

Full Length Research Paper

Lavudine therapy and hepatotoxicity as seen in a Nigerian tertiary antiretroviral treatment centre

Akande A. A^{1*}, Olaosebikan O. F¹, Jimoh A. K¹, Abdulazeez¹, ²Olawumi H. O

¹Department of Chemical Pathology and Immunology, University of Ilorin Teaching Hospital, PMB 1459, Ilorin, Kwara State, Nigeria.

²Department of Hematology and Blood transfusion Services, University of Ilorin Teaching Hospital, PMB 1459, Ilorin, Kwara State, Nigeria.

Accepted 18 April, 2020

Hepatic toxicity is a common complication of anti-retroviral treatment in HIV patients, usually indicated or heralded by the elevation of liver transaminases measured in the blood. There had been reported evidence of hepatic toxicity in all the three currently approved classes of anti-retroviral drugs. However, its severity in some cases may warrant stoppage of the treatment. This study assessed the hepato-toxicity among HIV patients on antiretroviral therapy with lavudine in a drug treatment centre in Nigeria. Liver function test (LFT) results of patients treated with lavudine (lamivudine, stavudine and nevirapine) antiretroviral drug was collated and analyzed initially as baseline data and later over a period of three months after treatment with lavudine for liver enzymes assessment. Sixty three (63) subjects in all were analyzed, 28 males and 35 females (M: F = 0.8:1). The results showed that there was a non-significant ($p > 0.45$) decrease in the serum transaminases and alkaline phosphatase of the pretreatment LFT compared with the LFT after three months of treatment with lavudine. The levels of serum total protein and albumin showed a concomitant but non-significant ($p > 0.20$) decrease over the same period. Antiretroviral treatment with lavudine may be associated with hepatic enzymes induction but not toxicity at least in the short run, however hepatic function test should be monitored every month for the first three months after starting a new drug regimen and followed by once in six month subsequently for a year.

Key words: Lavudine, hepatotoxicity, treatment centre, HIV /AIDS patient.

INTRODUCTION

Hepatic toxicity is due to increased rate of cytolysis and significantly elevated serum transaminase level. It is usually a common complication in HIV-infected patients undergoing anti-retroviral therapy (Anthony, 2001) and approximately found in 6 - 30% of treated subjects (Beisel, 1996). Hepatic toxicity may also lead to elevated serum levels of alkaline phosphatase and bilirubin, which may either occur early or later in the course of therapy (Bellini et al., 2003). Many authors with different conclusions have evaluated the risk factors for hepatic toxicity associated with anti-retroviral regimens. Female gender, obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Adverse drug reactions affecting the liver are more likely in people who have

chronic liver disease such as hepatitis and pre-existing liver damage conditions such as chronic alcoholism (Bellini et al., 2003). Patients who had viral hepatitis in addition to HIV were found to have nearly four times as likely to develop severe hepatic toxicity associated with anti-HIV drugs. A previous study by Bellini et al. (2003) reported some 10% of people had experienced liver damage severe enough to warrant stopping anti-HIV therapy after six months on various HAART regimens especially in about 50% of the people taking ritonavir. This is had been attributed to HAART-induced immune reconstitution, or exacerbation of hepatitis B or C as noted by Brau et al. (1997).

Elevated liver enzymes have been reported by Carton et al. (1999) and Ching-Lung et al. (1998) in people taking the three currently approved classes of anti-retroviral groups, while the risk of severe hepatic toxicity was indicated to be 5-fold higher for patients taking ritonavir in

*Corresponding author. E-mail: yinkaakande@yahoo.com.

Table 1. Liver Function Results of the Subjects (Pre and 3month Post Treatment).

Parameters	Pre-treatment (M ± SD)	3 months Post treatment (M ± SD)	p-value
ALT(UI/L)	11.38 ± 8.1	10.07 ± 11.3	0.45
AST(UI/L)	18.27 ± 14.8	12.89 ± 8.8	0.01*
ALP(UI/L)	29.7 ± 21.8	34.73 ± 25.5	0.19
TP (g/l)	71.39 ± 9.7	63.95 ± 12.4	0.00*
ALB(g/l)	34.38 ± 7.2	29.67 ± 7.6	0.00*

one study (Dienstag et al., 1995) and however, another study (Carton et al., 1999) reported a high rate of hepatic toxicity irrespective of drug class.

