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Original Article

Biochemistry Section

Alterations of Serum Transaminases in HIV patients on ART

USHA ADIGA, BN MALAWADI

ABSTRACT

Introduction: Elevation of liver enzymes is a sensitive signal of drug induced liver injury in HIV patients receiving Antiretroviral Therapy (ART). Studies reporting severe hepatotoxicity due to the administration of ART are available. Some researchers suggest that elevation of transaminases is not a major concern while treating HIV.

Aim: To compare transaminase levels of HIV patients on ART as compared to HIV patients who are yet to start ART (pre-ART) and non- HIV individuals.

Materials and Methods: A retrospective observational study on 80 non- HIV subjects (group I), 100 adult HIV patients who are yet to start ART (pre-ART) (group II) and 100 HIV patients on different ART regimens for 6 months (group III) was carried out in a medical college teaching hospital.

Patients' data like demographic profile, CD4 counts are collected from their medical records. Transaminases values were noted down from the clinical biochemistry laboratory. Statistical analysis was done by One way ANOVA followed by a post hoc test to compare liver enzymes between different groups. Correlation study is done using Pearson's correlation coefficient.

Results: Transaminase levels were significantly high ($p<0.0001$) in HIV patients on ART as compared to other groups. Pearson's correlation study showed a significant negative correlation between age and transaminases in group III ($p=0.021$ for AST, $p=0.039$ for ALT).

Conclusion: The present study suggests that ART regimens might be responsible for elevation of transaminases in HIV patients. However, elevation of liver enzymes is not a major concern as extent of elevation was small and ART patients showed significant improvement in CD4 counts after receiving therapy.

Keywords: Adverse drug reactions, Liver enzymes, Opportunistic infections

INTRODUCTION

Implementation and enforcement of various strategies by National AIDS Control Organization (NACO) improved Antiretroviral Therapy (ART) over the last few years. The introduction of Highly Active Antiretroviral Therapy (HAART) has reduced morbidity and mortality due to Acquired Immune Deficiency Syndrome (AIDS). 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 use makes the treatment more challenging. Studies have shown that treatment failure, toxic effects or non-compliance within the first eight months of therapy lead to discontinuation of therapy in nearly 25% of all patients [1,2]. 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 is common in HIV patients on ART [4-6], which improves despite continuation of therapy [7]. Such contradictory results by various studies necessitate a study on liver function tests in HIV patients who are on ART. A few studies are available on alterations in liver enzymes in patients on ART in India to the best of knowledge.

MATERIALS AND METHODS

A retrospective observational study including 80 non-HIV individuals (group I),100 adult HIV patients who are yet to start ART (group II) and 100 HIV patients on different ART regimens for 6 months (group III) was carried out in Karwar Institute of Medical Sciences, Karwar in Uttara Kannada district of Karnataka, India.

The sample size was calculated using the formula below;

$$N=4pq/d^2$$

Where:-

p:Expected prevalence; q:100-p; d:Degree of precision, 5%

Patients in group II and III were diagnosed to be HIV positive

and were attending the medical college hospital for regular follow-up monthly. Patients receiving ART regimens for six months were included and those with more than or less than six months of treatment were excluded. Patients in group II and III were evaluated in detail by collecting data of CD4 counts. Basal CD4 count was measured for group II and basal as well as follow-up CD4 count at 6 months was done for patients in group III.

The study was conducted between June 2015 to May 2016. Institutional ethics committee approval was sought before starting the study.

Inclusion Criteria

Group I: Non-HIV individuals attending OPD

Group II: Diagnosed HIV patients before starting ART

Group III: HIV patients on ART for 6 months

Exclusion Criteria

Alcoholics, history of liver disorders within 1 year, diabetes mellitus.

Patients in group I are in the age group of 49.84±2.01 years and consists of 53(66.25%) males and 27(33.75%) females. Group II patients were in the age group of 38.61±9.89 years, 33(33%) of them being males and 67(67%) of them being females. Mean age of group III patients was 35.83±2.52 years, 52(52%) of them being males and 48(48%) females.

DATA COLLECTION

Data was extracted from patient's medical records using data collection form. Patient's demographic details such as age, gender, marital status, medication prescribed including the name of the drug, baseline CD4 cell counts, follow-up CD4 count values were recorded. CD4 counts were estimated using flow cytometry. Transaminases values were noted down from the clinical biochemistry laboratory, where AST and ALT are 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 on ART had grade 1 hepatotoxicity as the calculated ratios being 1.69 for AST and 1.57 for ALT.

STATISTICAL ANALYSIS

It was done using PSPP 0.7 software. One-way ANOVA followed by Tukey-Kramer test, a post hoc-test was done to compare liver enzymes pair wise between the three groups. Paired student's 't' test was used to compare basal and follow-up (6 months) CD4 counts in group III. Pearson's correlation test was used to find the correlation between liver enzymes and age in HIV patients (group II and III together).

RESULTS

Transaminases were significantly high in patients on ART (group III) as compared to other two groups [Table/Fig-1]. Post-hoc test showed that serum transaminases were significantly high in patients on ART (group III) compared to HIV patients not started on ART (pre-ART) (group II) as well as non-HIV individuals (group I) [Table/Fig-2].There was no gender difference in transaminase levels.

CD4 count was increased highly significantly ($p<0.001$) in group III after 6 months of therapy.

Pearson's correlation study showed a significant negative correlation between age and transaminases in HIV patients on ART (group III) [Table/Fig-1].

Pearson's correlation study showed a significant negative correlation between age and transaminases in HIV patients on ART (group III) [Table/Fig-3].

