IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB)
ISSN: 2455-264X, Volume 5, Issue 6 (Nov. – Dec. 2019), PP 54-61
www.iosrjournals.org

Effect of first and second line fixed-dose combination (FDC) antiretroviral drugs on hepatic enzymes, serum protein and liver histology of albino Wistar rats.

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Abstract

Aims and objective: *Effect of first and second line fixed-dose combination (FDC) antiretroviral drugs on hepatic enzymes, serum protein and liver histology of albino Wistar rats was investigated.*

Materials and Methods: *Twenty five (25) male albinoWistar rats weighing between 220g and 250g were divided into five (5) groups (A, B_1, B_2, C_1 and C_2) with 5 rats in each group. Group A which served as control received normal rat pellet and clean water. Group B_1 received 17.14mg/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 6.43mg/kgbwt/12h of fixed-dose 3TC/ZDV + 6.43mg/kgbwt/12h of LPV/r as second line regimen for fifteen (15) days, while Group C_2 received same regimen for 30 days.*

Results: *Serum ALT activity of rats in Groups B_1 and B_2 differ significantly ($p<0.05$) with high activity observed at 15 and 30 days respectively when compared with Group A (control). There was time-dependent increase ($p<0.05$) in serum AST activity in Groups B_2, C_1 and C_2 compared with Group B_1. However, ALT/AST activity was not significant ($p>0.05$) compared to control. Serum ALP differed insignificantly ($p>0.05$) in all the treated groups when compared with control. Serum total bilirubin was significantly ($p<0.05$) high in all the treated groups when compared with control while serum globulin, albumin and total protein were significantly low ($p<0.05$). The liver histology revealed among others widened sinusoids, singly microvesicularsteatosis, glycogenated nucleus and congested central vein in the treated groups, but no pathological lesion was observed in control group.*

Conclusion: *Fixed-dose combination antiretroviral drugs showed toxic effect on hepatic function parameters in animal model treated groups.*

Keywords: *Hepatic enzymes, Serum Protein, Liver histology, First and second line FDC antiretroviral drugs.*

Date of Submission: 02-12-2019 Date of Acceptance: 18-12-2019

I. Introduction

Antiretroviral therapy (ART) refers to the use of pharmacological agents that have specific inhibitory effects on replication cycle of Human Immunodeficiency Virus (HIV). These agents are drugs used for the treatment of diseases caused by retroviruses, primarily HIV. Records from WHO shows that about 20.9 million (18.4 million - 21.7 million) people living with HIV are accessing antiretroviral (ARV) drugs, which is the current effective management of HIV [42]. They are different classes of ARV drugs which include the nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, chemokinereceptor antagonist and integrase inhibitors. Each of these classes of ARV drugs inhibits HIV replication at different stages in HIV life cycle [22]. The advent of drug expansion programs by pharmaceutical companies, research institutions and state agencies, has led to modification of ARV drugs to a fixed-dose combination (FDC) antiretroviral drugs generally referred to as combination Anti-Retroviral Therapy (cART) or highly active antiretroviral therapy (HAART), currently used in the treatment of HIV infection [42].

In 2016, the world health organization (WHO) reviewed and updated the consolidated ARV drugs guidelines published in June 2013, which addresses the use of ARV drugs as FDC for HIV treatment and prevention across a range of populations, based on the broad continuum of HIV care [43]. The recommendations were updated regarding preferred combination therapy as first line regimens for ARV-naive patients. It was

confirmed that regimens with clinical data demonstrating virologic and immunologic efficacy are those composed of 1 nonnucleoside reverse transcriptase inhibitor (NNRTI) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) or of 1 Protease Inhibitor (PI) (with or without ritonavir [RTV] boosting) + 2 NRTIs. The preferred NNRTI-based combination was recommended to be efavirenz (EFV) + 2 NRTIs, whereas the preferred PI-based combinations include either RTV-boosted atazanavir (ATV) or fosamprenavir (FPV), or lopinavir/ritonavir (LPV/r; co-formulated) + 2 NRTIs; also two NRTIs plus LPV/r or ATV/r was recommended as the preferred second-line regimen for individuals whom EFV-based are failing [41]. Imperatively, WHO continues to promote the optimization of first and second-line regimens to lower toxicity and pill burden and once-daily dosing, minimal or no cross-class resistance and a preference for regimens that can be used across all populations[1,39].