In addition, other studies reported severe cases of hepatic toxicity found more in patients who are taking the protease inhibitor (indinavir and ritonavir) and nevirapine. However, the occurrence of liver damage is probably due to many conditions. Studies using the combination of stavudine, lamivudine, and Nevirapine have demonstrated it's efficacy in-patient with HIV infection. Transiently elevated levels of hepatic enzymes and bilirubin have been observed occasionally during treatment with lamivudine (Anthony, 2001). Lactic acidosis and severe hepatomegally with steathosis including fatal cases have been reported (Bellini et al., 2003) with the use of nucleoside analogues alone or in combinations including lamivudine and other anti-retrovirals. Due to the paucity of knowledge in our environment, this study intended to access the biochemical hepatic effect of the lavudine combination used in a national anti-retroviral drug treatment centre.

MATERIALS AND METHODS

This was a prospective study to assess the liver function derangement associated with the use of lavudine (lamivudine, stavudine and nevirapine combination drug) among HIV patients in University of Ilorin Teaching hospital. A review of HIV infected persons attending the hematology HIV clinic and treated with this drug combination for a period of three months was performed including the initial base-line result. Data on aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), bilirubin (conjugated and total), total protein (TP) and albumin (ALB) parameter evaluated on laboratory assessment of liver function during this period were collated and evaluated.

Patient's liver function tests data analyzed in the study included males and females on lavudine antiretroviral drug who did not change their medication during the study period, had their baseline liver function test normal before the treatment or at least liver enzyme elevation of not more than two times the upper reference limits at the beginning of the treatment. Ethical clearance for the study was obtained from the hospital authority.

Data was analyzed using SPSS version 10. Statistical analysis of mean, standard deviation, Chi square test was used for discrete variables while correlations were compared by linear regression analysis. Differences were regarded as significant when $P < 0.05$.

RESULTS

A total of 63 patient's liver function test results were analyzed comprising 28 males and 35 females. (Male: female

ratio of 0.8:1). The mean age of the group was 36.2 ± 8.9 . The youngest and oldest among the male was 21 and 56 years respectively, while among the female it was 19 and 55 years respectively. The mean age of the male subjects was 36.3 ± 8.7 and female was 36.4 ± 8.5 .

In the studied population, there was a statistically significant reduction in the AST (18.27 ± 14.8 pre-treatment and 12.89 ± 8.8 post treatment ($p < 0.01$), serum total protein (71.4 ± 9.7 pretreatment and 63.9 ± 12.4 post treatment ($p < 0.00$) and serum albumin (34.4 ± 7.2 pretreatment and 29.7 ± 7.6 post treatment ($p < 0.00$). The reduction in ALT was not significant but an increment in ALP was noticed (Table 1).

The liver biochemical parameters amongst the male subjects were similar to the studied group. There was a significant reduction in AST (21.6 ± 16 pretreatment and 11.1 ± 8.9 post-treatment ($p < 0.01$), serum total protein (70 ± 9.8 pre-treatment and 63.8 ± 14.7 post-treatment ($p < 0.04$) and serum albumin (32.2 ± 8.3 pre-treatment and 27.8 ± 7.2 post-treatment ($p < 0.03$). The reduction in ALT was also significant ($p < 0.00$) However, there was an insignificant ($p < 0.24$) increment in ALP. Among the female subjects there was only a significant reduction in both the serum total protein (72.5 ± 9.9 pre-treatment and 64 ± 10.9 post-treatment ($p < 0.001$) and serum albumin (36.1 ± 6.2 pre-treatment and 31.2 ± 7.8 post-treatment ($p = 0.004$). The reduction in the serum AST and ALT values were not significant ($p > 0.9$ and 0.3 respectively).

The increment in the serum level of ALP (31.6 ± 25.3 pre-treatment and 36.3 ± 30.5 post-treatment ($p > 0.4$) was not significant. (Table 2).

Majority of the males (96.4%) and females (91.4%) showed evidence of grade 1 hepatic toxicity, while 3 patients - 1(3.6%) male and 2 (5.7%) females) had grade 2 hepatic toxicity. Only 1 female (2.9%) had grade 3 toxicity. No patient had a grade 4. (Table 3)

DISCUSSION

According to Verucchi et al. (2003) and Gisolf et al. (2000), antiretroviral therapy with three or more medications is the international standard of care for patients with the acquired immunodeficiency syndrome (AIDS) and elevated liver enzymes have been reported in people taking the three currently approved classes of anti-retroviral groups according to Carton (1999), Dienstag et al.

