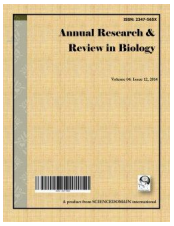

*Annual Research & Review in Biology*

*18(6): 1-7, 2017; Article no.ARRB.37288*
*ISSN: 2347-565X, NLM ID: 101632869*

# Comparison of Serum Transaminases and CD4 Counts in HIV Patients on ART Regimens Containing Zidovudine versus Stavudine

**Usha Adiga[1] and Sachidananda Adiga[2*]**

*[1]Department of Biochemistry, KSHEMA, Nitte University, India.*
*[2]Department of Pharmacology, KSHEMA, Nitte University, India.*

***Authors' contributions***

*This work was carried out in collaboration between both authors. Author UA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SA managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/ARRB/2017/37288
Editor(s):
(1) Saramma George, Human Physiology, Department of Biomedical Sciences, Faulty of Medicine, University of Botswana, Botswana
(2) George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA
Reviewers:
(1) Lívia Garcia Bertolacci-Rocha, Universidade Federal de Goiás, Brasil.
(2) Davies chisenga kalunga, Zambia.
(3) D. Atere Adedeji, Achievers University, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history/21648

***Original Research Article***

***Received 9th October 2017***
***Accepted 21st October 2017***
***Published 31st October 2017***

## ABSTRACT

**Introduction:** There has been a significant reduction in the mortality and morbidity associated with AIDS, due to the availability of highly active retroviral therapy (HAART). However adverse drug reactions related to ART use makes the treatment challenging. Aim of the study was to compare serum transaminases in HIV patients on two regimens; zidovudine versus stavudine, either of them administered in combination with nevirapine and lamivudine as well as to compare their efficacy, taking basal CD4 counts and after treatment CD4 counts as tools of comparison.
**Methods:** A retrospective observational study on 46 adult HIV patients, receiving AZT+3TC+NVP (ZLN) (group I) and 22 patients on D4T+3TC+NVP (SLN) (group II) was carried out. Data of baseline CD4 cell counts, serially monitored CD4 count values (once in 6 months) and serum transaminases were noted. Statistical analysis was done by using SPSS version 16.
**Results:** A very significant elevation of transaminases was observed at 6 months and 1 year in ZLN

**Corresponding author: E-mail: ushachidu@yahoo.com;*

group (P<0.01). CD4 counts were also significantly high (P<0.05). SLN group didn't show any significant differences in liver enzymes and CD4 counts at 6 months and 1 year. Extent of elevation of CD4 count was higher in ZLN group.

**Conclusion:** Zidovudine based regimen was associated with mild elevation of liver enzymes as compared to stavudine based regimen. Improvement in CD4 counts was better with zidovudine regimen. Zidovudine, even though associated with mild hepatotoxicity, was found to be beneficial.

*Keywords: Zidovudine; stavudine; AST; ALT; CD4 count.*

## 1. INTRODUCTION

The highly active antiretroviral therapy (HAART) has led to a significant reduction in acquired immune deficiency syndrome (AIDS) related morbidity and mortality. Access to antiretroviral therapy (ART) has improved tremendously over the last few years due to implementation and enforcement of various strategies by national AIDS control organization (NACO) in India. NACO has established ART centers in selected government hospitals which offer free treatment for HIV/AIDS and related opportunistic infections [1]. In India NACO offers systematic HIV care by providing drugs free of cost, a detailed counseling algorithm for psychosocial support and management of adverse reactions, with a special emphasis on adherence to ART. The treatment of HIV infection and AIDS is complex because of many reasons. The variety of tailor made ART regimens considering many associated factors, duration of treatment, adherence to treatment and opportunistic infections associated are the main contributing factors for the complexity of treatment. Besides that, adverse drug reactions (ADRs) related to ART use makes the treatment still more challenging. Studies have shown that nearly 25% of all patients discontinue their initial HAART regimen because of treatment failure, adverse drug reactions, noncompliance within the first eight months of therapy [2,3].

The sustained benefits of HAART have led to far greater numbers of HIV-1 infected cases receiving at least three drugs for greater periods of time. Highly active antiretroviral therapy (HAART), currently recommended is the cornerstone of management of patients with HIV infection. Nucleoside reverse transcriptase inhibitor (NRTI) like zidovudine (AZT) and nucleotide reverse transcriptase inhibitor (NtRTI) like tenofovir (TDF) are the most common medications given in first-line ART.

WHO treatment guidelines postulate a 'minimum package' of laboratory monitoring that includes an initial CD4 cell count prior to HAART, which should be repeated at least twice a year in treated patients [4,5]. Efficacy of various regimens can be compared by taking CD4 count, viral load as the tool of assessment.

