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Effect of Different Doses of Antiretroviral Drugs on Body Weight of Experimental Animals

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Anti-retroviral (ARV) drugs are medications used for the treatment of diseases caused by retroviruses, primarily HIV. HIV/AIDS is a condition in human in which the immune system starts to fail, resulting to life threatening opportunistic infections. This study investigated the effect of first and second line fixed-dose combination (FDC) antiretroviral drugs on body weight of experimental animals. Thirty-five (35) male Wistar rats (*Raths novegicus*) were divided into seven (7) experimental groups (A, B_1, B_2, C_1, C_2, D_1 and D_2). Group A received normal rat pellet and clean

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water. Group B_1 received 17.14 mg/kgbwt/24h of fixed-dose EFV/3TC/TDF as first line regimen for 15 days, while Group B_2 received same regimen for 30 days. Group C_1 received 6.43 mg/kgbwt/12h of fixed-dose 3TC/ZDVt3.57 mg/kgbwt/12h of LPV/r as second line regimen for fifteen (15) days, while Group C_2 received same regimen for 30 days. Group D_1 received first line regime for 30 days then switched to second line regimen for 15 days (a total of 45 days), while Group D_2 received first line regime for 30 days, then switched to second line regimen for another 30 days (a total of 60 days). First and second line regimens showed significant change ($P<0.05$) in serum level of hepatic parameters observed in 15, 30 and 45 days, while animals treated for 60 days was insignificant ($P>0.05$) in all the parameters compared to control. This study demonstrated that first and second line regimen did not expose the animals to untoward consequences of severe drug effect, but rather there was a significant ($p< 0.05$) weight gain which may rule out toxic effects of the regimens on long term repeated dosage. Thus, the use of these regimens in the management and treatment of HIV/AIDS should be encouraged while hepatic and cardiac functions of the recipients should be monitored First and second line.

Keywords: Anti-retroviral; HIV/AIDS; antiretroviral drugs; pharmacokinetics; HIV treatment.

1. INTRODUCTION

Anti-retroviral (ARV) drugs are medications used for the treatment of diseases caused by retroviruses, primarily HIV. Antiretroviral (ARV) drugs are classified based on their site of target and action on the HIV replication cycle. There are over thirty ARV drugs group into seven distinct classes as approved by United States Food and Drug Administration (US FDA). Each of the drug class inhibits a stage in HIV replication cycle. Different classes ARV exist including the nucleoside and nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), chemokine receptor (CCR5) antagonist, integrase strand transfer inhibitors (INSTIs) and post-attachment inhibitors (PAIs).

Each of these classes of drugs inhibits HIV replication at different stages in the HIV life cycle (Lundgren et al., 2015; Pinola et al., 2010). The use of antiretroviral (ARV) drugs for the management of HIV and AIDS has reduced HIV disease and significantly increased the life expectancy among HIV-infected patients (WHO, 2015). ARV drugs were given to more than half of the global populations living with HIV (PLWH) as at 2017, a record of 19.5 million people (WHO, 2018). Through so many research knowledge, antiretroviral drugs have been modified, such as fixed-dose combination (FDC) generally referred to as combination Anti-Retroviral Therapy (CART) or Highly Active Antiretroviral Therapy (HAART) which is currently used in the treatment of HIV infection.

One of the adverse effect of most therapeutic drugs is the alteration in body weight. Fixed dose (FDC) anti-retroviral drugs have been reported to cause weight gain. “Studies have shown that introduction of FDC antiretroviral drugs has brought about a dramatic shift from the weight loss and wasting that characterized HIV/AIDS to healthy weight, or even overweight and obesity compared to those seen in the general population” (Nansseu et al., 2018). “Combined ARV drug-induced suppression of viral replication and inflammation normalizes resting energy expenditure and allows weight regain in people living with HIV (PLWHIV)” (Tate et al., 2012). “Also, several studies have demonstrated that the degree of weight gain is associated with markers of combination ARV drug efficacy: Greater virological suppression, $CD4^+$ cell recovery and reduced resting energy expenditure” (Koethe et al., 2016; Taylor et al., 2014). This study assessed body weight of rats treated with first and second line fixed doses of anti-retroviral drugs versus first line with switch to second line combination.

