± 5.45[a]	294.25 ± 6.22[a]	49.75 ± 5.4	20.49 ± 2.51
2_B (1_{st} line for 30 days + 2nd line for another 30 days) = 60 days	217.75 ± 5.89[b]	284.00 ± 4.81[ab]	66.25 ± 1.49[ab]	30.54 ± 1.41[ab]

Values are presented as Mean ± Standard Error of Mean (SEM)

Legends: Initial bwt = body weight at baseline; Final bwt = body weight after treatment;[a] = significantly different when compared to Group 1 ($p<0.05$); [b] = significantly different when compared to Group 2_A ($p<0.05$); n = number of animals per group.

3.2. Histological examination of the Heart

Photomicrographs of H & E stained section of the heart of experimental animals are presented in Figures 1 to 3.

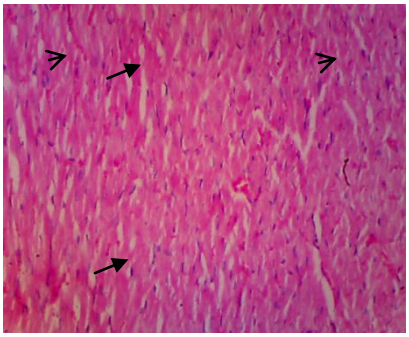

Figure 1: Photomicrograph of Heart Histology of Group 1 (rats receiving no treatment – control). Normal cardiac section showing heart tissue fibres (arrows) and nuclei (open-head arrow). No pathological changes seen. H & E (x100).

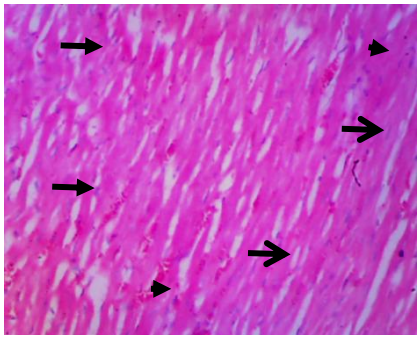

Figure 2: Photomicrograph of Heart Histology of Group 2_A (rats receiving first line regimen for 30 days then switched to second line regimen for 15 days). Section of heart tissue showing normal cardiac tissue evidence with cardiac muscle fibres (openhead arrow) and nuclei (arrow) and extravasated erythrocytes (arrowhead). H & E (x100)

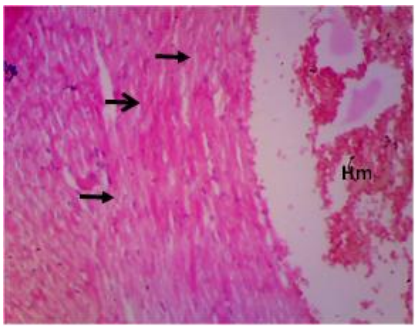

Figure 3: Photomicrograph of Heart Histology of Group 2_B (rats receiving first line regimen for 30 days then switched to second line regimen for another 30 days). Section of cardiac tissue shows cardiac muscle nuclei and fibres. Also seen is extravasated hemorrhage(Hm) in the left ventricle. H & E (x100).

IV. Discussion

There are evidences of antiretroviral drug-induced metabolic derangements and its potential risk for cardiovascular diseases (CVD) in the long-term[3]. Antiretroviral drug from second line regimens (NRTIs + PIs) have been reported to associate with increased risk of myocardial infarction [12] and cardiovascular abnormalities [21] with many changes resembling coronary artery disease [26]. Compelling evidence from animal models also indicates that zidovudine (ZDV), and some drugs from NRTIs class alone (first line regimen) have marked adverse effects on myocardial structure and function that are mediated by mitochondrial toxicity [22]. Inhibition of mitochondrial DNA polymerase by ZDV, causes mitochondrial damage, and leads to focal myocardial necrosis [7].Thus long term use of anti-HIV regimens may result in an infarct in the myocardium[3].

In line with the presence study, Hassan *et al.*,[14] earlier reported that elevations in LDH, CK and transaminases (well-known indicators of necrotic damage) activities are common biochemical abnormalities associated with both lines of anti-HIV regimens. The presence of LDH in muscle plays a very important role for muscular tissues through its ability to convert muscular lactic acid into pyruvic acid, an essential step in producing cellular energy. Moreover, LDH is not restricted to a specific type of muscle, it is found in various types of muscle, especially skeletal and cardiac muscles with a greater concentration in the myocardium of which elevated activity may result in myocardial injury [14]. These muscles are also known to contain CK which may be released into the blood with greater levels as a result of various muscular abnormalities including cardiac and skeletal muscle necrosis. Thus, high activity of CK in the serum may be an indication of damage to CK-rich tissue, such as in myocardial infarction, myositis, myocarditis and rhabdomyolysis[6].

In a clinical report, Meng*et al.*, [25]documented that use of anti-HIV regimens in ninety eight (98) HIV patients was associated with left ventricular (LV) morphological changes and diastolic dysfunction. Also, another experimental report demonstrated that hyperlipidemia can exert direct oxidative and nitrosative stress on myocardium, leading to cardiac dysfunction in rats and mice [29]. In a study conducted by Mak*et al.*,[23], substantial hyperlipidemia was observed to occur early (1–2 weeks), but significant decreases in LV systolic and diastolic function were revealed after 5 weeks of treatment with anti-HIV regimens. It was also observed that by 8 weeks, the systolic function deteriorated much further, and this was associated with prominent ventricular fibrosis and haemorrhage[23] as observed in this study.

Anti-HIV regimens have been implicated in metabolic complications of lipid metabolism. Reyskens*et al.*,[33] reported that rats treated with Lopinavir/Ritonavir (LPV/r) displayed elevated serum LDL-cholesterol and cardiac/hepatic tissue TAG concentration, identifying perturbed lipid metabolism as a relatively early occurrence. In healthy HIV-seronegative subjects, exposure to antiretroviral drugs of Protease Inhibitor class impaired insulin sensitivity [1], and increased serum TAG, VLDL-c and free fatty acid concentration without changing LDL-c or HDL-c[15]. This is in agreement with high concentration of TAG and VLDL-c observed in this study. In another study conducted by Reyskens*et al.*,[34] on cardio-metabolic effects of LPV/r, it was demonstrated that early changes triggered by LPV/r treatment include increased serum LDL-cholesterol and myocardial TAG concentration, together with decreased cardiac function. Moreso, studies have linked increased rates of incident CVD and diabetes mellitus with weight gain in HIV-infection patients receiving anti-HIV regimens[17,2,20].

In consonant withthe current studyand earlier study documented by Taylor *et al.*,[38] two months of treatment with first and second line anti-HIV regimens resulted in a significant increase in body weight of rats. These regimens have been reported to inhibit DNA polymerase-γ leading to depletion of adipocyte mitochondrial DNA and hence mitochondrial toxicity [30]. Depleted biologically active peripheral adipocytes are associated with increased circulating free fatty acids and selective uptake by the body system and deposition in the visceral/central adipose tissue, leading to anti-HIV regimens-associated weight gain [8].

V. Conclusion

Elevated serum activities of cardiac enzymes and high concentration of some lipid profile composition observed in this study is not unrelated to toxic effect of these regimens which may compromise cardiac cells integrity. Thus, findings from this study have revealed that treatment switch from first line to second line anti-HIV regimens exhibit toxic tendency on cardiac function parameters of the tested animals. However, while these regimens are inevitable in the management and treatment of HIV/AIDS, cardiac functions of the recipients should be routinely monitored.

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