However, virtually all ARV drugs carry risk of hepatotoxicity. Early clinical impression supported the view that NNRTIs were most frequently associated with adverse liver effects, followed by the PIs, and the NRTIs [23]. Hepatotoxicity, a case of liver dysfunction or damage, is in most cases associated with an overload of drugs or xenobiotics, producing a wide variety of clinical and histopathological indicators of hepatic injury. Drug-induced liver damage due to exposure of the organ to certain allopathic medication including ARV drugs has been documented in many studies [26,16]. The degree of this damage can be evaluated by determining the concentration of biochemical markers of the liver function. Therefore this study was designed to evaluate the effect on hepatic function parameters of albino Wistar rats following administration of first and second line FDC antiretroviral agents.

II. Materials and Methods

2.1. Drugs

The following combination ARV drugs were obtained from University of Uyo Teaching Hospital (UUTH) for the study: **i**. Fixed-dose combination (FDC) ofefavirenz(EFV-600mg) / lamivudine (3TC-300mg) / tenofovir (TDF-300mg) administered as first line regimen. **ii**. Fixed-dose combination (FDC) of Lamivudine (3TC - 150mg)/Zidovudine (ZVD-300mg) + Lopinavir (LPV - 200mg) / Ritonavir (RTV - 50mg) (LPV/r co-formulated) administered as second line regimen.

2.2. Experimental Animals

Animals (male albino Wistar rats) used for this work were purchased from the Animal House, Faculty of Basic Medical Sciences, University of Uyo, AkwaIbom State, Nigeria. The animals were kept in standard plastic cages and housed in a room with ambient temperature. They were allowed free access to rat pellet and clean water *ad libitum*. The rats were maintained under standard conditions and got acclimatised to the environment two weeks before the commencement of the experiment. Prior to the commencement of the study, ethical approval for the study was sought and obtained from the Ethical committee of the Faculty of Basic Medical Sciences, University of Uyo, Nigeria.

2.3. Preparation of Drug

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; 450mg 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 (1200mg) and 3TC/ZDV (450mg) 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 LPV/r (500mg of 250mg each) 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.

2.4. Grouping of Animals

A total of twenty five (25) male albino rats of the Wistar strain weighing between two hundred (200) and two hundred and fifty (250) grams was used in the study. The rats were divided into three groups (A, B, and C). Group A which has five (5) rats served as control. Groups B, and C has ten (10) rats each; they were sub-divided into B_1, B_2, C_1, and C_2. This gave a total of five (5) experimental groups of five (5) animals each. The cages were labeled accordingly ready for drug administration.

2.5. Drug Administration

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

Group B_1: Received 17.14mg/kg/bwt/24h of fixed-dose 3TC/TDF/EFV as first line regimen for fifteen (15) days.

Group B_2: Received 17.14mg/kg/bwt/24h of fixed-dose 3TC/TDF/EFV as first line regimen for thirty (30) days.

Group C_1: Received 6.43mg/kgbwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kgbwt/12h of LPV/r as second line for fifteen (15) days.

Group C_2: Received 6.43mg/kgbwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kgbwt/12h of LPV/r as second line regimen for thirty (30) days.

2.6. Collection of Sample for Analysis

At the end of administration period (15 and 30 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, and allowed to clot for 30 min before it was centrifuged for 10 min at 3000 rpm to obtain sera for biochemical analyses. The liver tissues were excised, routinely processed and stained using haematoxylin and eosin method. It was then viewed under light microscope for histopathological changes.

2.7. Evaluation of Serum Liver Function Parameters

Alanine amino transferase (ALT) and Aspartate amino transferase (AST) activities were assayed according to method recommended by International Federation of Clinical Chemistry, IFCC [18]. Activity of ALP was determined using the method described by Bowers and McComb[5]. Total bilirubin level in the serum was determined using the Jendrassik-Grof principle [19]. Total proteins were assayed by Biuret method modified by Weichselbaum[40] and Gornall[17]. Serum albumin was determined using bromocresol green binding method described by Doumas, Watson and Biggs [9]; while serum globulin was obtained from the difference between the serum total protein and albumin.

