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Research Article

EFFECT OF ANTIRETROVIRAL TREATMENT REGIMENS ON LIVER ENZYMES IN HUMAN IMMUNODEFICIENCY VIRUS PATIENTS

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ABSTRACT

Objective: Treatment of human immunodeficiency virus (HIV) with highly active antiretroviral therapy is complicated due to its effect on liver enzymes along with associated risk of opportunistic infection and its treatment. The objective of the study was to compare the effect of two zidovudine and lamivudine-based regimens on liver enzymes and to correlate them with age and CD4 count in HIV patients.

Methods: In this retrospective study, patients who have received zidovudine+lamivudine+nevirapine (ZLN) or zidovudine+lamivudine+efavirenz (ZLE) at least for 1 year were included. Baseline, 6-month, and 1-year values of aspartate amino transferase (AST), alanine amino transferase (ALT), and CD4 count were collected. One-way analysis of variance and unpaired t-test were used to compare the difference in AST, ALT, and CD4 count value within basal, 6 months, and 1 year of two group and between the groups, respectively. Pearson's correlation was used for correlation study.

Results: Elevation of AST levels in patients who had received ZLN regimen at different interval was significant statistically. There was a statistically significant elevation of ALT level at 6 months. There was no significant change in AST and ALT values in patients who had received ZLE regimen. Between the two regimens, there was statistically significant difference in AST and ALT values at 6 months and 1 year. There was no correlation between age and CD4 count with liver enzymes.

Conclusion: We conclude from the study that nevirapine containing zidovudine regimen showed a slight elevation in AST. The efavirenz regimen did not show a change in AST and ALT.

Keywords: Antiretroviral therapy, Alanine transaminase, Aspartate transaminase, CD4 count.

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INTRODUCTION

Treatment of human immunodeficiency virus (HIV) with highly active antiretroviral therapy (HAART) is very complicated. Coping with adverse effect and adherence to treatment are the major problems encountered by patient. Selection of suitable regimen and development of resistance are the challenges faced by the physician. Liver is the principle target of drug toxicity among patients receiving antiretroviral treatment. Different antiretroviral treatment (ART) regimens have a varying degree of hepatotoxicity.

Antiretroviral drug-related liver injury (ARLI) is defined as elevations in liver enzymes in serum, with alanine amino transferase (ALT) characteristically greater than aspartate amino transferase (AST). This is one major factor responsible for treatment discontinuation in HIV-infected patients [1]. Hence, early detection and skillful management of ARLI are very important among HIV-infected patients who are on HAART [2]. There is a wide variation in the criteria used in clinical studies to categorize the severity of hepatotoxicity. Some studies have utilized ALT parameters as minimal as 2 times the upper limits of normal while others have employed an absolute threshold (e.g. >100 IU/ml), regardless of baseline liver function tests [3,4]. Some studies have categorized the aminotransferase alteration as "mild" when enzyme hepatic enzyme levels (<5 times the upper reference limit), "moderate" (5–10 times the upper reference limit), or "marked" (>10 times the upper reference limit) [5,6].

Multiple factors such as alcoholism, lipid-lowering drugs, concomitant hepatitis infection, antitubercular drugs, various opportunistic infections, and cholangitis may be responsible for elevation in liver enzymes in addition to direct damage of hepatic cells by HIV [7-13]. The direct inflammation of hepatocyte caused by HIV was thought to be one of the mechanisms. It could be due to apoptosis induced by caspases [2,7,8]. Other studies have quoted mitochondrial dysfunction with a decrease in mitochondrial deoxyribonucleic acid in various tissues, and alteration in permeability in the mitochondrial membrane by HIV proteins was the reason for elevation in hepatic enzymes [12-19]. AST and ALT are hepatic enzymes that could be used as markers of hepatocellular injury [20].

Hepatotoxicity in HIV-infected patient may present as asymptomatic elevation of transaminase levels to liver failure due to fulminant hepatitis, a rare complication resulting in the death of patient despite the discontinuation of HAART. It is associated with jaundice, coagulopathy, and markedly elevated ALT levels [21]. Less severe cases of ART-related hepatotoxicity are associated with reversible abnormal serum ALT and/or AST levels in the presence or absence of clinical symptoms of liver injury [22]. A report also suggests that the use of nevirapine and efavirenz in HAART regimens was associated with hepatotoxicity [23]. As per the literature search, there were only few studies done to study the effect of HAART regimens on liver enzymes in Indian subcontinent [6,7]. Hence we designed this study to evaluate the effect of HAART regimen in HIV infected patients of Coastal Karnataka.

