ORIGINAL ARTICLE

Serum Alanine Aminotransferase Elevations in HIV Positive Patients on Antiretroviral Therapy in India

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Abstract

Background: Alanine aminotransferase (ALT) is commonly used to measure liver injury in resource limited settings. Elevations in ALT are predictive of increased mortality from liver disease and may be influenced by antiretroviral drugs and concomitant hepatitis B infection.

Methods: A cross-sectional analysis of the prevalence and predictors of elevated ALT (defined as> 40 IU/L) on HIV patients on antiretroviral therapy (ART) was conducted. Baseline ALT levels and at two weeks, six weeks, twelve weeks, twenty four weeks and one year were recorded for 320 patients on ART. Hepatitis B surface antigen was also recorded at baseline.

Results: Out of the total 320 patients, 249 were males and 71 females. A total of 252 patient records were used as controls who were not on ART. The mean ALT record before initiating ART was 30.6 IU/L. Peak rise in ALT was observed at twenty four weeks of therapy with mean ALT levels of 54.42 IU/L. Total toxicity was almost similar between the two regimes, nevirapine based being 17.62% and efavirenz based being 16.16%.Toxicty grades were lesser in Hepatitis B positive patients as compared with hepatitis B negative patients overall.

Conclusions: This study concludes that elevated ALT levels are seen in patients on antiretroviral therapy and persist throughout the course of first year, though maximum levels are seen at around twenty four weeks of therapy. Total hepatotoxicity was found to be 16.89%. Longer follow up of patients is required to assess the effect of ALT elevations on morbidity and mortality of patients and a close monitoring of ALT is required in patients on ART and other hepatotoxic therapies.

Introduction

India has the third largest HIV epidemic in the world. In 2016, HIV prevalence in India was an estimated 0.3%. This figure is small compared to most other middle-income countries but because of India's huge population (1.2 billion) this equates to 2.1 million people living with HIV. In the same year, an estimated 68,000 people died from AIDS-related illnesses and 43% adults are on antiretroviral treatment (ART).[1] Overall, India's HIV epidemic is slowing down, with a 19% decline in new HIV infections (130,000 in 2013), and a 38% decline in AIDS-related deaths between 2005 and 2013. Despite, this 51% of deaths in Asiaare in India.[2] HIV prevalence in India varies geographically. The five states with the highest HIV prevalence (Nagaland, Mizoram, Manipur, Andhra Pradesh and Karnataka) are in the south or east of the country. Some states in the north and northeast of the country, report rising HIV prevalence.[3]

Since the introduction of antiretroviral drugs, Human Immunodeficiency Virus (HIV) infection management has become more complex. HIV positive patients are receiving an array of drugs to treat and prevent opportunistic infection. With the increased availability of antiretroviral therapy, more people are now surviving with HIV but more are presenting with increasing liver disease.[4] Alanine aminotransferase (ALT) is a liver enzyme commonly used to measure liver disease in resource-limited settings. Elevated ALT is a highly specific indicator for liver injury and has been shown to be associated with deaths from liver disease in non-HIV infected populations.[5] Since it is often the only marker used to monitor liver disease in HIV infected individuals in resource-limited settings, understanding the prevalence and risks associated with elevations in ALT in these settings is important. Liver enzyme elevation is common in HIV patients in Sub-Saharan Africa.[6,7] and various risk factors have been described mainly in Europe and North America including; male sex, HIV itself, viral hepatitis, most antiretrovirals, anti-tuberculosis and lipid lowering drugs; alcohol, and metabolic syndrome.[6,8]

Certain antiretroviral (ARVs) drugs have well known documented toxicity. Although almost all drugs can cause toxicity, those found to cause liver toxicity include nevirapine, efavirenz, abacavir and lamivudine.[4,9] Previous studies have indicated liver toxicity ranging from 13-18%.[10–11] A retrospective cohort study that determined the incidence of NNRTI hepatotoxicity in a group of HIV-infected patients in New York City practice found that grade 3 - 4 elevations in ALT and/or AST levels occurred in 3 (1.1%) of 272 patients.[12] Another study in the US concluded that severe hepatotoxicity occurred throughout the course of NNRTI-based therapy and was more common among patients prescribed with NVP (occurring in 15.6%) than those prescribed with efavirenz (8.0%).[13,14] However, it is likely that co-infection with viral hepatitis was a contributing factor.[14]

