Liver Function Tests Abnormalities and Hepatitis B Virus & Hepatitis C Virus Co-infection in Human Immunodeficiency Virus (HIV)-infected Patients in India

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Background: **While highly active anti-retroviral therapy (HAART) has improved survival of HIV-infected patients, there is increasing liver disease and progressive Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) related liver disease.** ***Aims:*** **To study the liver function tests (LFT) and HBV and HCV co-infection in HIV-infected patients.** ***Material and Methods:*** **All HIV-positive patients presenting to a tertiary level hospital from April 2009 to April 2011 were evaluated. Baseline LFT, CD4/CD8 counts, ultrasound abdomen, HBsAg, IgG anti-HBc, HBVDNA, Anti-HCV and HCVRNA were done in all patients. LFT was repeated monthly or more frequently with anti-tubercular therapy (ATT)/HAART.** ***Results:*** **Abnormal LFT were seen in 143/320 (44.6%) HIV-infected patients (*n* = 320; M-282, F-38; mean age-35.4 ± 7.3 years). Baseline LFT was abnormal in 48 (15%) [hepatotropic viruses-19, alcohol-24, NAFLD-1, disseminated TB-1, idiopathic-03). Subsequent LFT derangement developed in 95/272 (34.9%). In the majority, the LFT abnormality was mild (119/143–83.2%) and multi-factorial [HAART 132 (76.4%), alcohol 69 (48.2%), ATT 31 (21.7%), HBV 16 (11.2%), HCV 15 (10.4%)]. Using multivariate analysis, abnormal LFT were associated with HAART (OR, 5.92; 95%CI, 2.83–12.37), ATT (OR, 2.06; 95%CI, 1.06–3.99) or HCV infection (OR, 2.54; 95%CI, 1.03–6.26). Significant hepatotoxicity requiring drug modification was seen in only 7 cases. HBV, HCV and HBV + HCV co-infection were seen in 37 (11.6%), 28 (8.8%) and 2 (0.6%) respectively. Occult co-infections were rare [HBV-1 (0.3%); HCV-3 (0.9%)].** ***Conclusion:*** **While LFT abnormalities in HIV are common, they are usually mild and multifactorial. HBV and HCV co-infections were seen in 11.6% and 8.8%, respectively. Occult HBV and HCV infections were rare. (J Clin Exp Hepatol 2017;7:1–8)**

Human immunodeficiency virus (HIV) infection is a major public health problem and it was estimated that at the end of 2014, 36.7 million people were living with HIV.[1] Asia-Pacific has 5 million people living with HIV which accounts for about 14% of the global burden of HIV-infected people.[2] The total number of people living with HIV in India was estimated to be 2.1 million (1.71 million–2.65 million) in 2015.[3]

Advances in highly effective antiretroviral therapy (HAART) have decreased the mortality due to AIDS-related illnesses. Prior to the use of HAART, extra-hepatic causes of death like opportunistic infections, lymphomas or wasting syndrome, which were related to severe immunodeficiency, were important. With increased survival of people living with HIV/AIDS (PLHA) with the use of HAART, there is an increasing occurrence of liver dysfunction and progressive hepatitis B virus (HBV) and hepatitis C virus (HCV) related chronic liver disease.[4,5] Liver disease has now become a leading cause of death in patients with HIV.[6]

Liver dysfunction in HIV infection is related to multiple factors including infectious and non-infectious causes. There are important differences in both the prevalence and severity of some of these common liver diseases including HBV and HCV in HIV-infected patients.[7–13] Co-infection of HBV and HCV is very common in HIV infected persons due to the shared routes of transmission. Other causes of liver dysfunction in HIV include higher rates of alcohol abuse; and hepatotoxicity of HAART and drugs used to treat opportunistic infections.[14–16]

India has higher heterosexual transmission of HIV, lower intravenous drug use and a lack of universal immunization for HBV. These factors are likely to affect the prevalence of HBV and HCV co-infection in the HIV-infected population. Despite the large number of HIV seropositive patients in India, there is paucity of data on liver dysfunction in PLHA and the prevalence of HBV and HCV infection in HIV-seropositive patients in India.