The complexity of ART regimens used, duration of treatment, adherence to treatment and opportunistic infections associated are the main contributing factors for the complexity of treatment. Adverse Drug Reactions (ADRs) due to ART makes the choice of regimen and treatment complicated. However, ART is associated with serious complications, hepatotoxicity being one among them. Alterations in liver function tests necessitate a need to monitor liver functions regularly. Reports are available which suggest that severe hepatotoxicity in ART patients resulted in discontinuation of therapy [3,4]. However, there are a good number of studies that suggest that alterations in liver enzymes are common in HIV patients on ART [6-9], which improves despite continuation of therapy [10]. Such contradictory results by various studies necessitate a study on liver function tests in HIV patients receiving ART.

The aim of the study was to compare serum transaminases (AST and ALT) in HIV patients on two regimens; zidovudine (AZT) versus stavudine (d4T), either of them administered in combination with nevirapine (NVP) and lamivudine (3TC) as well as to compare their efficacy, taking basal CD4 counts and after treatment CD4 counts as tools of comparison.

## 2. METHODOLOGY

A retrospective observational study on 46 adult HIV patients, receiving AZT+3TC+NVP (ZLN) (group I) and 22 patients on d4T+3TC+NVP (SLN) (group II) was carried out in Karwar Institute of Medical Sciences, Karwar. Institutional ethics committee approval was sought before starting the study. Permission letter from the head of the institution was obtained for this retrospective study. Data of

patients who were diagnosed to be HIV positive, receiving HAART and were attending the hospital for regular follow up once in six months was collected. Patients receiving above mentioned regimens at least for one year were included and those with less than six months of treatment were excluded. Patients were evaluated in detail by measuring transaminases and CD4 count, both basal as well as serial measurements once in 6 months and 1 year.

Data was extracted from patient's medical records using data collection form. Patient demography such as age, gender, medication prescribed (drug regimen), baseline CD4 cell counts, serially monitored CD4 count values (once in 6 months) and biochemical parameters. CD4 counts were estimated using flow cytometry. Transaminases values were noted down from the clinical biochemistry laboratory, where AST and ALT were estimated using automated chemistry analyzer, Transasia XL-640. Toxicity grade was calculated by dividing mean transaminase value by its upper normal limit, normal reference intervals for the liver enzymes being, AST – 5-37 U/L; ALT– 5-35 U/L.

Patients in group I, were in the age group of 38.88±7.01 years and consisted of 65.79% males and 34.21% females. They were receiving a standard drug dosage of AZT 300 mg twice daily, 3TC 150 mg twice daily or 300 mg once daily, NVP 200 mg once daily for a 2-week lead-in period and then as 200 mg twice daily. Mean duration of the treatment is 4.51±2 years.

Group II patients were in the age group of 36.91±8.38 years, 33.33% of them being males and 66.67% of them being females. They were on a standard drug dosages, d4T 60 mg once daily, 3TC, 150 mg twice daily or 300 mg once daily.

Statistical analysis was done by using SPSS version 16 software. Basal, 6 months and 1 year parameters were compared using One Way ANOVA followed by Tukey Kramer Post hoc test. Transaminases and CD4 counts of both the groups were compared by Unpaired 't'' test. Pearson's Correlation study was used to find the association between ALT and 6 months and 1 year CD4 counts.

## 3. RESULTS

A very significant elevation of transaminases was observed at 6 months and 1 year in ZLN group ($P<0.01$). CD4 counts were also significantly high ($P<0.05$).Post hoc test results show that significant elevation of transaminases were present at 6 months and 1 year as compared to basal values (Table 1).

There was no significant difference in the three parameters in SLN group at basal, 6 months and 1 year (Table 2). There was no significant difference in transaminases when both the groups were compared.

Extent of elevation of CD4 count at 6 months and 1 year for ZLN was 1.31 and 1.19 times respectively whereas 1.2 and 1.08 times respectively for SLN. Overall rise in CD4 count over 1 year were 200.26 ± 42.51 and 122.57±93.97 respectively for ZLN and SLN respectively.

There was no significant correlation between CD4 counts and ALT in either groups.

