

COMPARATIVE STUDY OF THREE ANTIRETROVIRAL DRUGS ON LIVER ENZYMES (ALANINE AMINOTRANSFERASE, ASPARTATE AMINOTRANSFERASE AND ALKALINE PHOSPHATASE)George Adieboye Oforibika^{1*} and Augustine Amadikwa Uwakwe²¹Department of Science Laboratory Technology, School of Science and Technology, Captain Elechi Amadi Polytechnic, Rumuola, Port Harcourt, Nigeria.²Department of Biochemistry, Faculty of Science, University of Port Harcourt, Port Harcourt, Nigeria.***Corresponding Author: George Adieboye Oforibika**

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ABSTRACT

This study comparatively evaluate the effects of nevirapine (nevrane), lamivudine and zidovudine on alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities of normal albino rats. A total of 63 albino rats were randomly divided into 5 groups labelled A, B, C, D and E and kept in a well ventilated room. Group A served as control and these rats were treated with distilled water. Rats in the groups B, C, D and E were treated with 4 different doses of the drugs (0.7, 1.4, 2.1 and 2.8mg/Kgbw) respectively. The drugs were administered once daily for 1, 2, 3, 4 and 5 weeks consecutively. Animals were sacrificed 24 hours after the last treatment. Blood samples were collected into heparinized sample bottles for analysis. Results obtained revealed that AST levels were highest in Nevran at week 3 of group B (178.00 ± 1.15 IU/L) when compared to the control (122.6 ± 8.45 IU/L). Significant differences ($p < 0.05$) existed among the 3 drugs at group B of week 1 and there was no significant differences between any at group E of week 5. Lamivudine had the highest activity for ALT at group D of week 3 (80.00 ± 1.15 IU/L) as compared to the control (44.67 ± 2.60 IU/L). Nevran and zidovudine were significantly different with the other drugs at group B of week 1 and group E of week 5. Mean ALP activity was greatest in Lamivudine at group C of week 1 (58.20 ± 0.06 IU/L) when compared to the control (46.73 ± 3.54 IU/L). There was no significant difference ($p > 0.05$) between any drug at group B of week 1 while at group E of week 5 Lamivudine was significantly different ($p < 0.05$) with the other drugs. Treatment of HIV/AIDS with ARVs could result to liver damage by hepatocellular injury or by necrosis of the liver due to prolonged treatment.

KEYWORDS: Antiretroviral drugs (ARVs), albino rats, HIV/AIDS, hepatocellular injury, liver.**1. INTRODUCTION**

HIV (Human Immunodeficiency Virus) is the virus which causes AIDS (Acquired Immunodeficiency Syndrome), a condition in humans in which progressive failure of the system allows life threatening opportunistic infections and cancers to thrive. Since the first reported case of AIDS in the USA with 800, 000 new infections occurring daily, the disease has become a global pandemic.

By the year 2006, AIDS had infected more than 65million people out of which 25million have died. In Nigeria, the acclaimed heart beat of Africa, the prevalence of HIV infection has been increasing steadily from 1.8% in 1991 to 3.8% in 1993, 4.5% in 1996, 5.4% in 1999 and 5.8% in 2001.^[1] Recently at the American Conference on the treatment of HIV held in Denver Colorado on May 10 2014 it was stated that the absolute number of people living with HIV in Nigeria had

increased by almost half a million in the three years (2010-2013).

It was stressed also that AIDS related mortality had also increased in the same time period to about 217,418. Until recently (with the advent of antiretroviral therapy), HIV infection was a death sentence, in most parts of the world due to non-availability of the anti AIDS drugs, ignorance, financial incapacity and other factors.^[1,2] The introduction of Highly Active Antiretroviral Therapy (HAART), a cocktail of nucleoside and non-nucleoside analogues capable of inhibiting reverse transcriptase and proteases in industrialized countries during the mid 1990's led to a well documented reduction in the risk of AIDS-defining illnesses and AIDS related mortality.^[3,4] Although antiretroviral treatment is not a cure for HIV/AIDS, it can significantly prolong and improve the lives of HIV infected people by suppressing viral loads

to non-detectable levels, improving immune status and reducing the incidence of opportunistic infections.