2. MATERIALS AND METHODS

2.1 Materials

A standard weighing balances.

2.2 Experimental Animals

Experimental Animals (male albino Wistar rats) used for this study were purchased from the Animal House, faculty of Basic Medical Science, University of Uyo. The animals were kept in standard plastic cages and housed in a good atmospheric condition under a 12-hour day/light cycle. They were allowed free access to

rat pellet and clean water *adlibilum.* The feeding lasted for a period of one month to get the desired weight of 200 g and above. During this period, the rats got acclimatized to the environment prior to the commencement of the experiment. Body weight of the animals was taken at baseline and weekly throughout the experimental period.

2.3 Drug Sample

The following fixed-dose combination (FDC) antiretroviral drugs (first and second line regimens) manufactured by Mylan Laboratories Limited, India were obtained from University of Uyo Teaching Hospital (UUTH) for the study.

i. First line Regimen: FDC of TDF/3TC3EFV (Symfi® or Telura®) containing two (2) NRTIs [Tenofovir Diisoproxil Fumarate (TDF)/Lamivudine (3TC)] and one (1) NNRTI [Efavirenz (EFV)] in one table. Thus, a single dose of TDF/3TC/EFV contains 300mg of TDF, 300mg of 3TC and 600mg of EFV.
ii. Second Line Regimen: FDC of 3TC/ZDV (Combivir®) containing two (2) NRTI [Lamivudine (3TC)/Zidovudine (ZDV] in one table, co-administered with boosted Lopinavir (LPV/r) (Kaletra®). A single dose of 3TC/ZDV contains 150mg of 3TC and 300mg of ZDV, while a dose of LPV/r is made up of 200 mg of LPV co-formulated with 50 mg of ritonavir (r).

2.4 Experimental Design

A total of thirty-five (35) male albino rats (*Rattus novegicus*) of the Wistar strain weighing between two hundred (200) and two hundred and fifty (250) grams were used in the study. The rats were divided into four groups (A, B, C and D). Group A which had five (5) rats served as control. Groups B, C, and D had ten (10) rats each; they were sub-divided into B_1, B_2, C_1, C_1, D_1 and D_2 . This gave a total of seven (7) experimental groups of five (5) animals each. The cages were labeled accordingly and drug administration carried out in (list 1).

2.5 Preparation of Stock Solution

Drugs used in the study were all presented in tablet form. Therapeutic dosage of the drugs for human adult weighing seventy (70) kg were 1200 mg of fixed-dose EFV/3TC/TDF; 450 mg of fixed-dose 3TC/ZDV and 250 mg of LPV/r respectively. To obtain the corresponding therapeutic dosage for the rat models one tablet each of 3TC/TDF/EFV (1200 mg) and 3TC/ZDV (450 mg) were crushed with pestle and mortar, dissolved in 100ml of distilled water to get stock solution of concentration of 12 mg/ml and 4.5 mg/ml respectively. Equally, two tables of LPV/r (500 mg of 250 mg each) were crushed and dissolved in 100ml of distilled water to give a concentration of 5.0 mg/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.

List 1. Experimental design

S/N	Groups	Specification
I	A	Normal animal fed with rat pellets and distilled water, received no treatment.
II	B_1	Received 17.14mg/kg/bwt/24h of fixed-dose 3TC/TDF/EFV as first line regimen for fifteen (15) days.
III	B_2	Received 17.14mg/kg/bwt/24h of fixed-dose 3TC/TDF/EFV as first line regimen for thirty (30) days.
IV	C_1	Received 6.43mg/kg/bwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kg/bwt/12h of LPV/r as second line regimen for fifteen (15) days.
V	C_2	Received 6.43mg/kg/bwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kg/bwt/12h of LPV/r as second line regimen for thirty (30) days.
VI	D_1	Received 17.14mg/kg/bwt/24h of fixed-dose 3TC/TDF/EFV as first line regimen for thirty (30)) days, then switched to 6.43mg/kg/bwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kg/bwt/12h of LPV/r as second line regimen for fifteen (15) days (a total of 45 days).
VII	D_2	Received 17.14mg/kg/bwt/24h of fixed-dose 3TC/TDF/EFV as first line regimen for thirty (30) days, then switch to 6.43mg/kg/bwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kg/bwt/12h of LPV/r as second line regimen for another thirty (30) days (a total of 60 days).