**Table 1. Comparison of parameters in patients on ZLN**

| | Basal | 6 months | 1 year | P value |
|---|---|---|---|---|
| AST | 32.2±2.22 | 43.49±3.49 | 44.71±3.30 | 0.007** |
| ALT | 30.9±2.06 | 42.99±3.36 | 44.79±3.07 | 0.002** |
| CD4 count | 356.2±57.84 | 468.1±60.54 | 560.8±67.93 | <0.05* |

**significant; **highly significant*

*Post hoc test for AST showed that,AST was elevated significantly at 6 months as well as 1 year (P=0.026 and P=0.012 respectively) as compared to basal levels.ALT levels at 6 months and 1 year were also significantly higher (P =0.013, P=0.003 respectively) compared to basal levels*

**Table 2. Comparison of parameters in patients on SLN**

| | Basal | 6 months | 1 year | P value |
|---|---|---|---|---|
| AST | 41.28±5.3 | 39.8±3.3 | 39.1±4.5 | 0.94 |
| ALT | 32.27±3.55 | 35.66±3.42 | 37.08±4.12 | 0.603 |
| CD4 count | 416.18±69.8 | 502.68±94.98 | 544.32±86.84 | 0.553 |

*Post Hoc tests were not significant*

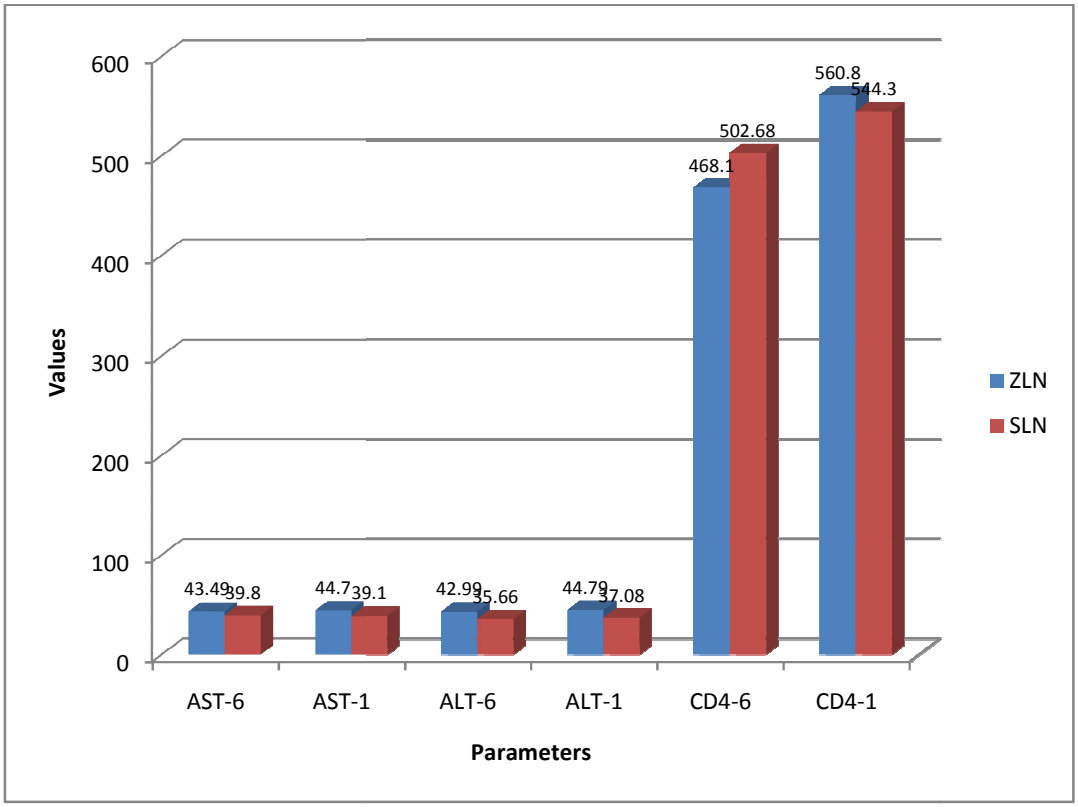


**Fig. 1. Comparison of parameters in ZLNx SLN**

**Table 3. Comparison of parameters at 6 months and 1 year: ZLN x SLN**

| Parameters | P value |
|---|---|
| AST-6 mon | 0.504 |
| AST-1 yr | 0.330 |
| ALT-6 mon | 0.181 |
| ALT-1 yr | 0.168 |
| CD4 count -6 mon | 0.753 |
| CD4 count-1 yr | 0.887 |

*None of the p values are significant*

## 4. DISCUSSION

Significant elevation was observed in transaminases in patients on ZLN regimen at 6 months and 1 year of therapy where as there was no significant difference was noted in those on SLN group.

This is supported by various reports which suggest an elevation of transaminases in HIV patients independent of drug regimen [8,11]. However, contradictory report is also available which states no significant difference in liver function tests in those on ART as compared to pre-ART group [12]. Elevation in transaminase levels in patients on ART could be due to the hepatotoxicity caused by zidovudine.