MATERIALS AND METHODS

Materials

This retrospective study was conducted in District Hospital, Karwar, Uttara Kannada, Karnataka, India, which was the recognized center of National AIDS Control Organization. Patients

of either gender and in the age group of 18–65 years who had received either zidovudine+lamivudine+nevirapine (ZLN) or zidovudine+lamivudine+efavirenz (ZLE) during 2008–2015 at least for 1 year during 2008–2015 were included in the study.

Methodology

After obtaining the institutional ethics committee permission, patients with a history of alcoholism, tuberculosis, concurrent hepatitis B virus (HBV), hepatitis C virus (HCV) infections, Pneumocystis jiroveci pneumonia, pre-existing hepatic disease, and receiving hepatotoxic drug and prophylactic therapy for HBV and HCV were excluded from the study. Patients' baseline, 6 months, and 1 year CD4 count, AST. and ALT values were recorded from the patient card.

Statistical analysis

The CD4 count, AST, and ALT values at basaline, 6 months, and 1 year were expressed as mean±standard deviation. The difference in AST, ALT, and CD4 count value of basaline, 6 months, and 1 year within the group was compared by one-way analysis of variance. Unpaired t-test was used to compare basaline, 6-month, and 1-year values of AST, ALT, and CD4 between the groups. Correlation between AST, ALT with age, and CD4 count of 6-month and 1-year value was done by Pearson's correlation coefficient**.** Percentage of patients with elevated liver enzymes was expressed in percentages**.** SPSS package20 was used to analyze the results. p<0.05 was considered statistically significant.

Table 1: Demographic characteristic of patients

S.No.	ZLN group	ZLE group
Number of patients enrolled	46	38
Male: female ratio	29:17	20:18
Mean age (in years)	38.39±1.12	38.02±1.06
BMI	20.37±0,59	18.52±0.85
CD 4 count at baseline	356.19±57.84	303.7±34.54
CD 4 count at 6 months	468.0±60.54	482.05±±49.28
CD 4 count at 1 year	560.80±67.93	520.47±53.88
p value	0.0703	0.0029*

One-way ANOVA test - CD4 count between different interval *p<0.005.
ZLN: Zidovudine+lamivudine+nevirapine, ZLE: Zidovudine+lamivudine+efavirenz, ANOVA: Analysis of variance

RESULTS

The details of patients screened were given in Fig. 1 (patient algorithm) and the patient characteristics are given in Table 1.

Comparison within the ZLN and ZLE at different interval

The CD4 count had increased considerably from 356.19±57.84 at baseline to 560.80±67.93 at the end of 1 year in ZLN group, while in ZLE group, the elevation was from 303.7±34.54 baseline to 520.47±53.88 which was statistically significant (p<0.005) as depicted in Table 1. There was a significant elevation of AST value from 32.20±2.219 at baseline to 44.71±3.30 at 1 year in ZLN group. However, there was no much change in the AST value at various intervals in ZLE-treated patient group (Table 2). In ZLN-treated patients, there was an initial rise in ALT value from 30.90±2.068 to 42.99±3.36 at 6 months followed by fall below the baseline value which was statistically significant (p<0.005). This type of variation was not evident in the ZLE-treated patient group (Table 2).

Comparison between ZLN and ZLE group

The change in the AST value between ZLN and ZLE at 6 months interval and 1 year was significant as shown in Table 3. The ALT values were also statistically significant at 6 months and 1 year interval. However, these patients were clinically asymptomatic.

Percentage of patients with mild elevation in AST and ALT levels

Eight percent patients had elevated AST levels in ZLE-treated group at 6 months and 1 year (28% at baseline) contrary to the fall of ALT levels in 5% patients at 6 months and 1 year interval in ZLE (36% at baseline to 31%). This gave an indication that ZLE was the better regimen without any change in liver enzyme as far as ARLI is considered (Fig. 2). In the ZLN-treated group, 21% and 26% of patients had mild elevation in AST value at 6 months and 1 year, respectively, considering the fact that 26% of patient had a mild rise of AST value at baseline, whereas 12% and 23% of patients has mild elevation in ALT levels at 6 months and 1 year interval, respectively, from baseline of 27% of patients (Fig. 3).