Note: Bw= Body weight

2.6 Statistical Analysis

Data were analyzed using SPSS statistical software package 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 $p<0.05$.

3. RESULTS AND DISSCUSION

3.1 Results

3.1.1 Assay of initial and final body weight

Table 1 shows the Mean **±** SD value of body weight at baseline, body weight at the end of treatment, absolute difference in body weight and percentage (%) change in body weight of male albino Wistar rats treated with first and second line FDC antiretroviral drugs. There was a significant difference in the initial body weight of animals in Groups B_1 and D_1 compared with Group A (control). Statistically significant increase ($p<0.05$) was observed in the final body weight of rats in Groups D_1 and D_2 respectively when compared with the control Group and other treated groups. These were rats treated with first line regimen for 30 days then switched to second line regimen for 15 days (Group D_1) and 30 days (Group D_2) respectively. However, final body weight of rats in groups B_1 and B_2 (rats treated with first line regimen for 15 days and 30 days respectively) as well as Groups C_1 and C_2 (rats treated with second line regimen for 15 days and 30 days respectively) showed non-significant change ($p<0.05$) compared to control. Of note was a statistically significant ($p<0.05$) loss of body weight in Groups B_1, and B_2, C_1, and C_2 whereas a significant ($p<0.05$) gain in body weight was observed in animal in Group D_2 when compared with the control. Also, rats in Group D1 showed gain in body weight though not statistically significant compared to the control. However, there was significant gain in body weight of rats in Groups D_1 and D_2 when compared with all other treated Groups.

3.2 Discussion

“Studies have shown that introduction of FDC antiretroviral drugs has brought about a dramatic shift from the weight loss and wasting that characterized HIV/AIDS to healthy weight, or even overweight and obesity compared to those seen in the general population” (Nansseu et al., 2018). According to Tate et al. (2012) combination ARV drug-induced suppression of viral replication and inflammation normalizes resting energy expenditure and allows weight regain in people living with HIV (PLWHIV). “Other several studies have demonstrated that the degree of weight gain is associated with markers of combination ARV drug efficacy: Greater virological suppression, $CD4^+$ cell recovery and reduced resting energy expenditure” (Koethe et al., 2016; Taylor et al., 2014). “It has also been reported that earlier initiation of combination ARV drug has led to fewer people with untreated HIV-infection experiencing the cachectic and wasted state that characterized early clinical experience; thus, weight gain early after combination ARV drug-initiation often represents effective viral suppression and $CD4^+$ recovery but also restoration of healthy pre-infection weight” (Yuh et al., 2015). Therefore, combination ARV drug can be associated with weight gain.

“Studies have also linked increased rates of incident CVD and diabetes mellitus with weight gain in HIV-infection patients receiving treatment” (Bares et al., 2018; Herrin et al., 2016; Kumar and Samaras, 2018). “In North American cohorts study, it was demonstrated that following combination ARV drug-initiation, weight gain typically occurs in the first 1-2 years” (Lakey et al., 2013) and plateaus over time (Koethe et al., 2016). “In another study from the Nutrition For Life (NFL) cohort in the United State, 38 patients followed for 12 months after initiating a PI-based combination ARV regimen experienced a mean increase in weight and body mass index (BMI) The same group in a large cohort study of 9,321 individuals, PI-based regimens was associated with a significant rise in BMI 1- year after initiation of FDC anti-HIV drugs compared to NNRTI-based regimens, however a predominantly modest weight gain was observed in this group” (Achhra et al., 2016).

In line with the present study, Adaramoye et al. (2015) have reported significant decreased in body weight of rats few weeks after treatment with LPV/r (a boosted protease inhibitor) which suggest drug toxicity at the early stage of treatment. Also, observations in this study is in consonant with earlier study by Reyskens et al. (2013) who documented that two months of treatment with ARV drugs resulted in a significant increase in body weight of rats indicating improved metabolic function.