Table 2. Pre and post treatment biochemical parameters by gender.

Parameter	MALE			FEMALE		
	Pre (m ± sd)	Post (m ± sd)	P value	Pre (m ± sd)	Post (m ± s d)	P value
ALT(IU/L)	12.24 ± 9.6	8.48 ± 4.8	0.119	11.31 ± 7	11.46 ± 14.5	0.956
AST(IU/L)	21.6 ± 16.1	11.1 ± 8.9	0.004*	17.14 ± 13.6	14.8 ± 8.5	0.345
ALP(IU/L)	28.4 ± 17	34.2 ± 17.8	0.236	31.6 ± 21.8	36.3 ± 30.5	0.341
TP (g/l)	70.00 ± 9.8	63.84 ± 14.7	0.040*	72.5 ± 9.9	63.9 7 ± 10.9	0.001*
ALB(g/l)	32.16 ± 8.3	27.8 ± 7.2	0.030*	36.1 ± 6.2	31.2 ± 7.8	0.004*

Table 3. Grading of hepatotoxicity among the subjects

	GRADE 1 1.25-2.5 X ULN	(%)	GRADE 2 >2.5-5.0 X ULN	(%)	GRADE 3 >5-10 X ULN	(%)	GRADE 4 >10 X ULN	(%)	TOTAL	(%)
MALE	27	96.4	1	3.6	0	0	0	0	28	44.4
FEMALE	32	91.4	2	5.7	1	2.9	0	0	35	55.6
TOTAL	59	93.7	3	4.8	1	1.5	0	0	63	100

(1995) and Chinget al. (1999)

Clinical studies grade liver injury based on the rise in serum transaminase enzyme levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) as grades 1 to 4 based on the fold raise, however, grades 3 and 4 which represent greater than five and ten fold raise respectively are considered significant (Group AID-SCT, 1996). This is consistent with the definition by the National Institute of Health/National Institute of Allergy and Infectious Disease (NIH/NIAID) grading of hepatic toxicity as a greater than five fold increase in serum transaminase levels with or without clinical hepatitis. Our study demonstrated that majority of our patients had liver injury (grade 1) and none had hepatic toxicity.

Hepatic toxicity has been associated with antiretroviral medications as well as cholesterol-lowering agents and several antibiotics (biaxin, bactrim) that people with HIV often use. Hepatic toxicity stems from mitochondrial damage, which is damage to the part of cells involved in energy production. Symptoms of hepatic toxicity are similar to symptoms of HBV disease: dark urine, fatigue and jaundice (Halliwell, 1991). It may be necessary as reported (Lenzo, 1997) to modify or discontinue certain therapies due to hepatic toxicity.

First-line drug treatment of HIV in a previous study (Liz, 2000) were changed because of toxic effects in 102 patients (11%), disruption in the medication supply in 66 patients (7 percent), sexual activity by women of reproductive age in 29 patients (3%), suspected treatment failure in 11 patients (1%), and tuberculosis in 21 patients (2%). Anemia and central nervous system symptoms were the most common toxic effect observed in the Liz (2000) study.

Our study showed that HIV positive patients who are on lamivudine therapy a combination of lamivudine (NRTI), stavudine (NRTI) and nevirapine (PI) for three months did

have an evidence of decreased hepatic synthetic function and intra hepatic cholestasis but observed rather a decrease in activities of the transaminase which are mainly enzymes of hepatocellular damage. This may probably be the initial stage of the antiretroviral induced hepatic toxicity which is characterized by the hepatocytes inflammation evidenced by the increased alkaline phosphatase and decreased serum total protein and albumin. The initial process, which is followed by the mitochondrial damage, is characterized by an increase in the transaminases as reported in earlier studies. (Matthiasa et al., 2006)

Lamivudine, which is one of the combinations in lamivudine therapy, have been shown to promote significantly reversible hepatic necroinflammatory (Martinez et al., 2001) activities and induced a sustained normalization of alanine aminotransferase levels in 68% of the patients. This is in contrast to another one of the combination – nevirapine, which has been implicated in hepatic toxicity in a dose related fashion. (NIMR, 2005). The disequilibrium effect of this combination could actually be responsible for the hepatic function picture seen in the individual as evident by our study.