2.8. Statistical Analysis

Data were analysed 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

The result presented in Table 1 shows that rats administered with 17.14mg/kgbwt/24h of fixed-dose EFV/3TC/TDF differ significantly ($p<0.05$) with high activity in serum ALT observed at 15 days (Group B_1) and 30 days (Group B_2) respectively when compared with control (Group A). Also, animals in Group B_2 showed time-dependent increase in ALT activity when compared with Group B_1. Serum ALT of rats treated with 6.43mg/kgbwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kgbwt/12h of LPV/r for 15 days (Group C_1) and 30 days (Group C_2) did not differ significantly ($p<0.05$) compared with Group A. However, there was time dependent increase in serum ALT activity observed in Group C_2 when compared with Group C_1. Time-dependent increase was also observed in serum AST activity in Groups B_2, C_1 and C_2 when compared with Group B_1; whereas no significant change ($p>0.05$) was observed in ALT/AST activity in all the treated groups compared to control. Serum ALP activity differed insignificantly ($p>0.05$) in all the treated groups when compared with the control. Statistically significant increase ($P<0.05$) in serum total bilirubin was observed in all the treated groups compared with control. Serum total protein was significantly ($p<0.05$) low in rats receiving 17.14mg/kgbwt/24h of fixed-dose EFV/3TC/TDF for 30 days (Group C_2) compared with the control, and also when compared with Groups B_1 and C_1. Equally, serum albumin and globulin showed significant ($p>0.05$) reduction in all the treated groups when compared with the control group.

Table 1: Effect of treatment with first line regimen (17.14mg/kgbwt/24h of fixed-dose EFV/3TC/TDF) and second line regimen (6.43mg/kgbwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kgbwt/12h of LPV/r) on hepatic enzymes in male albino Wistar rats.

GROUPS (n=5)	ALT(UL)	AST(UL)	ALT/AST	ALP(UL)
A (Control)	48.83 ± 1.88	127.80 ± 10.07	2.84 ± 0.39	222.00 ± 1.15
B_1 (1st Line) 15days	59.05 ± 3.66[a]	95.37 ± 3.74	2.17 ± 0.50	72.50 ± 7.79
B_2 (1stLine) 30days	63.90 ± 6.98[ab]	139.37 ± 8.92[b]	3.05 ± 0.53	158.50 ± 8.66
C_1 (2ndLine) 15days	45.08 ± 3.55[c]	148.50 ± 5.53[b]	3.59 ± 0.80	178.50 ± 6.45
C_2 (2ndLine) 30days	51.87 ± 2.90[d]	154.85 ± 18.05[b]	3.15 ± 0.44	166.75 ± 7.49

Values are expressed as Mean ± SEM**.**ALT – Alanine amino transaminase; AST – Aspartate amino transaminase; ALP – Alkaline Phosphatase; [a] = significantly different when compared to Group A ($p<0.05$); [b] = significantly different when compared to Group B_1 ($p<0.05$); [c] = significantly 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 ($p<0.05$); n = number of animals per group.

Table 2: Effect of treatment with first line regimen (17.14mg/kgbwt/24h of fixed-dose EFV/3TC/TDF) and second line regimen (6.43mg/kgbwt/12h of fixed-dose 3TC/ZDV + 3.57mg/kgbwt/12h of LPV/r) on serum protein in male albino Wistar rats.

GROUPS (n=5)	T-BIL (µmol/L)	TP (g/dl)	ALB (g/L)	GLB (g/L)	ALB/GLB
A (Control)	3.63 ± 0.31	7.99 ± 0.28	51.80±2.21	28.05±1.40	1.85±0.12
B_1 (1st Line) 15days	12.05 ± 0.99[a]	8.63 ± 0.11	58.18±1.96	28.13±0.82	2.08±0.13
B_2 (1stLine) 30days	12.87 ± 1.62[ac]	8.09 ± 0.37	52.98±11.05	27.90±2.12	1.93±0.44
C_1 (2ndLine) 15days	8.67 ± 0.97[ab]	7.84 ± 0.21	50.80±1.27	27.55±0.99	1.84±0.04
C_2 (2ndLine) 30days	11.30 ± 1.23[a]	7.06± 0.45[abd]	45.28±4.40	25.25±0.06	1.79±0.17

Values are expressed as Mean ± SEM.T-BIL – Total Bilirubin; TP – Total Protein; ALB – Albumin; GLB – Globulin; [a] = significantly different when compared to Group A ($p<0.05$); [b] = significantly different when compared to Group B_1 ($p<0.05$); [c] = significantly 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 ($p<0.05$); n = number of animals per group.

3.2. Histological examination of the liver

Photomicrographs of H & E stained section of the liver of experimental animals are presented in Figures 1 to 5.