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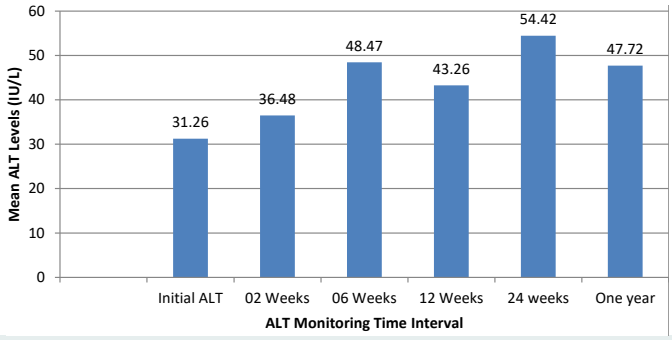

Fig. 1: Mean ALT levels

In a Switzerland cohort of 2365 HIV-infected individuals not co-infected with either HBV or HCV, 385 (16%) had chronically elevated ALT (defined as > 2 × upper limit of normal)[4]. A post-mortem study of 86 HIV-infected individuals undergoing autopsy in rural South Africa demonstrated that 10% had liver related conditions at the time ofdeath.[15]

Liver toxicity particularly is one of the many side effects of ART. Certain factors have been associated with the development of liver toxicity such as hepatitis co-infection, numerous other liver diseases, including alcohol-related injuries, drug-induced hepatotoxicity, metabolic fatty liver, vascular and autoimmune diseases, infectious diseases and hepato-biliary malignancies. These conditions can affect the clinical management and prognosis of HIV infection.[8,9,16] The severity of liver toxicity ranges from transient elevations in transaminases to hepatic failure and death.[4] Drug toxicity is graded according to serum ALT results as follows: Grade 0 (< 1.25 × Upper Limit of Norma l [ULN]); Grade 1 (1.25 - 2.5× ULN); Grade 2 (2.6 - 5×ULN); Grade 3 (5.1 - 10× ULN) and Grade 4 (>10× ULN).[17]

No published data exists on prevalence of elevated liver enzymes in HIV positive patients on ART in India. Therefore this study aims at prevalence of elevated liver enzymes in HIV patients on ART in New Delhi.

Methods

This retrospective study was done at Apex Immunodeficiency Center (AIDC), Base Hospital, Delhi Cantt in which 320 adult patients records were used for data collection. Prior ethical clearance was obtained from the hospital ethics committee. Patient clearance was not required as the data was collected from the AIDC records and the patients identity was concealed. Base line ALT was recorded and then after two weeks, six weeks, twelve weeks, twenty four weeks and one year. Hepatitis B surface antigen was recorded at baseline only. Patients were being screened for CD4 count and HIV RNA (Quantitative) every six months.

Inclusion criteria

Patients who initiated ART during 2014-16 were included in the study.

Patients who started first line ART during the study period were included.

Exclusion criteria

Patients not having baseline ALT records.

Patients transferred in from other centers.

Poorly adherent patients on ART.

Patients having any evidence of clinical, immunological or virological failure.

Patients on other drugs with hepatotoxic potential.

Patients with serum creatinine of more than 2 mg%.

The liver enzymes ALT and AST were measured using COBAS Integra Chemistry Analyzer, Roche Diagnostics, Mannheim, Germany. CD4 counts were determined with a FACS counter (Becton and Dickinson, Immunocytometry Systems, San Jose, CA).Hepatitis B virus surface antigen tests were analysed using the Architect analyser (Abbort, Illinois, USA).

Statistical analysis

Data was analysed using the Statistical Package for Social Sciences (SPSS) version 22.0. The Pearson Chi-square p value was used to determine whether a statistically significant association existed between variables. Using a 95% confidence level, a P value of less than or equal to 0.05 ($P \leq 0.05$), was considered to be statistically significant. The paired t-test was used to compare the monitoring periods ALT means to the initial ALTand determine whether the difference was significant or not. The independent t-test was used to compare the initial ALT mean and the one year ALT mean of the patients with Hepatitis B co-infection or otherwise.

Results

Out of the total 320 patients, 249 were males and 71 females. The period of study extended from July 2014 through August 2016. Age of the patients ranged from 26 to 81 years. Adherence counseling and avoidance of substance abuse is routinely done in all our patients on ART at our center. Out of the total patients, 208 patients were on Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV), 166 being males and 42 females. Rest 112 patients were on Tenofovir (TDF), Lamivudine (3TC) and Nevirapine (NPV), 83 being males and 29 females.