However people taking antiretroviral drugs are likely to experience some side effects during their treatment.^[4,5] Some of which are: dyslipidemia, lipodystrophy, lactic acidosis, severe liver problems, anaemia, and renal tubular disorders.^[5,6] In the bid to save lives, as many patients as possible are put on potent ART but limited attention has been given to the side effects. There is usually unavailability of proper laboratory monitoring.

Antiretroviral drug related liver injury (ARLI) is defined by elevations in liver enzymes in plasma or serum, with alanine aminotransferase (ALT) characteristically greater than aspartate aminotransferase (AST). It is among the major causes of treatment discontinuation in HIV-infected patients.^[7] Recent surveys have shown that there is an increase in the occurrence of hepatic injury in HAART treated patients. Also life threatening hepatotoxic events and end-stage liver disease has been seen in most patients on HAART.

As the use of HAART increases, coupled with the new antiretroviral medications that have been made available, ARLI has come into the limelight due to its negative impact on clinical outcomes.^[8] Drug associated hepatotoxicity creates an extra economic burden on already strained medical budgets, as there will be additional visits and hospital admissions are usually needed for proper patient care and management.

Drug discontinuation hinders maintenance of HIV suppression. Many of the HAART treatment regimens are hepatotoxic. The liver is among the important organs needed in the metabolism of these drugs and also detoxification. Thus the liver must be monitored closely. Also those HAART regimens that have shown signs of toxicity should be identified and adjustments made immediately to improve the patient's treatment. Limited attention has been given to the several dilemmas and side effects of antiretroviral drugs (ARVs); including the balance between cost and toxicity as these are major ongoing challenges in resource limited settings.

Because of the limited availability, cost and convenience of fixed dose combinations, most patients receive first line regimen including Nevirapine, Zidovudine and Lamivudine without monitoring and considering side effects. The aim of the study was to comparatively study the effects of three antiretroviral drugs (Nevirapine, Zidovudine and Lamivudine) on liver enzymes (Alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) activities of normal albino rats.

2. MATERIALS AND METHODS

The three (3) antiretroviral drugs samples namely Lamivudine, Zidovudine and Nevran used in this study were obtained from Barata Pharmaceutical Stores which is NAFDAC approved and located at Rumuokuta

junction along Ikwerre Road Port Harcourt, Rivers State, Nigeria. Zidovudine (300mg) manufactured by CIPA Ltd Plot No. L. 139 Verna Goa 403922 India for Evans Medical PLC, KM 32 Lagos-Ibadan Expressway. Batch No: K82625. MDF: 01/2011. EXP: 12/2013. NAFDAC Reg No.: 04-6915. Nevran 300mg: manufactured by Ranbaxy laboratories LTD, Paonta Sahib, Dist. Simour. Batch No: 235556. MDF: 12/2011. EXP: 11/2013. NAFDAC Reg No: 04-2708. Lamivudine 300mg: manufactured by Cipla LTD, Plot No L-139 Verna, Goa 403722, India for Evans Medical PLC, Km 32 Lagos-Ibadan Expressway, Lagos State. Batch No: E120365. MDF: 03/2012. EXP: 02/2014. NAFDAC Reg No: 04-7521.

Specimen (animal) used for the experiment: sixty-three(63) albino rats were purchased from the department of Human Physiology, University of Nigeria, Enugu Campus (UNEC) and acclimatized for one week in the animal house of Biochemistry Department, University of Port Harcourt located at the Botanical garden Choba Park. During acclimatization, the animals were fed with rat pellets, water and libitum. Chemicals and reagents: all chemicals and reagents used in this study were obtained from Randox Laboratories UK. Preparation of Drug solution for administration: based on the daily requirement, 1 tablet each of Nevran, Lamivudine and Zidovudin were ground to a fine powder and dissolve in 100ml of distilled water to make a therapeutic dose concentration of 0.6g(4.29mg/KgBW) which served as the stock solution from which four other concentrations are being prepared.

