Liver Function Abnormalities In HIV Positive Patients And Its Correlation With Cd4 Count

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Abstract

Background: Human immunodeficiency virus (HIV) infection leads to profound and irreversible immunosuppression. Liver function abnormalities are commonly seen in HIV-infected patients, and highly active antiretroviral therapy (HAART) has led to complete modification of the pattern of hepatic events in HIV infection. The early recognition and diagnosis of these events will be helpful for the safe and effective use of HAART and enhance the survival rates among HIV-infected people.

Objectives: This study was done to identify the liver function abnormalities in HIV-positive patients and their correlation with CD4 count.

Materials and Methods: The study included 250 HIV positive patients selected from Jawaharlal Nehru Institute of Medical Sciences and Hospital from September 2019 to August 2021. Complete blood picture, blood urea, serum creatinine, liver function tests (LFTs), CD4 count, hepatitis B surface antigen, anti-hepatitis C virus, RBS, INR has been done for all the patients. Based on CD4 count, the study population was divided into three groups. Group I included 82 patients with CD4 count < 200 cells per cu.mm, group II included 89 patients with a CD4 count between 201 and 350, and group III included 79 Patients with CD4 count >350. About 141/250 patients were on TLE (ART Regimen) and 92/250 on TLD.

Results: In the present study, the distribution of patients by serum bilirubin stratified by CD4 count showed that the majority of 157 out of 250 patients show a moderate increase in serum bilirubin. Their relative distribution is (51.6%) in CD4< 200 group and 45.9 % in 200-350, 93.5% in > 350 CD4 groups (P <0.001). In the present study the relative distribution of patients with mild increase in INR is 47.1%, 42.1%,10.7%,among <200, 201-350,>350 CD4 groups respectively (p < 0.001).

Conclusion: HIV-infected patients are at a greater risk of liver function abnormalities. The derangement in liver function is more, with the decrease in CD4 count. Serum bilirubin and INR are commonly deranged liver function parameters with its prevalence more among patients with declining CD4 count (The incidence of liver function abnormality increases with the severity of the disease. Early detection of the exact cause and appropriate treatment of these abnormalities will reduce morbidity and mortality in HIV/AIDS patients.

Keywords: CD4 count, Human immunodeficiency virus infection, HIV positive, Liver function abnormality.

INTRODUCTION

Diseases of the hepatobiliary system are significant problems in patients with human immuno virus(HIV) infection. It has been estimated that approximately 15% of the deaths of patients with HIV infection are related to liver disease. 1 These complex mechanisms[1-2] of liver injury in HIV infected patients include; 1. Hepatotoxicity related to antiretroviral drugs. 2. Idiosyncratic or immuno-allergic mechanisms. 3. Direct cytotoxicity. 4. Co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. 5. Opportunistic infections. 6. Alcohol-related liver disease. 7. NASH with associated metabolic syndromes. 8. Drugs. The development of HAART (regimen consisting of nucleoside reverse transcriptase inhibitors [NRTIs], protease inhibitors [PIs], and non-NRTIs [NNRTIs]) has resulted in a significant decline in morbidity and mortality among HIV-infected patients[3]. HAART has also modified the pattern of hepatic events in HIV-infection, and the liver should be an important consideration when treating HIV-

infected patients [4]. Liver cells, including Kupffer cells[KC's], might be infected by HIV-1, and these cells might be involved in certain liver lesions observed during HIV-1 infection, particularly sinusoidal abnormalities [4].
Pathogenesis of liver fibrosis can be explained by a direct effect on hepatocytes, hepatic stellate cells (HSCs), and KCs. In the absence of productive infection, glycoprotein 120 (gp120) binding to chemokine receptor type 4 (CXCR4) may induce apoptosis of hepatocytes and activation of HSCs.
In vitro studies suggest HIV-infection of KCs leads to productive infection[5-8]. HIV also induces hepatocyte apoptosis in vitro via gp120 signalling through C-X-C chemokine receptor type 4 (CXCR4) in the absence of infection. HIV-infection of Gastrointestinal [GI] tract associated CD4+ T-cells leads to increased permeability to bacterial endotoxins such as lipopolysaccharide (LPS). Elevated levels of LPS have been shown to contribute to liver disease progression in alcoholic liver disease[9-10] as well as in Nonalcoholic fatty liver disease [NAFLD] and Nonalcoholic steatohepatitis [NASH][11-13].