The baseline ALT levels were used as the control group which indicated the levels of ALT in HIV positive patients who were not on treatment. A total of 252 patient records were used as controls who were not on ART. Out of these 252 controls, 161 were males and 91 females. The mean ALT record before initiating ART was 30.6 IU/L. ALT was recorded at two, six, twelve, twenty four weeks and one year from starting ART. Table 1 depicts mean ALT values at different monitoring periods. Fifty eight patients(18.12%) had elevated ALT levels before initiation of ART.

Peak rise in ALT was observed at twenty four weeks of therapy with mean ALT levels of 54.42 IU/L (Figure 1). Mean ALT levels at initiation and two weeks after therapy were statically insignificant (P= 0.091) though it was significant during latter part of therapy as compared to baseline.

Toxicity was observed in both nevirapine as well as efavirenz based regimes. Toxicity in nevirapine based regimes remained almost static from two weeks till about twelve weeks of therapy (14.1 – 14.5%) reaching a maximum at twenty four weeks (22.9%). Toxicity in efavirenz based regimes remained higher than nevrapine based group reaching at 22.6% at twenty four weeks and dropping down to 6.4% at

Table 1: Toxicity grades at varying intervals in treatment regimens

Monitoring periods	ART regimen	(n)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Cumulative toxicity (%/n)
Two weeks	NVP based	78	14.2	0.3	0.0	0.0	14.5/11
	EFV based	178	14.8	0.2	1.2	0.0	16.2/29
Six weeks	NVP based	57	11.3	2.3	0.6	0.2	14.4/8
	EFV based	134	18.7	1.4	0.0	0.0	20.1/27
Twelve weeks	NVP based	62	9.2	3.2	1.7	0.0	14.1/9
	EFV based	146	11.6	3.9	0.0	0.0	15.5/23
Twenty four weeks	NVP based	63	19.4	3.5	0.0	0.0	22.9/14
	EFV based	187	21.5	0.9	0.2	0.0	22.6/42
One year	NVP based	61	17.2	5.2	0.0	0.0	22.4/14
	EFV based	165	4.3	2.1	0.0	0.0	6.4/11

ART: Antiretroviral therapy, NVP: Nevirapine, EFV: Efavirenz

Table 2: Cumulative toxicity in treatment regimens

Type of regimen	Mild toxicity		Severe toxicity		
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%/n)
NVP- based	14.26	2.9	0.46	0.0	
Total	17.16		0.46		17.62/12
EFV- based	14.18	1.7	0.28	0.0	
Total	15.88		0.28		16.16/26

P value = 0.95

Table 3: Toxicity grades in patients with hepatitis B co-infection or otherwise

Monitoring periods	Hep B status	(n)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%/n)
Two weeks	Positive	35	28.7	1.1	0.0	0.0	29.8/10
	Negative	163	10.8	0.3	0.0	0.0	11.1/18
Six weeks	Positive	18	1.8	0.3	0.0	0.0	2.1/1
	Negative	104	14.8	0.3	0.0	0.0	15.1/16
Twelve weeks	Positive	22	12.8	10.6	0.0	0.0	23.4/5
	Negative	187	11.7	4.2	0.0	0.0	15.9/30
Twenty four weeks	Positive	43	14.8	2.4	0.0	0.0	17.2/7
	Negative	179	17.6	4.8	0.0	0.0	22.4/40
One year	Positive	27	8.6	1.2	0.0	0.0	9.8/3
	Negative	148	12.7	7.4	0.0	0.0	20.1/30

P value= 0.02

one year. Table 1 shows the toxicity due to nevirapine and efavirenz based regimes at varying intervals till one year of therapy.

Total toxicity was almost similar between the two regimes, nevirapine based being 17.62% and efavirenz based being 16.16%. Majority of this cumulative toxicity was mild in both the groups(NVP 17.16 and EFV 15.18%). Severe toxicity was slightly higher in nevirapine based group(0.46%) than efavirenz based group(0.28%). Table 2 shows the cumulative toxicity in the two treatment regimens.

