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Hepatotoxicity in HIV infected patients with HBsAg and Anti-HCV antibodies receiving Antiretroviral therapy containing protease Inhibitors

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Abstract
Background: Twenty-one antiretroviral drugs have been accepted by the U.S. Food and Drug Administration (FDA) for the treatment of HIV. This study was done to study the protease inhibitors.
Objectives: to determine the correlation of Hepatotoxicity in HIV patients with HBsAg and anti-HCV antibodies.
Methods: A Hospital based cross sectional study among 280 HIV seropositive patient who reported to ART centre for treatment at LLRM Medical College & Hospital, Meerut. The patients reconfirmed to be HIV positive underwent liver function test (LFT), hepatitis test and CD4 cell count before initiation of therapy. Epi info 7 was used for analysis.
Results: ALT levels which were normal in 258 (92%) patients and raised in 22 (8%) patients before initiation of therapy and were found to be normal in 112 (40%) patients and raised in 168 (60%) patients after 9 months of initiation of therapy and both before and after initiation of therapy were found to be statistically highly significant.
Conclusion: Hepatotoxicity developed in HBs Ag and HCV coinfected patients was significantly higher as compared to patients without coinfection, showed that viral hepatitis coinfections are self-determining risk factors for hepatotoxicity.

Keywords: Hepatotoxicity, HIV, Protease Inhibitors

1. Introduction

HIV is unique in structure from other retroviruses [1]. It is more virulent, more infective and is the source of the majority of HIV infections globally [2]. Conventionally, pharmaceutical agents that are combined to make up highly active antiretroviral therapy can be distributed into three categories, namely, Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and Protease inhibitors (PIs). Twenty-one antiretroviral drugs have been accepted by the U.S. Food and Drug Administration (FDA) for the treatment of HIV. However, in approximately 6% to 30% of treated patients, antiretroviral therapy is associated with significant escalations in serum liver enzymes, which may need discontinuation of HIV treatment [3-6]. Several studies have stated that HCV and/or HBV coinfected patients are at more risk to develop severe hepatotoxicity following initiation of antiretroviral therapy containing HIV-1 protease inhibitors, especially full-dose ritonavir and tipranavir [7-9]. The study will be useful for Giving knowledge of alternative therapy to be given in HIV patients with increased hepatotoxicity due to Protease Inhibitors. Adjustment of dose in HIV patients receiving Protease Inhibitors. Defining the interactions of Protease Inhibitors and role of Chronic viral hepatitis in development of drug Induced toxicity.

2. Material and Methods

The study includes newly diagnosed 280 HIV seropositive patients (aged between 10 and 50 years) who reported to ART centre for treatment at LLRM Medical College & Hospital, Meerut and followed inclusion and exclusion criteria.

Inclusion Criteria

- Newly diagnosed HIV seropositive patients intending to take HAART therapy including Protease Inhibitors.
- Aged 10-50 years.
- Who gave their informed consent forms duly signed.

Exclusion Criteria

- Liver tumors.
- Alcoholic patients
- Patients with bone disorders.
- Patients with congestive heart failure or any chronic disorders.
- HIV patients who have already been receiving HAART therapy including Protease Inhibitors.

The formula used for calculation of sample size (n) was:

$$n= z^2pq/d^2$$

Where in,
z (at 95% confidence levels) = 1.96~2
P (Estimated prevalence of HIV) = 26
q (1 − p) = 74
d (Allowable error) = 5%

Therefore, $n = 2 \times 2\times 26 \times 74/25 = 308$.

Out of total 308 patients.

- 11 patients were lost to follow up.
- 8 patients died during the course of treatment.
- 9 patients changed the regimen.

Total 280 patients were studied during the study period.

The patients reconfirmed to be HIV positive underwent liver function test (LFT), hepatitis test and CD4 cell count before initiation of therapy. All the Liver enzyme tests and CD4 cell count were reperformed at 3, 6 and 9 months of follow up after receiving ART therapy that included protease Inhibitors.