In a randomized trial, (Mehta et al., 2006) lamivudine in combination with Zidovudine and Efavirez had better antiretroviral activity with fewer side effects. However, lamivudine is widely used and considered to be one of the best-tolerated antiretroviral agents. In patients infected with hepatitis B virus (HBV) and HIV, a brief rise in transaminase levels may develop during the first month of therapy with lamivudine (Ngondi, 2006). This transient increase subsides thereafter, and patients have experienced clinical improvement while continuing lamivudine therapy. Hepatitis C co-infection is another consideration in HIV patient especially the females who are more susceptible to the infection through sexual intercourse more than the males (Gonzales, 2003).

Stavudine is rarely associated with hepatic dysfunction. One case of hepatitis, steatosis and lactic acidosis has been reported by the panel on clinical practices for treatment on HIV infection (PCPTH, 2005) in an obese woman who began taking stavudine after being stable on lamivudine. High serum aminotransferase concentrations have been reported (Patrice, 2005) in association with protease inhibitors, but hepatitis is rare. All anti-retrovirals can adversely affect the liver. Hepatic toxicity has been commonly associated with non-nucleoside reverse-transcriptase inhibitors (NNRTIs) such as nevirapine and ritonavir. Studies by Reisler, (2001) and WHO (2004) found hepatic toxicity in 12.5% of patients receiving nevirapine and 30% of patients receiving ritonavir. Co-infection with hepatitis B or C may be an additional risk factor for the development of hepatic events when certain hepatic toxic antiretroviral agents are used as concluded in the above studies.

The total protein and albumin significantly reduced three months after commencement of stavudine in the same set of patients as observed in our study. In extra vascular spaces, the sulphhydryl group of plasma proteins, including plasma albumin serve as antioxidants (Staszewski, 1999) with enzymes and scavenging chemicals such as vitamin C and vitamin E also having antioxidant activities. Malnutrition can have a severe impact on the specific antigen-antibody components of the immune system and can also compromise general bodily defense mechanisms (Sulkowski, 2000). This is common in HIV-infection prior to the introduction of highly active antiretroviral therapy (HAART). In a study in Cameroon (Ngondi, 2006) a greater reduction in plasma albumin concentration as an indicator of malnutrition was found in patients on HAART when compared to pre HAART patients. Studies (Mehta, 2006) have also shown that low plasma albumin is associated with faster HIV disease progression and suggest that low albumin levels are probably a consequence of HIV infection rather than merely reflective of some individuals inherently having low albumin levels.

In conclusion antiretroviral treatment with stavudine may be associated with hepatic enzymes induction of grade 1 at-least in the short run, however hepatic function test should be monitored once every month for the first three months after starting treatment regimen and followed by once in six month for at least a year. The treatment approaches to HIV/AIDS should revolve around supplementing the liver's processing mechanism and accelerating the transformative processes of the medication by both hepatic and Kupffer cells handling the increased and chronic drug load. However, more evidence of HIV disease and effects of its management upon liver need to be studied to acquire a more complete biochemical picture of liver de-compensation and toxicity.