Various studies suggest hepatotoxic effects of ART regimens [9]. Nevirapine is known to have more hepatotoxic effects compared to efavirenz [13]. It has been shown that initiation of HAART results in hepatotoxicity within weeks to months [14,15]. There are reports which suggest cessation of therapy due to severe hepatotoxicity [6,7]. But elevation of liver enzymes was not a major concern in our study subjects, as it was a mild elevation (grade 1) and there was a significant improvement in CD4 counts in those patients at 6 months. It has been suggested that elevation in liver enzymes, especially ALT is common [8]. HAART should not be denied for this reason, as liver enzymes decrease spontaneously even after 10 fold elevation [10]. It has also been shown that the time required for improvements in transaminase levels is the similar for patients who stopped therapy compared to those continued treatment despite hepatotoxicity [10]. Whenever ART is administered, the benefit in terms of

improvement in CD4 count, demerit in terms of liver toxicity has to be weighed. Patients have to be followed up monthly for liver function tests.

Extent of elevation of CD4 count was more in ZLN group. Elevation of CD4 count implies a better improvement with zidovudine based regimen compared to stavudine based one.Drug induced liver injury is defined by WHO as elevation in ALT and/or AST more than 5-10 times the upper normal limit. As elevation of liver enzymes is mild in ZLN patients, it doesn't fit in to WHO criteria. We cannot attribute the increased liver enzymes to ART regimens as we have not ruled out various confounding factors. Risk factor for elevation of liver enzymes during HAART therapy are co-infections with HBV, HCV, tuberculosis patients on antitubercular drugs [16,17]. Non- exclusion of these confounding factors become the limitation of our study.

James et al. [18] reported an elevated serum aminotransferase levels in a pregnant woman approximately 5 months after beginning combination antiretroviral therapy with zidovudine in his case report. Aminotransferase abnormalities improved after discontinuation of antiretroviral medications. Another case, laboratory abnormalities developed after 3 months of initiation of zidovudine based regimen. Despite initial improvement after discontinuing antiretroviral medications, fulminant hepatic failure developed and patient died.

Contradictory reports are also available. Kalyesubula et al. [19] reported that incidence of severe hepatotoxicity within three months of first-line antiretroviral therapy was low, suggesting that routine measurement of transaminases may not be necessary in all patients initiating HAART. Routine measurement may be important in following patients on HAART and concurrent TB treatment as well as those with jaundice to avoid missing hepatotoxicity. The authors also found in their study that most of the transaminase elevations returned to normal despite continuation of HAART. The similar finding has also been reported in other studies [20-22].

The clinical use of Zidovudine (AZT) is constrained due to its adverse reactions including hepatic steatosis and toxicity. However, the mechanism of hepatic lipid accumulation and hepatotoxicity in AZT-treated individuals is unknown. Study by Banerjee et al. [23] suggested that AZT-induced hepatic fat accumulation and injury is mediated through increased oxidative and nitrative stress, lipid peroxidation, protein modifications and inflammation.

## 5. LIMITATIONS OF THE STUDY

Small sample size as well as non-exclusion of confounding factors like tuberculosis, HBV, HCV patients were the limitations of our study.

## 6. CONCLUSION

It could be concluded from the study that zidovudine based regimen was associated with mild elevation of liver enzymes as compared to stavudine based regimen. However elevations were statistically insignificant. Improvements in CD4 counts were higher in zidovudine regimen. Regular monitoring of liver function tests are suggested in patients receiving zidovudine regimen.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. National AIDS Control Organization. Ministry of Health and Family Welfare, Government of India; 2009.
   Available:https://nacoonline.org/NACO
   (Accessed on 16 November 2011)
2. d'Arminio Monforte A, Lepri AC, Rezza G, Pezzoti P, Antinori A, Phillips AN, et al. Insights into the reasons for discontinuation of the first highly active antretroviral therapy (HAART) regimen in a cohort of antiretroviral naove patients: Italian cohort of antiretroviral Naove patients. AIDS. 2000;14:499-507.
3. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: Risk factors for virologic failure and adverse drug reactions. Ann Intern Med. 1999;131:81-7.
4. Surmounting challenges: Procurement of antiretroviral medicines in low- and middle-income countries.
   Available:http://apps.who.int/medicinedocs/en/d/Js4892e/
5. Stover J, Bollinger L, Avila C. Estimating the impact and cost of the WHO 2010

recommendations for antiretroviral therapy. AIDS Research and Treatment. 2011;7. Article ID: 738271