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This study was carried out with an aim to study the prevalence and causes of liver function test abnormalities in HIV-infected patients and the prevalence of co-infection with HBV and HCV in HIV-infected patients.

MATERIAL AND METHODS

The study was carried out among HIV-infected persons seen at an Armed Forces tertiary hospital in Delhi from April 2009-April 2011 attending outpatient or inpatient care.

Inclusion criteria

All HIV positive cases diagnosed using standard diagnostic criteria and receiving treatment or on regular follow up at the hospital were included in the study.

Evaluation of patients

Detailed history was taken from all patients with special reference to duration of HIV infection, mode of infection, previous history of jaundice, HBV or HCV infection. A thorough clinical examination was carried out and stigmata of chronic liver disease, hepatosplenomegaly, ascites, etc. if present were noted. Excessive alcohol use was defined as more than 140 g ethanol per week for men and more than 70 g ethanol per week for women. All the registered patients were asked regarding alcohol and drug use and medication including HAART, ATT and other hepatotoxic drugs.

In ART-naïve patients, initiation of HAART was deferred by 8–12 weeks unless the CD4 counts were <50 cells/μL. In patients already on HAART, patient on protease inhibitors were given rifabutin instead of rifampicin. In patients on nevirapine-based HAART, efavirenz was substituted for nevirapine. The ATT regimen was modified if patients became jaundiced, or became symptomatic with AST/ALT > 3 X ULN or if transaminases rose to >5 X ULN in asymptomatic patients.

Investigations

Evaluation in all cases

A. *Basic investigation-* including Hemoglobin (Hb), total leucocytes count (TLC), differential leucocytes count (DLC), platelet count, X-ray chest, ultrasound abdomen and LFT were done in all patients. The LFT included serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum alkaline phosphatase (SAP) and serum albumin. Abnormal values were defined as serum Bilirubin ≥1.5 mg/dl, ALT/AST≥50 IU/ml. Isolated rise in SAP was considered abnormal if it was ≥3 times upper limit of normal (ULN).

Patients were followed up at an interval of one month or earlier in case of new introduction of HAART or ATT or if they were symptomatic. In patients with normal liver functions, the LFT were repeated three monthly. In patients with symptoms or derangement of liver function tests, the tests were repeated earlier.

Liver tests abnormalities were graded according to the AIDS Clinical Trial Group grading as below[17]:

Grade I: AST/ALT 1.25–2.5 x ULN (50–100 IU/L)
Grade II: AST/ALT 2.6–5 x ULN (101–200 IU/L)
Grade III: AST/ALT 5.1–10 x ULN (201–400 IU/L)
Grade IV: AST/ALT > 10 x ULN (> 400 IU/L)

B. *Evaluation of HIV disease-* CD4 and CD8 counts were done in all patients. All patients were screened for opportunistic infections especially TB.

C. *Evaluation for HBV/HCV co-infection-* Hepatitis B surface antigen (HBsAg) by ELISA, IgG hepatitis B core antibody (Anti-HBc), Anti-HCV, HBVDNA (quantitative) and HCVRNA (quantitative) by polymerase chain reaction (PCR) were done in all patients.

Evaluation in specific cases for deranged liver function

Besides the above investigations, in patients with jaundice or deranged transaminases, further evaluation was done as indicated depending on the profile of the case. These included antibodies for hepatitis A virus (IgM Anti-HAV), antibodies for hepatitis E virus (IgM Anti-HEV), IgM Anti-HBc, Cytomegalovirus (CMV) DNA and Herpes Simplex virus (HSV) serology. Liver biopsy was done as indicated after consent of the patient.