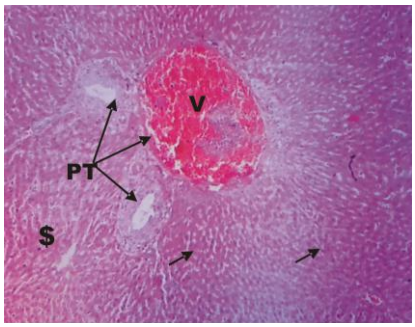

Figure 1: Photomicrograph of Liver Histology of Group A (rats receiving no treatment – control). The histology of the liver section shows arrays of hepatocytes (arrows) with dilated sinusoids ($) and blood vessels (V) of the portal triad (PT). All appear normal. H & E (x100).

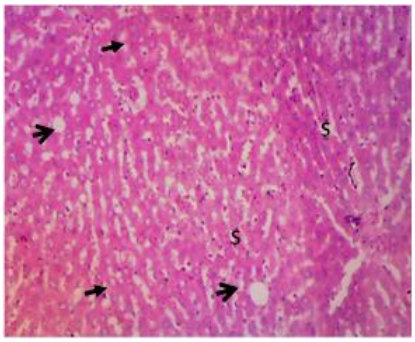

Figure 2: Photomicrograph of Liver Histology of Group B_1 (rats receiving first line regimen for 15 days). Section of liver tissue shows arrays of liver cells (arrows), widened sinusoid ($), focal singly microvesicularsteatosis (open arrow) and glycogenated nucle us (arrowhead).H & E (x100).

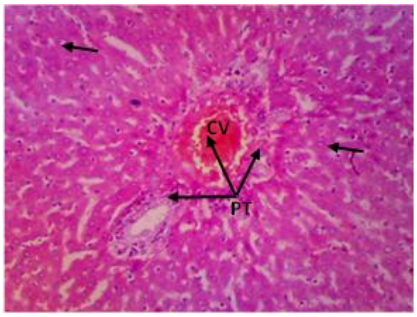

Figure 3: Photomicrograph of Liver Histology of Group B_2 (rats receiving first line regimen for 30 days). Section of liver tissues shows arrays of hepato-cytes (arrows), portal traid (PT) with congested vessel (CV),also seen is periportal mono-nuclear inflammatory infiltrate/macr ophage. H & E (x100).

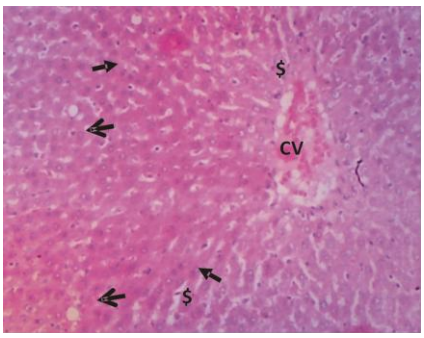

Figure 4: Photomicrograph of Liver Histology of Group C_1 (rats receiving second line regimen for 15 days). The histology section of the liver tissue shows arrays of hepatocyte (arrows), widened sinusoid ($) congested central vein (CV), and singly microvesicularsteatosis (opened arrow). H & E (x100).

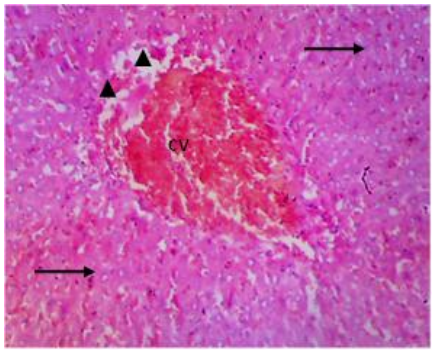

Figure 5: Photomicrograph of Liver Histology of Group C_2 (rats receiving second line regimen for 30 days). Section of the liver tissue shows arrays of liver cells (arrows) widened congested Central Vein (CV), there are focal fatty changes (open head arrow) and glycogenated nuclei (arrowhead) of the liver cells. H & E (x100).

IV. Discussion

Several enzymes that trigger important chemical reactions in the body are produced and found within the cells of the liver, however, damage or injury to the liver cause elevations in the liver enzyme levels [30]. Studies have shown that in patients commencing fixed-dose combination (FDC) antiretroviral drugs, fourteen to twenty percent (14-20%) will experience derangement in hepatic function parameters [21,36] indicating hepatic injury. FDC of EFV/3TC/TDF and FDC of 3TC/ZDV + LPV/r are standard drugs recommended by WHO as preferred first and second line anti-HIV regimens respectively [43] for management and treatment of HIV/AIDS.