Out of the total 320 patients, 64 (20.0%) were found positive for Hepatitis B surface antigen (HBsAg). Table 3 shows toxicity grades in patients with Hepatitis B positive or otherwise. Patients had highest toxicity at two weeks (29.8%) and by one year these levels had come down to 9.8%. Toxicity grades were lesser in Hepatitis B positive patients as compared with hepatitis B negative patients overall.

Discussion

Mean ALT levels were always higher during two, six, twelve, twenty four weeks and one year as compared to baseline levels. Elevated ALT levels were noted throughout the treatment period for the patients on ART. Though other causes like viral hepatitis, kidney failure and alcoholism can cause rise in ALT levels, antiretroviral therapy has an effect on liver.[4] The nonnucleoside reverse transcriptase inhibitors (NNRTIs) typically cause either hypersensitivity reactions or direct drug toxicity and therefore have 2 peaks of onset, within days to weeks or several months after initiation.[18] Nevirapine (NVP) is the NNRTI most associated with hepatotoxicity, although hypersensitivity reactions resulting in liver failure have been reported with the newer NNRTI etravirine.[19] Efavirenz can also cause hepatotoxicity but does so less frequently than NVP or etravirine. In our study toxicity due to efavirenz was higher than nevirapine in the initial half of the study but than declined over the next half to less than nevirapine, although cumulative toxicity of efavirenz was lesser than nevirapine. The maximum toxicity was observed at twenty four weeks, 22.9% for nevirapine and 22.6% for efavirenz in our study. Shanyengana LP et al[11] documented a maximum toxicity of 26.5 and 28.2 % for nevirapine and efavirenz respectively. Other similar studies from Tanzania and Ethiopia have documented a prevalence of 13 and 32% respectively.[8,20] The difference could be due to different risk factors, alcohol abuse, co- infection, different treatment regimens, pretreatment ALT elevations and duration of treatment.

Severe hepatotoxicity (grades 3 and 4) was higher among patients on nevirapine based regimens (0.46vs 0.28%). These results are in sync with a US based study[14]which concluded that severe hepatotoxicity was more common among patients prescribed with nevirapine (15.6%) than those prescribed with efavirenz (8.0%) based regimens and are different from a Namibian study[11] which observed that severe hepatotoxicity was higher (1.6%) in patients who were enrolled on efavirenz based regimes than patients who were enrolled on nevirapine based regimes (1.1%). Similarly, other studies conducted in Botswana and Nigeria found that 3.4% and 16% of nevirapine and 0.9% and 8.0% of efavirenz treated patients developed hepatotoxicity respectively.[9,21] Our study demonstrated higher prevalence of milder toxicity (17.16 % and 15.88 %) and a very low prevalence of severe toxicity (0.46 and 0.28%). The results of our study are similar to the results of a study done in Ethiopia which showed higher mild toxicity levels (22.3% grade 1 toxicity levels, 7.8% grade 2 toxicity levels) and lower severe toxicity levels (1.1% and 0.74% for grade 3 and 4 toxicity respectively).[20] A study done in New York City, USA had similar results to our findings with mild toxicity (grade 1 and 2) of 16.7% and severe toxicity (grade 3 and 4) of 1.4%.[12] Lower results were also found in a study conducted in Tanzania which found 0.3% severe hepatotoxicity.[8]

Hepatitis B has been shown to be contributing factor in patients on ART for liver injury in South Africa and Switzerland.[4,15] Our study showed Hepatitis B related toxicity at two and twelve weeks only and at other times it was much lower as compared to Hepatitis B negative patients.

Limitations of study

This study had few limitations. Firstly, data on alcohol and illicit drugs, which could have caused elevated ALT, was not available. Secondly, the effect

of Lamivudine in causing a rise in ALT could not be made out, though both the groups had lamivudine as part of therapy.

Conclusions

This study concludes that elevated ALT levels are seen in patients on antiretroviral therapy and persist throughout the course of first year, though maximum levels are seen at around twenty four weeks of therapy. Total hepatotoxicity was found to be 16.89%. Slightly higher toxicity was observed in nevirapine based regime as compared to efavirenz based regime. Hepatitis B co-infected patients showed a higher toxicity levels at two and twelve weeks of therapy, at other times it was lower than hepatitis B uninfected. Longer follow up of patients is required to assess the effect of ALT elevations on morbidity and mortality of patients and a close monitoring of ALT is required in patients on ART and other hepatotoxic therapies.

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