3. Results

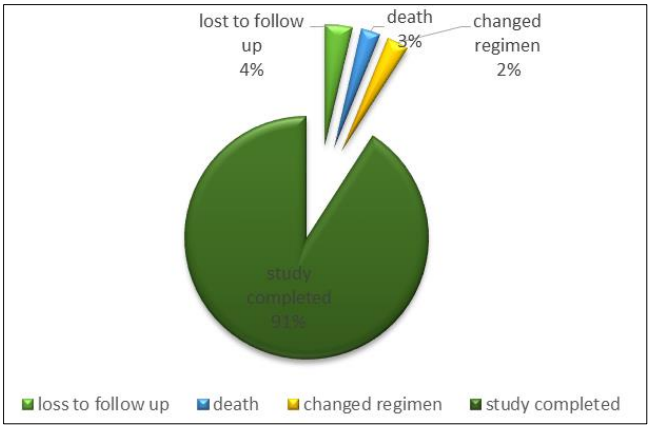

Fig 1: Distribution of Study participants.

As per figure 1, out of 308 study patients who have given consent, 280 (91%) have completed the study, 11 (4%) were lost to follow up (LTFU), 9 (3%) changed the regimen while almost 8 (2%) died during the course of treatment.

Table 1: HIV patients with increased liver enzymes before and after initiation of HAART therapy.

	Before Initiation of therapy		After initiation of therapy						
			3 months		6 months		9 months		
	Normal (%)	Raised (%)	Normal (%)	Raised (%)	Normal (%)	Raised (%)	Normal (%)	Raised (%)	p- value
ALT	258 (92)	22 (08)	240 (85)	40 (15)	138 (49)	142 (51)	112 (40)	168 (60)	<0.001**
AST	255 (91)	25(09)	235 (84)	45 (16)	130 (46)	150 (54)	106 (38)	174 (62)	<0.001**
ALP	109 (39)	171 (61)	105(38)	175 (62)	100 (35)	180 (65)	64(23)	216 (77)	<0.001**

* Statistically significant

** Statistically highly significant

According to Table 1, liver enzymes were studied in patients before and after initiation of study at 3, 6 & 9 months. ALT levels which were normal in 258 (92%) patients and raised in 22 (8%) patients before initiation of therapy and were found to be normal in 112 (40%) patients and raised in 168 (60%) patients after 9 months of initiation of therapy and both before and after initiation of therapy were found to be statistically highly significant. AST levels which were normal in 255 (91%) patients and raised in 25 (9%) patients before initiation of therapy and were found to be normal in 106 (38%) patients and raised in 174 (62%) patients after 0 months of initiation of therapy, and association was highly significant *(p<0.001).*

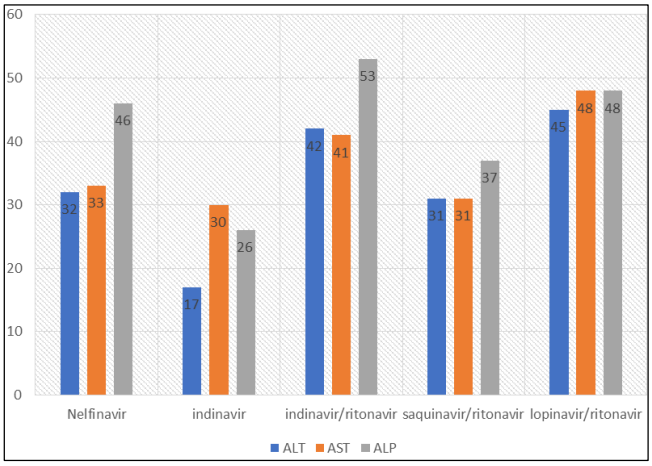

Fig 2: HIV patients with increased liver enzymes receiving ART- PIs Therapy.

As per figure 2, on comparison of Liver enzymes before and after initiation of Protease Inhibitors, it was seen that there was significant increase in liver enzymes levels after initiation of therapy as compared to before. The significant level was seen in all liver enzymes i.e ALT, AST & ALP with protease inhibitors but the toxicity level was seen highest with Lopinavir/Ritonavir (47%), Indinavir/Ritonavir (45%), Nelfinavir (37%), Saquinavir/Ritonavir (33%) and Indinavir (24%).

Table 2: HIV Patients coinfected with HBsAg and HCV Antibody.