Table 2: CD4 counts, liver enzyme values with two treatments

Interval	AST IU/L (ZLN)	AST IU/L (ZLE)	ALT IU/L (ZLN)	ALT IU/L (ZLE)
Baseline	32.20±2.219	33.41±1.92	30.90±2.068	33.20±2.47
6 month	43.497±3.44	35.78±2.546	42.99±3.36	34.05±3.31
1 year	44.71±3.30	34.1±2.34	22.2±3.37	32.51±2.306
P value	0.007*	0.755	0.002**	0.928

One-way ANOVA test, *p<0.05, **p<0.005 (within the group at different intervals). ZLN: Zidovudine+lamivudine+nevirapine (n=46), ZLE: Zidovudine+lamivudine+efavirenz (n=38), ANOVA: Analysis of variance, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

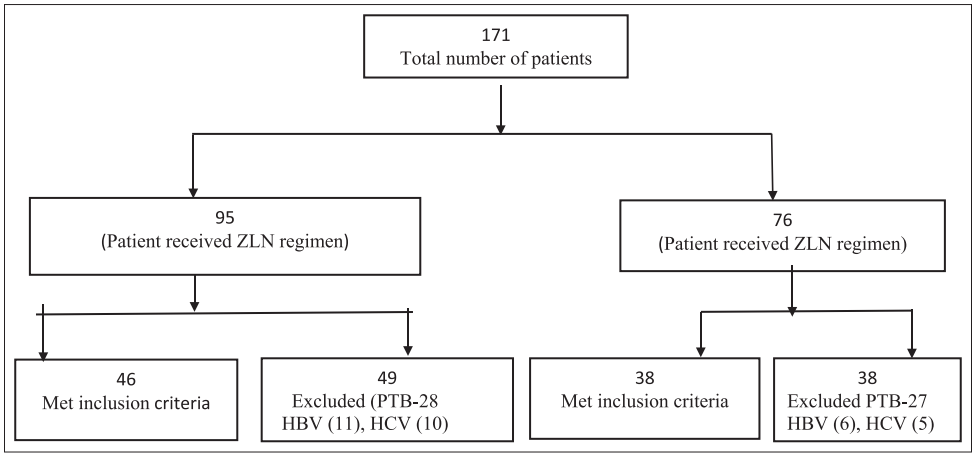

Fig. 1: Details of patients screened for the study

We correlated the AST and ALT at 6 months and 1 year with CD4 count at the same interval and patients' age. It was found that there was a negative correlation between AST and ALT levels with CD4 count at the end of 1 year in both groups as shown in Table 4. However, it was statistically not significant. There was a negative correlation between age and AST and ALT values in both groups at 6 month interval. However, we could not draw conclusion from this because the correlation was statistically not significant (Table 5).

Table 3: Liver enzyme at different interval in ART regimens

Interval	ZLN IU/L	ZLE IU/L	p value
Baseline (AST)	32.20±2.219	33.41±1.92	-
6 months (AST)	43.497±3.44	35.78±2.546	0.0347*
1 year (AST)	44.71±3.30	34.1±2.34	0.0048**
Baseline (ALT)	30.90±2.068	33.20±2.47	-
6 months (ALT)	42.99±3.36	34.05±3.31	0.0234*
1 year (ALT)	22.2±3.37	32.51±2.306	0.0017**

Between the groups (unpaired test), *p<0.05, (n=46)**p<0.005.
ZLN: Zidovudine+lamivudine+nevirapine, ZLE: Zidovudine+lamivudine+efavirenz, (n=38) AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ART: Antiretroviral treatment

Table 4: Correlation between liver enzymes with CD4 count at different interval

Liver enzymes	CD4 count at 6 months	CD4 count at 1 year
AST 6 months (ZLN group)	−0.0209 (0.8905)	-
AST 6 months (ZLE group	0.761 (0.6499)	-
ALT 6 months (ZLN group)	0.461 (0.7607)	-
ALT 6 months (ZLE group)	−0.761 (0.6499)	-
AST 1 year (ZLN group)	-	−0.1524 (0.312)
AST 1 year (ZLE group)	-	−0.0327 (0.8453)
ALT 1 year (ZLN group)	-	−0.0865 (0.5674)
ALT 1 year (ZLE group)	-	−0.179 (0.2823)

Pearson's correlation (two-tailed *P* value). (n=38) Zidovudine+lamivudine+nevirapine, (n=46) ZLE: Zidovudine+lamivudine+efavirenz, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