AIMS AND OBJECTIVES

1. To study and describe the "liver function abnormalities in HIV positive patients and their correlation with CD4 count."
2. To compare liver function enzymes in HIV positive groups, divided based on CD4 count.

PATIENTS AND METHODS

1. A cross-sectional study was conducted for a duration of two years, w.e.f September 2019 to August 2021, JNIMS Imphal, Manipur, in the Department of Medicine, in collaboration with the Department of Microbiology and the Department of Biochemistry, after prior approval from institutional ethical committee. Data collection was done by simple random sampling or by lottery method.

A questionnaire for detailed history was taken from all the patients, and a thorough physical examination was done.
Patients meeting inclusion criteria (All HIV –seropositive patients, seropositivity being confirmed by NACO guidelines(RAPID DIAGNOSTIC TESTS), Age ->18 years and< 65 years, sex – male, female, transgender were taken as study subjects. Pregnant females and non-consenting individuals are excluded.

DIAGNOSTIC TESTS: All routine investigations Complete Blood count, Liver function tests, INR, Kidney function tests, Urine routine examination, Fasting blood sugar, serum triglycerides and CD4 count are done.
SGOT AND SGPT are done by Vitros 250 dry chemistry method.
HbsAg and anti-HCV antibodies were tested using 3rd generation ELISA from Qualisa HbsAg and Qualisa anti HCV, Qualpro Diagnostics, Goa, India, respectively, following standard protocol and manufacturer's instructions with adequate quality control.
The diagnosis of HIV positivity was based on clinical seropositivity being confirmed using "Rapid Diagnostic Tests(RDT's)" supplied by NACO, as per NACO guidelines.

The observations made were entered in the database programme SPSS version 21 for Windows. An appropriate statistical analysis was applied.

RESULTS

The study was conducted on a total of 250 HIV positive patients divided into three groups based on their CD4 count (CD4 <200, CD4 201-350, CD4 >350 cells per cu mm), and liver function abnormalities were analysed among three different groups.

The commonest age group in < 200 CD4 group is 61-70, and in > 201-350 group is 31-40, where as in >350 group it is < 30 years age, which constituted 55.6%, 44.3%,52.5% in respective groups.This finding is statistically significant.The mean age of study population is 39.30 ± 11.50. Elderly age group are more in the CD4 group < 200 cells per cu mm.The Male study subjects in respective cd4 groups <200,20-350,>350 is 37.3% , 32.7%, 30.1%, where as Female % is 25.3 %, 41.1%,32.7%. Transgender % in the respective groups is 50%, 0%, 50%.

About 38 patients were positive for Anti HCV antibody,7 patients were positive for HBsAg, 5 were VDRL positive, 8 patients were receiving Anti-tubercular therapy, 112 patients were smokers, and 117 were alcoholics.

The number of study subjects in each respective CD4 group is 82 in CD4 group <200, 89 in CD4 group 201-350,79 in CD4 group >350. 144 patients were anemic, 11 patients had azotemia, 12 patients had abnormal serum creatinine. The majority of patients have blood sugar in the pre-diabetic range. 13 patients have borderline hypercholesterolemia and hypertriglyceridemia in 49 patients.

There was a statistically significant correlation for CD4 count with Serum bilirubin INR (Table 1 and Table 4) abnormality. Serum bilirubin and INR derangement are more in the group CD4 < 200 cells per cu.table 1- Correlation of Serum bilirubin with CD4 count.