REFERENCES

Anthony B (2001). Hepatitis, HIV and Your Liver. AIDS Community

- Research Initiative of America community forum summary.
 Beisel WR (1996). Nutrition and Immune function. *J. Nutrition*.126:2611S-2615S.
 Bellini C, Keiser O, Chave JP, Furrer HJ, Bucher H, Kaiser L, Telenti A, Cavassini M (2003). Frequent liver dysfunction after lamivudine withdrawal in hiv-hepatitis b co-infection. *Antivir Ther.* 8 (Suppl.1): abstract no. 992.
 Brau N, Leaf HL, Wieczorek RL, Margolis DM (1997). Severe hepatitis in three AIDS patients treated with indinavir. *Lancet.* 349:924-925.
 Carton JA, Maradona JA, Asensi V (1999). Lamivudine for chronic hepatitis B and HIV coinfection. *AIDS.*13: 1002-1003.
 Ching-Lung L, Rong-Nan C, Nancy WY, Leung, Ting-Tsung C, Richard Guan, Dar IT, Keng-Yeen N, Pui-Chee W, Julie CD, Judy Barber, Sally LS, Fraser DG (1998). A One-Year Trial of Lamivudine for Chronic Hepatitis B. *The New Engl. J. Med.* Vol. 339:61-62.
 Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin R (1995). A preliminary trial of lamivudine for chronic hepatitis B infection. *N. Engl. J. Med.* 333:1657-1661.
 Verucchi G et al (2003). Incidence of Liver Toxicity in HIV-Infected Patients Receiving Isolated Dual Nucleoside Analogue Antiretroviral Therapy. *J. Acquir. Immune Defic. Syndr.* 33(4): 546-548.
 Gonzalez SA, Talal AH (2003). Hepatitis C virus in human immunodeficiency virus-infected individuals: an emerging comorbidity with significant implications. *Semin. Liver Dis.* 23(2):.149-166.
 Gisolf EH, Dreezen C, Danner SA, Weel JL, Weverling GJ (2000). Risk factors for hepatotoxicity in HIV-1 infected patients receiving ritonavir and saquinavir with or without stavudine, Prometheus Study Group. *Clin. Infect. Dis.* 31:1234-1239.
 Group AIDSCT (1996).Table of grading severity of adult adverse experiences. Rockville, MD: US Division of AIDS, National Institute of Allergy and Infectious Disease.
 Halliwell B (1991). Reactive oxygen species in living systems: source, Biochemistry and role in human disease. *Am. J. Med.*114-122.
 Lenzo NP, Garas BA, French MA (1997). Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient: a case report. *AIDS.*11:1294-1296.
 Liz H (2001). Adverse effects associated with antiretroviral therapy. *Bulletin of experimental treatments for AIDS.*1-11
 Matthiasa B et al (2006). Uridine supplementation enhances hepatic mitochondrial function in thymidine-analogue treated HIV-infected patients. *AIDS.* 2-8
 Martinez E, Blanco JL, Arnaiz JA et al (2001). Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS.*15:1261-1268.
 Mehta SH , Astemborski J, Sterling TR, Thomas DL, Vlahov D (2006). Serum Albumin as a Prognostic Indicator for HIV Disease Progression, *AIDS Res. Hum. Retroviruses.* 22:14 -21
 Ngondi JL, Oben J, Forkah DM, Hame LH, Mbanya D (2006). The effect of different combination therapies on oxidative stress markers in HIV infected patients in Cameroun. *AIDS Res. Therapy.* 3:1-7.
 Nigeria Institute of Medical Research (2005). Training manuals for Doctors on the use of antiretroviral drugs in Nigeria. 1st Edition.
 PCPTH (Panel on Clinical Practices for Treatment of HIV Infection.) (2005). Guidelines for the use of antiretroviral agents in HIV -infected adults and adolescents. Washington, D.C.: Government Printing Office.
 Patrice S, Paul L, Macarthur C, Francine N, Gerry B, Gyrlande B, Erik G, Stefan Kenel-Pierre BS, Peter FW, Roy G, Warren DJ Jr, Jean William P, Daniel WF (2005). Antiretroviral Therapy in a Thousand Patients with AIDS in Haiti. *New J. Med.* NO 22. Vol. 353: 2325-2334.
 Reisler R, Liou S, Servoss J, Robbins G, Theodore D, Murphy R, Chung R (2001). Incidence of hepatotoxicity and mortality in 21 adult antiretroviral treatment trials. Program and abstracts of The 1st IAS Conference on HIV Pathogenesis and Treatment; Buenos Aires, Argentina. p. 43.
 World Health Organization (2004). Scaling up antiretroviral therapy in resource-limited settings. Geneva.
 Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, Stryker R, Johnson P, Labriola DF, Farina D, Manion DJ, Ruiz NM (1999). Efavirenz plus Zidovudine and Lamivudine, Efavirenz plus Indinavir, and Indinavir plus Zidovudine and Lamivudine in

the Treatment of HIV-1 Infection in Adults. *N. Engl. J. Med.* 341:1865-1873.

Sulkowski MS, Thomas DL, Chaisson RE, Moore RD (2000).
Hepatotoxicity associated with antiretroviral therapy in adults infected

with human immunodeficiency virus and the role of Hepatitis C or B virus infection. *JAMA.* 283: 74–80.