	Group I	Group II	Group III	p-value
Basal CD4 count	-	260.78±20.67	224.11±28.57	>0.05
Follow-up CD4 count	-	-	431.83±37.41	-
AST	24.46±0.95	30.31±1.24	62.6±6.67	<0.0001***
ALT	22.55±1.63	32.05±2.5	55.03±3.66	<0.0001***

[Table/Fig-1]: Comparison of CD4 counts and transaminase.
***p<0.0001-very highly significant
Comparison of CD4 count – Student's paired't' test
Comparison of liver enzymes – One way ANOVA

Comparison	p-value
AST of Group I vs Group III	0.0002**
ALT of Group I vs Group III	<0.0001***
AST of Group II vs Group III	0.019*
ALT of Group II vs Group III	0.02*
AST & ALT of Group I vs Group II	>0.05

[Table/Fig-2]: Results of Tukey Kramer test (Post-hoc test).
*p<0.05-significant
**p<0.001- highly significant
***p<0.0001- very highly significant

Correlation between	Pearson's correlation coefficient (r)	p-value
Age & AST	-0.4198	0.021*
Age & ALT	-0.3796	0.039*

[Table/Fig-3]: Correlation study results.
*p<0.05-significant

DISCUSSION

Serum transaminases levels were statistically significantly high in HIV patients receiving ART (group III) as compared to non-HIV (group I) and HIV patients who are yet to start the therapy (group II) [Table/Fig-1]. This is supported by various reports which suggest an elevation of transaminases in HIV patients independent of drug regimen [5,8]. 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 [9].

Elevation in transaminase levels in patients on ART could be due to the hepatotoxicity caused by various ART regimens. Elevated liver enzymes in group III and no significant difference in liver enzymes between group I and II, suggest that ART regimens might be contributing to elevation of liver enzymes. Various studies suggest hepatotoxic effects of ART regimens [6]. Nevirapine is known to have more hepatotoxic effects compared to efavirenz [10]. It has been shown that initiation of HAART results in hepatotoxicity within weeks to months [11,12].There are reports which suggest cessation of therapy due to severe hepatotoxicity [3,4]. 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 [5]. HAART should not be denied for this reason, as liver enzymes decrease spontaneously even after 10 fold elevation [7]. 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 who continued treatment despite hepatotoxicity [7]. Instead patients have to be followed up monthly for liver function tests.

Drug induced liver injury is defined by WHO as elevation in ALT and/or AST more than 5-10 times the upper normal limit [13]. As elevation of liver enzymes is mild in group III 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 [13,14]. Non- exclusion of these confounding factors becomes the limitation of our study.

Negative correlation was observed between age and transaminases in group III in the present study, indicating a higher risk of hepatotoxicity in younger age group [Table/Fig-3]. This fact is supported by a Jordanian study by Judi et al., [15]. Contradictory reports are given by Spengler and colleagues [16]. No gender difference in liver enzymes was observed in HIV patients with therapy in our study. On the contrary, gender difference was reported in a study by Nagu and colleagues [5].

LIMTATIONS

HIV patients on ART, irrespective of the regimen were included in the study. Liver enzyme alterations in different specific regimens were not studied.

CONCLUSION

It can be concluded from this study that ART regimens might be responsible for elevation of transaminases in HIV patients. Extent of elevation of liver enzymes has to be weighed with the improvement in CD4 counts after ART. Further, studies need to be done by considering factors like coexisting medications and co-infections.

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REFERENCES

[1] 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 antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naove patients: Italian cohort of antiretroviral Naove patients. *AIDS*. 2000;14(5):499-507.

[2] 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(2):81-87.

[3] 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.

[4] Padmapriyadarsini C, 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. *Int J Infect Dis*. 2013;17(12):e1154-59.

[5] Nagu TJ, Kanyangarara M, Hawkins C, Hertmark E, Chalamila G, Spiegelman D, et al. Elevated alanine aminotransferase in antiretroviral-naïve HIV-infected African patients: magnitude and risk factors. *HIV Med*. 2012 ;13(9):541-48.

[6] 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.

[7] Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. 2002;186(1):23-31.

[8] 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 Yaoundé, Cameroon. *African Journal of Clinical and Experimental Microbiology*. 2010;11(3):174-78.

[9] 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.

[10] Minzi OM, Irunde H , Moshiro C. HIV patients presenting common adverse drug events caused by highly active antiretroviral therapy in Tanzania. *Tanzan J Health Res*. 2009;11(1):05-10.

[11] 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. MTCT Plus program, Abidjan, C˜ote d'Ivoire. *BMC Infectious Diseases*. 2010;10:188.

[12] van Griensven J, Zachariah R, Rasschaert F, Mugabo J, Atté EF, 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. *Trans R Soc Trop Med Hyg*. 2010;104(2):148-53.

[13] Sulkowski MS, 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.
[14] Monforte Ade A, 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*. 200;28(2):114-23.
[15] Judi L, Toukan A, Khader Y, Ajlouni K, Khatib MA. Prevalence of elevated hepatic transaminases among Jordanian patients with type 2 diabetes mellitus. *Ann Saudi Med*. 2010;30(1):25-32.
[16] Spengler U, Lichterfeld M, Rockstroh JK. Antiretroviral drug toxicity- a challenge to the hepatologist? *J Hepatol.* 2002;36(2):283-94.

AUTHOR(S):
1. Dr. Usha Adiga
2. Dr. BN Malawadi

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, Karwar Institute of Medical Sciences, Karwar, Karnataka, India.
2. Assistant Professor, Department of Biochemistry, Karwar Institute of Medical Sciences, Karwar, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Usha Adiga,
Associate Professor, Department of Biochemistry,
Karwar Institute of Medical Sciences, Kodibag, Karwar,
Karnataka-581301, India.
E-mail: ushachidu@yahoo.com

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