Serum Bilirubin	CD4 count			Total	P-value
	<200	201-350	>350		
0.2-2 mg/dL	1 (1.6%)	15 (24.2%)	46 (74.2%)	62 (100%)	<0.001
2.1-3 mg/dL (Mild)	0 (0%)	2 (6.5%)	29 (93.5%)	31 (100%)	
>3 mg/dL (Moderate)	81 (51.6%)	72 (45.9%)	4 (2.5%)	157 (100%)	
Total	**82 (32.8%)**	**89 (35.6%)**	**79 (31.6%)**	**250 (100%)**	

Table 2- Correlation of SGOT with CD4 count

SGOT	CD4 count			Total	P-value
	<200	201-350	>350		
<31 IU/L	39 (30.5%)	47 (36.7%)	42 (32.8%)	128 (100%)	0.723
>32 IU/L	43 (35.2%)	42 (34.4%)	37 (30.3%)	122 (100%)	
Total	**82 (32.8%)**	**89 (35.6%)**	**79 (31.6%)**	**250 (100%)**	

Table 3- Correlation of SGPT with CD4 count

SGPT	CD4 count			Total	P-value
	<200	201-350	>350		
5-65 IU/L	40 (32%)	44 (35.2%)	41 (32.8%)	125 (100%)	0.917
>65 IU/L	42 (33.6%)	45 (36%)	38 (30.4%)	125 (100%)	
Total	**82 (32.8%)**	**89 (35.6%)**	**79 (31.6%)**	**250 (100%)**	

. Serum glutamate oxaloacetate transaminase (SGOT), Serum glutamate pyruvate transaminase (SGPT), Serum Albumin (Table 2,3 and 5) abnormalities are more in the group with CD4 < 200 cells per cu.mm, but there was no statistically significant correlation.

Table 4- Correlation of INR with CD4 count

INR	CD4 count			Total	P-value
	<200	201-350	>350		
Normal (<1.7)	10 (8.8%)	38 (33.3%)	66 (57.9%)	114 (100%)	<0.001
Mild increase (1.7-2.3)	57 (47.1%)	51 (42.1%)	13 (10.7%)	121 (100%)	
Moderate increase (>2.3)	15 (100%)	0 (0%)	0 (0%)	15 (100%)	
Total	**82 (32.8%)**	**89 (35.6%)**	**79 (31.6%)**	**250 (100%)**	

Table 5- Correlation of Serum Albumin with CD4 count

Albumin	CD4 count			Total	P-value
	<200	201-350	>350		
Moderate Hypo (<2.8 g/dl)	16 (39%)	15 (36.6%)	10 (24.4%)	41 (100%)	0.669
Mild Hypo(2.8-3.5)	19 (27.1%)	26 (37.1%)	25 (35.7%)	70 (100%)	
>3.5	47 (33.8%)	48 (34.5%)	44 (31.7%)	139 (100%)	
Total	**82 (32.8%)**	**89 (35.6%)**	**79 (31.6%)**	**250 (100%)**	

In the present study there is raise in SGOT (Grade I) 35.2%,34.4%,30.3% of study subjects in CD4 groups <200, 201-350 and >350 respectively (p = 0.72). SGPT raise (Grade I) in 33.6%, 36%,30.4% of study subjects from respective groups of CD4 <200, 201-350, >350 respectively (p = 0.91). In the present study the relative distribution of patients with mild increase in INR is 47.1%42.1%,10.7% among <200,201-350, and>350 CD4 groups respectively (p<0.001). Serum bilirubin stratified by CD4 count showed that the majority (157 out of 250) patients show a moderate increase in serum bilirubin.Their relative distribution is (51.6%) in CD4< 200

group and 45.9 % in 200-350, 93.5% in > 350 CD4 groups(P <0.001). In the present study there is distribution of patients by moderate hypoalbuminemia in 39%, 36.6%,24.4% in the respective CD4 groups <200, 201-350, >350 among the subjects with serum albumin < 2.8 g/dl (p = 0.669).

DISCUSSION

The mean age of the study population in this study was 39.30 years. In the study done by Ejilemele*et al*[14], the mean age was 35.6 years. In Sterling *et al*.'s study [15], the mean age was 42 years. In the study by Maj Sunny Pathania *et al*. [18], the mean age is 40.59 ± 11.20 years. In the present study, the mean age group is similar to the other studies.