Table 1. Effect of treatment with first and second line FDC antiretroviral drugs (17.14mg/kgbwt/24h of EFV/3TC/TDF and 6.43mg/kgbwt/12h of 3TC/ZDV + 3.57MG/KGBWT/12h of LPV/r) on body weight in male albino wistar rats

GROUP (n=5)	Initial bwt (g)	Final bwt (g)	Absolute difference (g)	Percentage increase (%)
A (Control)	208.25 ± 2.14	254.00 ± 5.28	43.25 ± 2.78	20.77 ± 1.25
B_1 (1st Line) 15 days	231.50 ± 1.85^{a}	242.25 ± 1.89	10.75 ± 1.03^{a}	4.65 ± 0.45^{a}
B_2 (1st Line) 30 days	220.00 ± 2.27^{c}	242.00 ± 3.85	22.00 ± 1.83^{ab}	3.89 ± 0.27^{a}
C_1 (2nd Line) 15 days	250.25 ± 4.23^{ab}	260.00 ± 4.69^{b}	20.25 ± 0.75^{ac}	9.99 ± 0.75^{abc}
C_2 (2nd Line) 30 days	227.50 ± 5.87^{e}	247.50± 5.17	20.00 ± 1.87^{ab}	8.84 ± 0.97^{abc}
D_1 (B_2 to C_1) 45 days	244.00 ± 5.45^{ade}	294.25 ± 6.22^{abcde}	49.75 ± 5.4^{bcde}	20.49 ± 2.51^{bcde}
D_2 (B_2 to C_2) 60 days	217.75 ± 5.89^{bct}	284.00 ± 4.81^{abcde}	66.25 ± 1.49^{abcdet}	30.54 ± 1.41^{abcdet}

Values are presented as Mean ± Standard Error of Mean (SEM).
Source: Computed by the researcher using data obtained from weight of animals (2019).
Legends: Initial bwt = body weight at baseline; Final bwt = body weight after treatment; [a] = significant different when compared to Group a (p<0.05); [b] = significant different when compared to Group B_1 (p<0.05); c = significant different when compared to Group B_2 (p<0.05); [d] = significantly different when compared to Group C_1 (p<0.05); [e] = significantly different when compared to Group C_2 (p<0.05); [f] = significantly different when compared to Group D_1 (p<0.05); n = number of animals per group

"Studies have also demonstrated different mechanisms that adversely affect adipocyte metabolism and viability. Anti-HIV drugs from PI drug class have been associated with impaired release of metabolically important adipokines, such as adiponectin" (Cunha et al., 2015), "which regulates hepectic lipid metabolism genes involved in lipogenesis and cholesterol synthesis and transport, enhances skeletal muscle fatty acid oxidation and transport and has anti-inflammatory and anti-oxidative properties" (v). Therefore, treatment with PI can attenuate adipokine levels (adiponectic, leptin) and subsequently increase overall energy expenditure thereby contributing to weight loss (Reyskens et al., 2013).

"Equally, combination ARV drugs from NRTIs drug class is reported to inhibit DNA polymerase-r leading to depletion of adipocyte mitochondrial DNA and hence mitochondrial toxicity" (12). "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 FDC anti-HIV drugs-associated weight gain" (Cunha et al., 2015; Akpan et al., 2019).

4. CONCLUSION

Conclusively, weight loss was observed in early treatment suggesting drug toxicities at this stage. However, subsequent treatment with repeated dosage of the regimen (on switching from first to second line regimen) recorded a significant gain in body weight. Summarily, it was observed that animals with the heaviest drug burden and long-term exposure to drugs (60 days) differed insignificantly in nearly all the assayed parameters when compared with the control group. Therefore, it may be inferred that the body system must have adjusted on long term administration of the drug through a negative feedback mechanism.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (Chat GPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

Permission and approval for animal studies were obtained from the College of Health Sciences Animal Ethics Committee, University of Uyo, Nigeria.

HUMAN AND ANIMAL RIGHTS

The care and use of animals in this study was in accordance with the National Institute of Health Guide for the Care and Use of laboratory Animals (NIH, 1996).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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