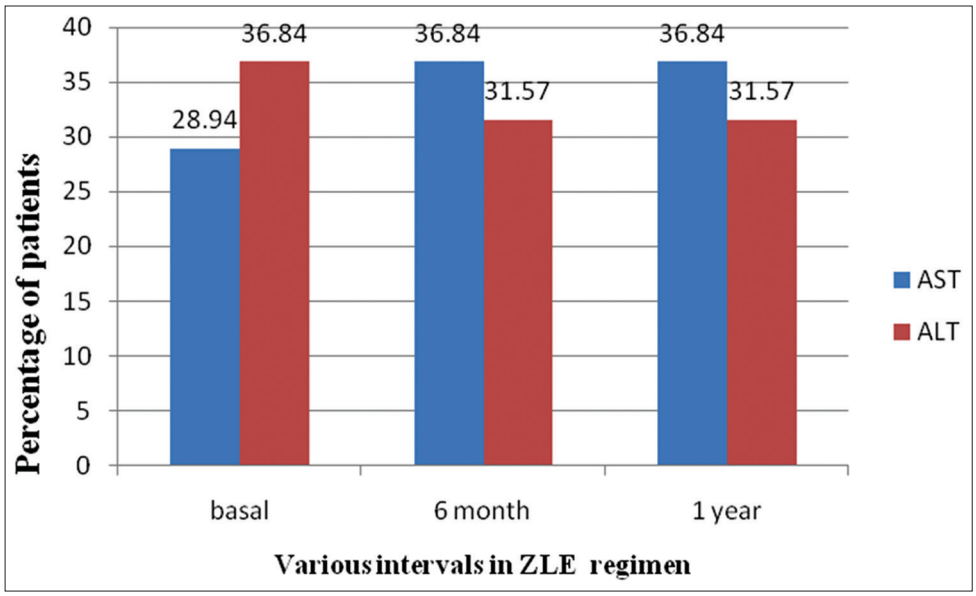

Fig. 2: Percentage of patients with increase in enzyme levels in Zidovudine+lamivudine+efavirenz regimen (n=38)

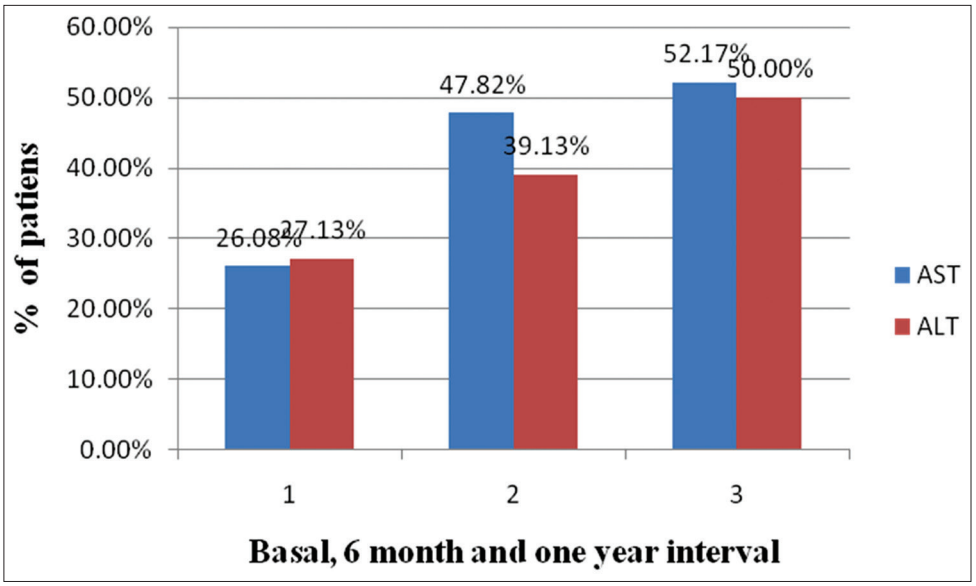

Fig. 3: Percentage of patients having elevated liver enzymes in Zidovudine+lamivudine+nevirapine regimen (n=46)

Table 5: Correlation between age and liver enzymes

Group	AST (6 months)	ALT (6 months)	AST (1 year)	ALT (1 year)
Age (ZLN)	−0.214 (0.513)	−0.0421 (0.78)	0.034 (0.826)	0.028 (0.85)
Age (ZLE)	−0.053 (0.75)	−0.053 (0.075)	−0.011 (0.94)	0.062 (0.709)

Pearson's correlation (two tailed p value). Zidovudine+lamivudine+nevirapine, ZLE: Zidovudine+lamivudine+efavirenz, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