Liver function test abnormalities

In the present study there is raise in SGOT (Grade I) 35.2%,34.4%,30.3% of study subjects in CD4 groups <200, 201-350 and >350 respectively (p = 0.72). In the study by Fengxiang *et al*. [16], SGOT raise was seen in 11.83%, 12.94%,12.34% of study subjects among the CD4 groups, same as above. In the study by Savita*et al*[1],(2015) SGOT rise is seen in 59.7%, 26.9%, 13.4% of study subjects, in the respective CD4 groups <200,201-350,>350. There is an SGOT raise inversely proportional to the CD4 count, which is confounding with the findings of Savita *et al*. one, and the finding is statistically insignificant. SGPT raise (Grade I) in 33.6%, 36%,30.4% of study subjects from respective groups of CD4 <200, 201-350, >350 respectively (p = 0.91). In the study by Savita*et al*[1], SGPT raise was seen in 63.3%,28.3%,8.3%. in respective CD4 groups of CD4< 200,201-350,>350. In the study by Dusingize*et al*[17], the prevalence of elevated AST and/or ALT was 6.6% compared to 12.6% in HIV infected women, with the highest prevalence (16.4%) in HIV-infected women with CD4 <200 cells /µl.There is SGPT raise and is inversely proportional to CD4 count, and the finding is statistically insignificant. Mild increase in INR is 47.1%,42.1%,10.7%,among <200, 201-350, and >350 CD4 groups respectively (p < 0.001) In the study by Savita *et al*.[1] (2015) INR raise was seen in 31.4%, 42.9%,25.7% of study subjects from respective CD4 groups <200,201-350,>350 respectively, among the total study subjects with increase INR. In this study, the higher is the value of CD4 count lower is the INR value, and the finding is statistically significant. Serum bilirubin stratified by CD4 count showed that the majority of 157 out of 250 patients show a moderate increase in serum bilirubin.Their relative distribution is (51.6%) in CD4< 200 group and 45.9 % in 200-350, 93.5% in > 350 CD4 groups(P <0.001). In the study by Savita *et.al*[1] bilirubin raised was observed in 50%,25%,25% of study subjects from respective CD4 groups <200,201-350,>350 respectively, among the study subjects with an increase in bilirubin**.** In the study by Pathania *et.al*[18], hyperbilirubinemia was noticed in 27/247 (10.93%) patients. However, only 8 patients were icteric (grade III in 6 patients and grade IV in 2 patients). Bilirubin raises were found to be inversely proportional to CD4count, and the finding is statistically significant. Moderate hypoalbuminemia in 39%, 36.6%,24.4% in the respective CD4 groups <200, 201-350, >350 among the subjects with serum albumin < 2.8 g/dl (p = 0.669). In the study by Savita *et al*[1], the albumin below 3.2g/dl was seen in 49.2%,26.2%,24.6% of study subjects from the respective CD4 groups <200,201-350,>350. In the study by Dusingize*et al*[17], the odds of having serum albumin <3.5 g/dl was 2.6 –fold higher in HIV + women with CD4 counts <200 and 1.6 fold higher in those with cd4 between 200 and 350 cells/µl. In the present study, there is a directly proportional drop in serum albumin that is a synthetic liver function, with the decrease in CD4 count, but the finding is statistically insignificant.

LIMITATIONS OF THE STUDY

The limitations of our study are many confounding factors causing liver function abnormalities and lacking case selection eliminating these confounding factors. Subgroup analysis couldn't be done.

CONCLUSION

Liver function abnormalities are common among HIV patients. The derangement in liver function is more, with the decrease in CD4 count. Serum bilirubin and INR are commonly deranged liver function parameters with its prevalence more among patients with declining CD4 count (<200 cells/µl). Liver enzyme rise with the decline in CD4 count needs more extensive study. Early detection of the exact cause and appropriate treatment of these abnormalities will reduce morbidity and mortality in HIV/AIDS patients.

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