In the present study, effect on hepatic function parameters in male albino Wistar rat administered with first and second line FDC antiretroviral drugs was investigated. Significant increase ($P<0.05$) with high activity of serum alanine amino transaminases (ALT) was observed in rats treated with first line regimen for 15 and 30 days (Group B_1 and B_2) respectively, but no significant change ($P<0.05$) of the enzyme activity was observed in Groups C_1 and C_2 (rat treated with second line regimen) when compared with Group A (control). Equally, high activity of serum aspartate amino transaminases (AST) was observed in rat receiving second line regimen for 15 and 30 days (Groups C_1 and C_2) respectively, though not significant ($P<0.05$) compared with control, but it was significant ($P<0.05$) when compared with group B_1. Also, time dependent increase in AST activity was observed in Groups B_2 when compared with B_1.

In line with the present work, other studies have associated increase serum levels of transaminases with ARV drug-induced liver injury [20]. Efavirenz (EFV), a component of many FDC antiretroviral drugs used as first line regimen has been linked with hepatotoxicity in both human and animal studies [25,10,34]. Equally, Zidovudine (ZDV), a component of second line regimen has been implicated in cases of hepatic injury in advanced AIDS patients [31]. Elias *et al.,*[12] had observed increased serum ALT and AST actvity in animals treated with EFV independently as a monotherapy. Also, in two cases reported by Edelman *et al*[11] and Patil*et al*[32], fixed-dose efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF) was implicated in hepatotoxicity, with remarkably high activity of transaminases. ALT is a metabolic enzyme expressed primarily in the liver. Serum ALT activity is the most frequently reliable biomarker of hepatotoxicity since by virtue of its location in the liver plays a vital role in amino acid metabolism and gluconeogenesis. ALT being hepato-specific principally found in the cytosol of hepatocytes, its estimation is more specific for liver abnormalities. It has been shown to be significantly elevated in hepatobiliary disease. Thus, high serum ALT activity is typically associated with hepatocellular membrane damage and leakage of enzyme from hepatocytes [3]. AST is found in the liver and other organs including heart, muscle, brain and kidney. Thus, injury to any of these tissues can cause an elevated serum activity of this enzyme. When damage to heart or liver cells occurs, AST being intracellular enzyme is released into the peripheral blood. Though it is considered a less specific biomarker enzyme for hepatocellular injury, its significant concentration in the serum could be a sign for hepatocellular necrosis. However, the ratio of serum AST to ALT can be used to differentiate liver damage from other organ damage [30].

Contrary to serum activities of transaminases, activity of serum alkaline phosphatase (ALP) observed in this study was statistically insignificant (P<0.05) with low activity in all the treated groups compared with the control. Though some studies have implicated high activity of serum ALP along with ALT and AST in cases of hepatic dysfunction associated with ARV drugs, the present findings is consistent with the work documented by Oladipo*et al*[28], where serum ALP showed significant reduction in albino Wistar rats treated with ARV drug, while the activities of transaminases were high. Also, Abubakar*et al*[2]reported that AST and ALT activities of HIV positive patients treated with antiretroviral drugs was significantly higher (p<0.05) compared with non-treated group, while ALP activity was significantly lower (p <0.05) in the same group compared with non-treated group. In a similar vein, Goni*et al*[16] observed that there was no statistically significant difference between the mean serum levels of ALP enzyme among the study group of HIV/HBV co-infected and HIV mono-infected patients on antiretroviral drugs compared with ALT and AST levels which were significantly high and moderate respectively. Similarly, Patil*et al*[32] reported that transaminases (ALT and AST) activities were remarkably high in patient treated with ARV drugs while ALP level remain insignificantly difference, and the patient did not develop signs of hepatic encephalopathy.

In a study carried out by Cello [6] unexplained high levels of ALP was observed while the transaminases remained insignificant in an antiretroviral therapy (ART) naïve HIV-positive patient; this raised the suspicion of a co-existing HIV infection, cholecystitis, which was hitherto undetected in the subjects with AIDS. By these findings, ALP was noted as a fruitful marker for identifying more underlying HIV infection. The liver is an important site of the HIV replication, thus, HIV attacks the liver cells directly, causing cell death and the release of the cellular contents into the surrounding medium, of which the enzymes constitute 20 percent [29]. This according to documented studies could be responsible for the increase activity in the serum enzymes in the HIV-infected patients implying that elevated activity of ALP in the serum of HIV-infected individuals could be due to already deteriorated effect on the body system by the virus and/or other host factors before introduction of ARV drug. However, this study was carried out in healthy and HIV-free biological system of rats.