DISCUSSION

Antiretroviral therapy can elevate liver enzymes, i.e., ALT or/and AST levels in patients receiving nevirapine and high dose of tenofovir as one of the agents in HAART [24,25]. The elevation of alanine transferase is considered to be the hallmark of ARLI. It has been graded from Grade 1 to Grade 4 depending on the ALT elevation. Although Grade 1 (40–120 IU/L) and Grade 2 (120–200 IU/L) will have minimal clinical implication, Grade 3 (201–399 IU/L) and Grade 4 (more than 400 IU/L) may be associated with significant clinical outcome in 5–10% of patients treated with combination ART [23,26-28]. Our study also supports this view in that the slight elevation in AST at 6 month and 1 year after treatment with ZLN was not associated with any clinical manifestation. However there was no alteration in enzyme levels in ZLE group.

The patient adherence to HAART treatment and patient compliance during initial period will be very important aspect in HIV treatment. Bhanukumar *et al.* stated that it is very important to keep the patients under strict observation during the initial weeks of nevirapine therapy [29]. Coffie *et al*. quoted the median delay between nevirapine-based regimen and occurrence of toxicity was 2.5 months while van Griensven *et al.* quoted that maximum hepatotoxicity was seen after 6 months of treatment [30,31]. In our study, the maximum elevation in AST and ALT levels was seen at 6 months, though we did not estimated the enzyme level at monthly interval (Tables 2 and 3). This hepatotoxicity is important as it may lead to treatment discontinuation if it is of severe degree [32]. Apart from this hepatotoxicity, it is also important to understand the genetic variability of HIV-2 and resistant to antiretroviral drugs in patients receiving HAART if facilities are available to improve patient compliance as suggested by Johnson *et al.* [33].

In our study, although there were more than 20% of patients with mild elevation in AST levels at 6 months and 1 year interval in ZLN regimen, the mild elevation in ZLE treatment was seen in mere 5% of patients. However, no patient in our study population had Grade 2 or higher ARLI, i.e., >3 times the upper limit normal. This could be due to the stringent exclusion criteria such as concomitant viral infection, tuberculosis, and other opportunistic infection apart from alcoholics and pre-existing liver diseases. This is in contrast to the study of Sulkowski *et a*l. in which 10.8% of patients and 8.9% of patients had more than 5 times the AST and ALT, respectively, though there is no mention regarding the milder degree [34].

Antoneo *et al*. study showed a moderately strong positive correlation found between AST with viral load where as weak correlation with ALT level [35]. Our study showed a weak negative correlation between CD4 count and AST and ALT levels at 1 year. This finding of our study strengthens Jose study because we correlated with CD4 count where as they correlated with viral load. This could be possibly related to the increase in CD4 count at 1 year interval which has reduced the viral mediated liver injury. This could be in turn due to the effect of apoptosis induced by the viral proteins such as Tat, Nef, Vpr, protease, and gp120 in different cell groups. These findings support partially the theories of liver damage due to mitochondrial disturbance and the stimulation of the caspase cascade in the induction of apoptosis.

Our study arrived at the conclusion that age was negatively correlated with AST and ALT values of both ZLN and ZLE regimens at 6 months (Table 5) though it was not statistically significant. However, this correlation was not significant at 1 year values in both the regimens. Our study strengthens the view of Usha *et al.* and Judi *et al*. [36,37]. It proved the fact that the younger patient tolerates the drug therapy better than that the older patients. However, there are some studies which contradict our findings [38].

The limitation of our study was that we did not had a control group, i.e., those patients who were HIV positive without receiving either of these drug regimen. If we had that control group, we could have drawn some conclusion. Further studies need to be designed to have a clear influence of ART on enzyme level after excluding all the confounding factors and proper control group.

CONCLUSIONS

We conclude from the study that nevirapine-based regimen showed significant elevation in AST while ALT shows initial rise at 6 months followed by reduction. The efavirenz regimen did not show alteration in AST and ALT. Improvement in CD4 count could reduce the virus-mediated hepatic injury in patient receiving ART.

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AUTHORS' CONTRIBUTION

Adiga Sachidananda MN: Contributed in designing the study protocol, preparation of data template, statistical analysis, and manuscript writing. Adiga Usha S: Contributed in designing the study protocol, submission and getting approval by ethics committee, data collection and statistical analysis, and manuscript writing.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest that is directly relevant to the content of this original research article.

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