Four (4) other concentrations of the three drugs are prepared from the stock solutions which are 0.1g (0.7mg/KgBW), 0.2g (1.4mg/KgBW), 0.3g (2.1mg/KgBW), 0.4 g (2.8mg /KgBW) which are 16.7ml, 33.3ml, 50.0ml and 66.7ml of the stock solution respectively. These are then made up to 100ml by dilution with distilled water.

Experimental procedure: a total of sixty-three(63) albino rats of weight range (124-194g/BW) were randomly divided into five groups labelled A, B, C, D and E where group A served as control and rats (n=5rats/dose) were treated with distilled water. Rats in groups B, C, D and E (n=5rats/dose) were orally treated with 4 different doses (0.7, 1.4, 2.1 and 2.8) of the three drugs for 5weeks. Animals were sacrificed twenty-four (24) hours after last treatment.

2.1 Experimental design

Drug administration to rats: 0.25ml of drug solution was administered at the different concentrations to the animals in the groups.

2.2 Collection of Blood and Preparation of Serum

The rats were withdrawn from the cages in each of the group twenty four (24) hours after the last administration of the drugs for 1, 2, 3, 4, and 5 weeks and placed in a

desiccator containing cotton wool soaked in chloroform to anaesthetize the rats. The blood samples were obtained by cutting the jugular vein of the rat on the neck by means of surgical blade and put in anticoagulant sample bottles smeared with lithium-heparin and fluoride oxalate. The blood samples were spun at 5000rpm using MSE Centrifuge to obtain plasma. The animal was dissected and only the liver collected for pathological studies.

2.3 Measurement of AST (SGOT) and ALT (SGPT)

The activities of glutamic pyruvate transaminase and glutamic -oxaloacetate transaminase was analysed

according to the method specified by Reitman and Frankel (1957). Measurement of Alkaline Phosphatase (ALP): Plasma alkaline phosphatases activity was measured.

Tables 1 to 3 show the effects of three different antiretroviral drugs (Zidovudine Nevran and Lamivudine) on Aspartate Aminotransfrase (AST) (Table 1), Alanine Aminotransferase (AAT) (Table 2) and Alkaline Phosphatase (ALP) (Table 3) levels (IU/L) treated for 5 weeks of study.

Table 1: Effect of Antiretroviral Drugs (Zidovudine Nevran and Lamivudine) on AST Levels (IU/L) treated for 5 weeks.

DRUG TREATMENT/CONTROL GROUPS		WEEKS OF TREATMENT				
		WK1	WK2	WK3	WK4	WK5
GROUP A (CONTROL- Distil water)				M±SEM		
				122.67±8.45		
ZIDOVUDINE	(0.7mg/kgBW)	105.00±1.15 ^{abb}	108.00±1.15	96.00±1.15 ^a	136.00±1.15 ^a	136.00±1.15 ^a
	(1.4mg/kgBW)	108.00±1.15 ^a	105.00±1.15	108.00±1.15 ^a	67.00±1.15 ^a	136.00±1.15 ^a
	(2.1mg/kgBW)	112.00±1.15 ^a	102.00±1.15	136.00±1.15 ^a	89.00±1.15 ^a	36.00±1.15 ^a
	(2.8mg/kgBW)	130.00±1.15	120.00±1.15 ^a	126.00±1.15 ^a	108.00±1.15 ^a	41.00±1.15 ^a
NEVRAN	(0.7mg/kgBW)	134.00±1.15 ^{abb}	141.00±1.15 ^a	178.00±1.15 ^a	76.00±1.15 ^a	23.00±1.15 ^a
	(1.4mg/kgBW)	130.00±1.15	148.00±1.15 ^a	112.00±1.15 ^a	76.00±1.15 ^a	67.00±1.15 ^a
	(2.1mg/kgBW)	141.00±1.15 ^a	156.00±1.15 ^a	125.00±1.15 ^a	89.00±1.15 ^a	76.00±1.15 ^a
	(2.8mg/kgBW)	141.00±0.58 ^a	130.00±1.15 ^a	108.00±1.15 ^a	89.00±1.15 ^a	36.00±1.15 ^a
LAMIVUDINE	(0.7mg/kgBW)	165.00±0.58 ^{abb}	112.00±1.15	148.00±1.15	89.00±1.15	94.00±1.15
	(0.14mg/kgBW)	148.00±1.15 ^a	148.00±1.15 ^a	141.00±1.15 ^a	59.00±1.15 ^a	59.00±1.15 ^a
	(2.1mg/kgBW)	156.00±1.15 ^a	136.00±1.15 ^a	148.00±1.15 ^a	89.00±1.15 ^a	36.00±1.15 ^a
	(2.8mg/kgBW)	136.00±1.15 ^a	130.00±1.15 ^a	141.00±1.15 ^a	67.00±1.15 ^a	41.00±1.15 ^a