6. Johan VG, Naeyer LD, Uwera J, Asiimwe A, Gazille C, Reid T. Success with antiretroviral treatment for children in Kigali, Rwanda: Experience with health center/nurse-based care. BMC Pediatrics. 2008;8:39.
7. Padma PC, Bhavani PK, Tang A, Kumar H, Ponnuraja C, Narendran G, et al. Early changes in hepatic function among HIV–tuberculosis patients treated with nevirapine or efavirenz along with rifampin-based anti-tuberculosis therapy C. International Journal of Infectious Diseases. 2013;17:e1154–e1159.
8. Nagu TJ, Kanyangarara M, Hawkins C, Hertmark E, Chalamila G, Spiegelman G, et al. Elevated alanine aminotransferase in antiretroviral-naïve HIV-infected African patients: Magnitude and risk factors. HIV Medicine. 2012;13(9):541–548.
9. Bonacini M, Louie S, Weisman K. Hepatotoxicity of antiviral medications. In: Kaplowitz N, DeLeve L, eds. Drug-induced liver disease. New York: Marcel Dekker. 2002;519–48.
10. Wit FWNM, Weverling GJ, Weel J, Jurriaans S, Lange JMA. Incidence and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis. 2002;186(1):23–31.
11. Lucien KFH, Clement ANJ, Fon NP, Weledji P, Ndikvu CP. The effects of antiretroviral treatment on liver function enzymes among HIV-infected out patients attending the central hospital of Yaounde, Cameroon. African Journal of Clinical and Experimental Microbiology. 2010;11(3): 174-78.
12. Osakunor DNM, Obirikorang C, Fianu V, Asare I, Dakorah M. Hepatic enzyme alterations in HIV patients on antiretroviral therapy: A case-control study in a hospital setting in Ghana. PLoS ONE. 2015;10(8): e0134449.
13. Minzi OM, Irunde H, Moshiro C. HIV patients presenting common adverse drug events caused by highly active antiretroviral therapy in Tanzania. Tanzania Journal of Health Research. 2009;11(1):5–10.
14. Coffie PA, Tonwe-Gold B, Tanon AK, Amani-Bosse C, Bedikou G, Abrams EJ, et al. Incidence and risk factors of severe adverse events with nevirapine based antiretroviral therapy in HIV-infected women. MTCTPlusprogram, Abidjan, Cˆote d'Ivoire. BMC Infectious Diseases. 2010;10:188.
15. Griensven JV, Zachariah RF, Rasschaert J, Mugabo E, Att´e F, Reid T. Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: Incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2010;104(2):148–153.
16. Sulkowski M, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA. 2000;283(1):74–80.
17. Monforte AA, Bugarini R, Pezzotti P, De Luca A, Antinori A, Mussini C, et al. Low frequency of severe hepatotoxicity and association with HCV coinfection in HIV-positive patients treated with HAART. J Acquir Immune Defic Syndr. 2001;28(2): 114–23.
18. James BH, Jeanne SS, Gerda GZ, George D, Wendel J. Hepatotoxicity with antiretroviral treatment of pregnant women. Obstet Gynecol. 2001;98(5):909-911.
19. Kalyesubula R, Kagimu M, Opio KC, Kiguba R, Semitala CF, Schlech WF, Katabira ET. Hepatotoxicity from first line antiretroviral therapy: An experience from a resource limited setting. African Health Sciences. 2011;11(1):16–23.
20. Hahn JA, Maier M, Byakika-Tusiime J, Oyugi JH, Bangsberg DR. Hepatotoxicity during nevirapine based fixed-dose combination antiretroviral therapy in Kampala, Uganda. J Int Assoc Physicians AIDS Care (Chic Ill). 2007;6(2):83-6.
21. Núñez M, Lana R, Mendoza JL, Martín-Carbonero L, Soriano V. Risk factors for severe hepatic injury following the introduction of HAART. J Acquir Imm Def Syndr. 2001;27:426-31.
22. Martínez E, Blanco J, Arnaiz JA, Pérez-Cuevas JB, Mocroft A, Cruceta A, Marcos MA, Milinkovic A, García-Viejo MA, Mallolas J, Carné X, Phillips A, Gatell JM. Hepatotoxicity in HIV-infected patients

receiving nevirapine-containing antiretroviral therapy. AIDS. 2001;15:1261-8.

23. Banerjee A, Abdelmegeed MA, Jang S, Song BJ. Zidovudine (AZT) and hepatic lipid accumulation: Implication of inflammation, oxidative and endoplasmic reticulum stress mediators. PLoS ONE. 2013;8(10):e76850.
DOI: 10.1371/journal.pone.0076850



*Peer-review history:*
*The peer review history for this paper can be accessed here:*
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