	Positive (%)	Negative (%)	p-value
HBs Ag	78 (28)	202 (72)	<0.05*
HCV Antibody	53 (19)	227 (81)	<0.001**

Table 2 shows that, before initiation of therapy 78 (28%) patients were HBsAg positive and 202 (72%) patients were HBsAg negative and it was found to be statistically significant association. In case of HCV Antibody before the initiation of therapy 53 (19%) patients were HCV positive and 227 (81%) patients were HCV negative, it was found to be highly significant association and 227(81%) patients were HCV antibody negative.

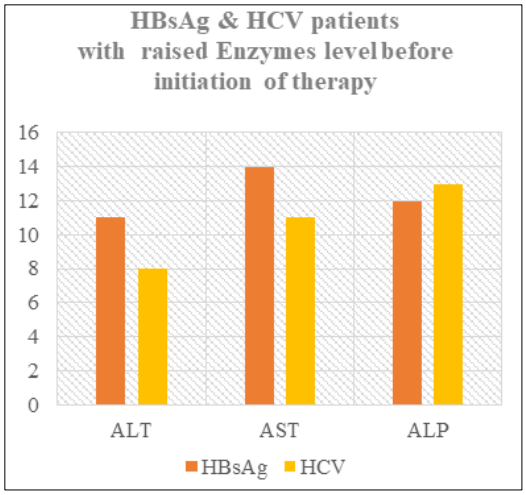

Fig 3: HIV coinfected Patients with raised Liver enzymes before and after receiving ART -PIs Therapy.

Figure 3 depicts that, before initiation of therapy no. of HBsAg positive and HCV positive patients with increased ALT levels were 11% and 8 %, after initiation of therapy it increased to 30% and 18%.
Before initiation of therapy no. of HBsAg positive and HCV positive patients with increased AST levels were 14% and 11 %, after initiation of therapy it increased to 32% and 20% and before initiation of therapy no. of HBsAg positive and HCV positive patients with increased ALP levels were 12% and 13 %, after initiation of therapy it increased to 39% and 22%.

Table 3: Patients with CD4 cell count after initiation of therapy

CD_4 Cell Count	No. of HIV Patients (%)
>500	228 (81)
<500	52 (19) *
Total (%)	280 (100)

Table 3 depicts that, after initiation of therapy 228 (81%) patients had CD4 cell count more than 500 and 52 (19%) patients had CD4 cell count less than 500 which can lead to the inference that in patients with CD4 <500 apart from HIV other external factor are also involved which is found to be statistically significant after initiation of therapy.

4. Discussion

The present study describes possible connections between antiretroviral therapies- Protease Inhibitor Drugs, used to treat HIV infection and adverse drug reactions encountered predominantly in the liver. Similarly, hepatitis B and /or C virus co-infection has been associated with a greater risk of Drug Induced liver Toxicity, compared with those with no Hepatitis. In the study by Wit *et al*. the use of low-dose ritonavir-based ART (i.e., ⩾200 mg/day) was not associated with any cases of grade 4 hepatotoxicity. Furthermore, in a randomized controlled trial that compared lopinavir therapy boosted with low-dose ritonavir and nelfinavir, only 4.5% of lopinavir/ritonavir recipients developed an AST or ALT level >5 times the ULN, which was like the incidence observed in nelfinavir recipients (5.2%).[10] Recently, Hsu *et al*. reported that, in patients with mild hepatic impairment, ritonavir exposure (measured as the area under the curve [AUC]) increased by 40%; 95% CI, 17%–66%) and peak concentration increased by 27% (95%, CI5%–53%), compared with values in control patients [11].

5. Conclusion

Hepatotoxicity developed in HBs Ag and HCV coinfected patients was significantly higher as compared to patients without coinfection, showed that viral hepatitis coinfections are self-determining risk factors for hepatotoxicity. The incidence of hepatotoxicity was significantly low within starting 3 months of treatment with first line antiretroviral regimens, but raised abruptly in later 6 months of treatment, suggesting that frequent measurement of transaminases in the first three months may not be necessary in all patients initiating HAART. Bigger and longer duration follow up studies are needed to verify the finding.

6. References

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