AST: Aspartate Aminotransfrase, Values are expressed in mean ± standard error of the mean (M±SEM), Superscript a: indicates significant difference (p<0.05) with control, Superscript b: indicates significant difference (p<0.05) at 0.7mg/KgBW of week 1, Superscript c: indicates significant difference (p<0.05) at 2.8mg/KgBW of week 5.

Table 2: Effect of Antiretroviral Drugs (Zidovudine Nevran and Lamivudine) on AAT Levels (IU/L) treated for 5 weeks.

DRUG TREATMENT/CONTROL GROUPS		WEEKS OF TREATMENT				
		WK1	WK2	WK3	WK4	WK5
GROUP A (CONTROL-Distil water)				M±SEM		
				44.67±2.60		
ZIDOVUDINE	(0.7mg/kgBW)	45.00±1.15 ^{bb}	43.00±1.15	52.00±1.15 ^a	49.00±1.15	49.00±1.15 ^a
	(1.4mg/kgBW)	45.00±1.15	36.00±1.15	52.00±1.15 ^a	34.00±1.15 ^a	73.00±1.15 ^a
	(2.1mg/kgBW)	47.00±1.15	45.00±1.15	50.00±1.15	20.00±1.15 ^a	24.00±1.15 ^a
	(2.8mg/kgBW)	49.00±1.15	47.00±1.15	56.00±1.15 ^a	34.00±1.15 ^a	36.00±1.15 ^{acc}
NEVRAN	(0.7mg/kgBW)	64.00±1.15 ^{abb}	43.00±1.15	47.00±1.15	38.00±1.15	22.00±1.15 ^a
	(1.4mg/kgBW)	50.00±1.15	45.00±1.15	40.00±1.15	62.00±1.15 ^a	25.00±1.15 ^a
	(2.1mg/kgBW)	49.00±1.15	45.00±1.15	49.00±1.15	38.00±1.15	27.00±1.15 ^a
	(2.8mg/kgBW)	44.00±0.58	49.00±1.15	60.00±1.15 ^a	38.00±1.15	17.00±1.15 ^{acc}
LAMIVUDINE	(0.7mg/kgBW)	44.00±0.58 ^{abb}	38.00±1.15	40.00±1.15	25.00±1.15 ^a	30.00±1.15
	(0.14mg/kgBW)	54.00±1.15 ^a	64.00±1.15 ^a	66.00±1.15 ^a	20.00±1.15 ^a	23.00±1.15 ^a
	(2.1mg/kgBW)	56.00±1.15 ^a	72.00±1.15 ^a	80.00±1.15 ^a	28.00±1.15 ^a	23.00±1.15 ^a
	(2.8mg/kgBW)	52.00±1.15 ^a	45.00±1.15	75.00±1.15 ^a	40.00±1.15	23.00±1.15 ^{acc}

AAT: Alanine Aminotransferase, Values are expressed in mean ± standard error of the mean (M±SEM), Superscript a: indicates significant difference (p<0.05) with control, Superscript b: indicates significant difference (p<0.05) at 0.7mg/KgBW of week 1, Superscript c: indicates significant difference (p<0.05) at 2.8mg/KgBW of week 5.