Statistically significant increase (P<0.05) in serum total bilirubin concentration was observed in all the treated groups when compared with the control. This is in consonant with other studies which have associated drugs from non-nucleoside reverse transcriptase inhibitors (NNRTIs) class with high concentration of total bilirubin [37, 38]. Bilirubin is a tetrapyrole produced during the normal breakdown of haemoglobin[8]. In the liver, uridinediphosphate (UDP)-glucuronyltransferase converts bilirubin to a mixture of monoglucuronides and diglucuronides referred to as conjugated bilirubin, which is then secreted into the bile by an ATP-dependent transporter [7]. The bile in turn serves as a means for excretion of bilirubin from the body; thus, bilirubin level serves as a measure of liver and bile tract function. Total bilirubin includes both the conjugated and unconjugated (free) forms of bilirubin and, if elevated, is usually indicative of liver damage or hemolysis [13]. Accumulation of bilirubin or its conjugates in body tissues results in a disease condition called jaundice, which is characterized by high plasma bilirubin levels and deposition of yellow bilirubin pigments in skin, sclera, mucous membranes, and other less visible tissues [44]. Hepatic injury caused by drugs results in hyperbilirubinemia associated with high activity of hepatic enzymes; thus impaired metabolism of bilirubin indicates compromised excretory capacity of the liver [24] hence, the significant increase in levels of total bilirubin and high activity of hepatic enzymes observed in this study.

Serum total protein was statistically significant (P>0.05) with low concentration observed in Group C_2, rats treated with second line regimen for 30 days when compared with control. However, serum levels of albumin, globulin and albumin/globulin observed in this study differ insignificantly (P<0.05) in all the treated groups compared with the control. Umar *et al.,*[37] had reported lowered level of total protein, and albumin in rats treated with ARV drugs. Protein is primarily synthesized in the liver and consists mainly of albumin and few globulins. Changes in total protein levels are due mostly to changes in albumin concentration [27]. Total protein and albumin concentration are the markers of biosynthetic capacity of the liver; thus, defect in synthesis of total protein and albumin generally reflects defective metabolic capacity of the liver [7]. Therefore, the observed reduction in total protein levels concentration in this study suggests hepatic dysfunction and suppression of the synthetic function of the liver.

Albumin is a protein primarily synthesized by the hepatic parenchymal cells. Its primary function is to maintain colloidal osmotic pressure in the vascular and extravascular areas of the body and prevent oedema. Thus, low level of serum protein slows mRNA synthesis of albumin and results in lower or insignificant serum levels of albumin as well as globulin. Low albumin levels indicate poor liver function and contribute to peripheral oedema and ascites sometimes seen in very late stage liver disease [15], however, albumin levels are usually normal in chronic liver disease until significant liver damage is present.

Some changes in morphology and liver architecture were observed in this study. This is in corroboration with studies conducted by other researchers [14,10,4,12,34] who reported marked pathological lesion in liver histology of rats treated with ARV drugs. Liver cells or hepatocytes are grouped in interconnected plates and constitute two-thirds of the mass of the liver. Hepatocytes, with their high degree of metabolic activities, are

readily altered by toxins, especially drugs, and may demonstrate the histological cell responses such as fatty changes and necrosis. With severe metabolic disruption by toxins or drugs, the hepatocytes undergo hydropic degeneration and become inflamed due to metabolic injury. A buildup of necrotic cells and leakage of cellular debris into the lumina of sinusoids and vessels cause their occlusion. The vascular supply of hepatocytes becomes insufficient due to dysfunctional sinusoids and vessels and leads to abnormal transportation throughout the liver [33].Inflammation of the liver cells by toxins or drugs is usually marked by changes such as widened sinusoid, widened congested central vein, singly microvesicular steatosis with focal fatty changes, glycogenated nuclei and kupfer cells hyper plasia[14]. Inhibition of mtDNA by antiretroviral drug may impair mitochondrial function. Mitochondria are involved in fatty acid oxidation, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Impairment of mitochondrial fatty acid oxidation leads to an intracellular increase of triacylglycerol and non-esterified fatty acids, the cause of microvesicularsteatosis[35] observed in this study.

V. Conclusion

First line anti-HIV regimen containing fixed-dose EFV/3TC/TDF exhibits toxic effect on hepatic function parameters in mammal model. Hence, EFV component of the regimen is implicated. Second line anti-HIV regimen containing fixed-dose 3TC/ZDV + LPV/r may exert adverse effect on already compromised hepatic function due to host and/or risk factors. Therefore prior to administration, test of liver function on individuals due for these regimens is recommended.

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