Table 3: Effect of Antiretroviral Drugs (Zidovudine Nevran and Lamivudine) on ALP Levels (IU/L) treated for 5 weeks.

		WEEKS OF TREATMENT				
		WK1	WK2	WK3	WK4	WK5
DRUG TREATMENT/CONTROL GROUPS				M±SEM		
GROUP A (CONTROL-Distil water)				44.67±2.60		
ZIDOVUDINE	(0.7mg/kgBW)	47.20±0.12	56.27±0.09	56.30±1.15	33.60±0.12	33.60±0.12 ^a
	(1.4mg/kgBW)	50.00±1.15	53.10±0.06	53.10±1.15	53.00±0.09	28.70±0.12 ^a
	(2.1mg/kgBW)	44.40±0.12	56.20±0.06	56.30±1.15	41.20±0.12	39.50±0.12 ^a
	(2.8mg/kgBW)	47.70±0.12	56.23±0.07	56.00±1.15	42.77±1.43	28.00±0.12 ^{acc}
NEVRAN	(0.7mg/kgBW)	44.40±0.23	46.90±0.00	46.87±1.15	44.10±0.12	22.00±0.12 ^a
	(1.4mg/kgBW)	41.70±0.12	45.50±1.15 ^a	44.13±0.19	44.10±0.12	25.00±0.12 ^a
	(2.1mg/kgBW)	55.30±0.15	50.00±1.15	50.13±0.19	55.90±0.12 ^a	27.00±0.12 ^a
	(2.8mg/kgBW)	50.00±1.15	53.10±0.06	53.10±0.12	55.90±0.12 ^a	17.00±0.12 ^{acc}
LAMIVUDINE	(0.7mg/kgBW)	52.50±0.21	56.30±0.06	56.57±0.12	50.00±0.12	30.00±0.12
	(0.14mg/kgBW)	58.20±0.06	50.00±1.15	50.10±0.21	50.00±0.12	23.00±0.12 ^a
	(2.1mg/kgBW)	38.70±0.12	50.00±1.15	50.00±0.12	44.10±0.12	23.00±0.12 ^a
	(2.8mg/kgBW)	41.70±0.12	56.30±0.06	56.30±0.12	52.90±0.12 ^a	23.00±0.12 ^{acc}

ALP: Alkaline Phosphatase, Values are expressed in mean ± standard error of the mean (M±SEM), Superscript a: indicates significant difference (p<0.05) with control, Superscript b: indicates significant difference (p<0.05) at 0.7mg/KgBW of week 1, Superscript c: indicates significant difference (p<0.05) at 2.8mg/KgBW of week 5.

2. RESULTS AND DISCUSSION

The results from table 1 showed that mean plasma aspartate amino transferase (AST) activity significantly decreased when compared to the mean control value of 122.67±8.45 for rats treated with Nevran. In table 2 there were significant decreases along the weeks in groups D and E for the drug Zidovudine. Lamivudine followed similar trend as Nevran. When compared with each other there were significant differences (P<0.05) among all group B of week 1 while there were no significant differences between any two drugs at group E of week 5.

For ALT, Nevran had significant decreases (p< 0.05) at week 5 for all groups while Zidovudine had significant increases (p<0.05) when both were compared to the control. Lamivudine also had the same trend as Zidovudine except for weeks 4 and 5. Nevran was significantly different (P<0.05) with the other two drugs at group B of week 1. In week 5 at group E, it was observed that Zidovudine was significantly different (P<0.05) with both of the other drugs. Nevran had significant increases at groups D and E when compared to the mean control value (46.73±3.54) for ALP.

Zidovudine followed this trend. Lamivudine had significant increases in all the weeks. In drug to drug comparison there was no significant difference (p>0.05) between the drugs at group E of week 5. In the face of global AIDS pandemic, advancement in the treatment of the disease has been strikingly impressive. For example, patients on antiretroviral therapy now live for more than a decade than those without.^[5,8] But problems still remain since hepatotoxicity has been a major side effect of antiretroviral drugs limiting their use in treatment regimens.

ALT is present in higher concentrations in the liver and to a lesser extent in the kidneys, heart, skeletal muscle, pancreas, spleen and lung. Increased levels of ALT are generally as a result of liver disease linked to hepatic necrosis such as cirrhosis, carcinoma, viral or toxic hepatitis and obstructive jaundice. Typically ALT is generally higher than AST in acute viral or toxic hepatitis, whereas for most patients with chronic hepatic disease, ALT levels are generally lower than AST levels. Elevated ALT levels have also been found in extensive trauma, muscle disease, hypoxia, myocardial infarction, circulatory failure and also shock and haemolytic disease (Allston, 1993). Elevated activities of these enzymes indicate cell damage which might have resulted from several mechanisms which include metabolic host mediated injury, hypersensitivity reactions, mitochondrion toxicity and immune reconstitution. All the nucleoside and non-nucleoside analogues have been implicated although the degree varies from one drug to the other.

The three drugs used in this study –Nevran (NNRTI), Zidovudine and Lamivudine (NRTI) exhibit this but hypersensitivity is more prevalent in Nevran (NNRTIs) than Zidovudine and Lamivudine (NRTIs) as seen in the research work. This is also supported by Ren et al., 2002. This is because both drug classes NRTIs and NNRTIs inhibit the same target, the reverse transcriptase enzyme. NRTIs bind at the active site thus inhibiting the DNA polymerase γ from the host cell while their counterpart NNRTIs bind on the enzyme thus changing its shape and also inhibiting the DNA polymerase γ .^[9,10]

ALP is a nonspecific enzyme which hydrolyses aliphatic, aromatic or heterolytic phosphate compounds. ALP is produced by osteoroblast of bones. Moderate increase in ALP levels is seen in hepatic diseases such as infective

hepatitis, alcoholic hepatitis or hepatocellular carcinoma. Very high activity of serum ALP than normal maybe noticed in extrahepatic obstruction or cholestasis.^[11,12] Increases in ALT and AST with lesser increases or normal ALP favours cell necrosis and are common symptoms of hepatotoxicity while increases in ALP and γ glutamyl transpeptidase were indicative of cholestasis. In this study γ glutamyl transpeptidase and serum bilirubin wasn't tested. At the clinical level, the mitochondria deficiency is responsible for the adverse effects such as life threatening lactic acidosis, hepatic steatosis and possible fat redistribution syndromes which are grouped as NRTI induced mitochondrial cythopathy.^[13]

Zidovudine has been involved in cases of fatal hepatic failure in advanced AIDS patients. These patients developed massive hepatomegalysis and microvesicular steatosis which progressed to fulminant hepatic failure.^[14] Zidovudine cams also cause acute hepatitis due to hypersensitivity which resolved itself exactly 10 days after cessation of therapy. In such patients Zidovudine is usually replaced with didanosine. Less report has been gotten on Lamivudine causing hepatic toxicity as compared to Zidovudine and Nevran on short term duration of administration.

These may be due to the low affinity of Lamivudine for mitochondria DNA polymerase γ .^[13] However Lamivudine is widely used and considered to be the best tolerated among the 3 drugs. Long term administration of Nevran can cause life threatening liver hepatotoxicity especially on women with high CD4⁺ counts but newer NNRTIs (efavirenz) have been produced with lesser effect.^[15] These findings suggest that greater increases in ALT than ALP maybe associated with hepatocellular injury. The study calls for the inclusion of hepatoprotective agents in the treatment regimen a.^[16]

4. CONCLUSION AND RECOMMENDATIONS

In conclusion, antiretroviral treatment with NRTIs and NNRTIs may be associated with hepatocellular injury. There should be close monitoring of liver enzymes to prevent life threatening events. Also, there should be inclusion of hepatoprotective agents in the treatment regimen. Furthermore, the researcher discovered that the overall incidence of severe hepatic injury was not significantly different between NRTIs and NNRTIs.

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