Statistical analysis

Statistical analysis was done using IBM SPSS V22.0. Armonk, NY:IBM Corp. Frequency table and cross tabulation were used to evaluate the factors associated with abnormal values of liver enzymes. Univariate models were used to examine each variable with the presence of any abnormal liver function test. Each variable for which the *P* value was significant or two variables related clinically were included in the multivariate model. Cross tabulation was also used to compare those with and without liver function abnormalities, and to compare different variables. Odds ratio was calculated using backward regression analysis. *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 320 patients (282 males, 38 females) were included in the study. Mean CD4 count was 272 cells/mm^3; and 37.5% had CD4 count < 200 cells/mm^3. History of significant alcohol intake was recorded in 40.6%. HBV and HCV co-infection were seen in 11.6% and 8.8% patients respectively. A total of 254 (79.4%) patients received HAART. Baseline characteristics of these 320 HIV infected patients are depicted in Table 1. Three patients died during the course of study. The mean duration of follow up of the patients was 13 months (1–164 months).

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Table 1 Baseline Characteristics of HIV-infected Patients*

Parameters	*n* = 320
Age (years)	35.4 ± 7.3
Males:Female sex	282 (88.5%):38 (11.5%)
BMI (kg/m^2)	21.8 ± 2.7
Duration of HIV infection (months)	30 ± 53.8
CD4 count (/mm^3)	272 ± 187
CD4 < 200/mm^3	120 (37.5%)
CD4 > 200/mm^3	200 (62.5%)
Significant alcohol consumption	130 (40.6%)
HBsAg positive	37 (11.6%)
Anti HCV positive	28 (8.8%)
Combined HBV and HCV	02 (0.6%)
Occult HBV	01 (0.3%)
Occult HCV	03 (0.9%)
Medication use	
a) Cotrimoxazole	152 (47.5%)
b) Fluconazole	84 (26.3%)
c) HAART	254 (79.4%)
d) ATT	48 (15%)
Baseline LFT	
e) Bilirubin (mg/dl)	1.05
f) ALT (IU/ml)	±242.1
g) AST (IU/ml)	±164.34
h) SAP (IU/ml)	96.1 ± 61.9

ATT, anti-tubercular therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; SAP, serum alkaline phosphatase.
*Values are Mean ± SD or percentages (%).

Table 2 Grades of Abnormal Liver Function Tests on Baseline and on Follow up in Absolute Numbers (%).

Grades	At baseline (*n* = 320)	At follow up (*n* = 320)
0 (<50 IU/ml)	272 (85%)	137 (42.8%)
I (51–100 IU/ml)	42 (13.1%)	119 (37.2%)
II (101–200 IU/ml)	2 (0.6%)	16 (5%)
III (201–400 IU/ml)	2 (0.6%)	6 (1.8%)
IV (>400 IU/ml)	2 (0.6%)	2 (0.6%)

IU, international units.

Overall prevalence of liver function test abnormalities

Overall 143 subjects (44.7%) in the study had abnormal liver tests result during the study period, either at baseline or during follow up. The majority of patients had mild derangement of liver function tests and only four patients presented with icterus. Grade I liver dysfunction was seen in 119 (83.2%), grade II liver dysfunction in 16 (14%), grade III liver dysfunction in 6 (4%) and grade IV in only 2 (1.4%) patients. Significantly isolated rise in SAP was seen in 3 (2%) patients (Table 2).

Baseline abnormalities in liver function tests

Abnormal LFT was present at baseline in 48 patients (15%). None of the patients were on HAART at the time of baseline tests. The majority of patients with baseline abnormalities of liver function tests had mild derangements: grade I in 42 (87.5%), grade II in 2 (4.2%), grade III in 2 (4.2%) and grade IV in 2 (4.2%) (Table 2).

The causes of derangement of LFT at base line were co-infection with hepatotropic virus in 19 patients, significant alcohol consumption in 24, NAFLD in 1 and disseminated TB in 1 patient. In 3 patients, there was no obvious cause of derangement of liver functions. Among the deranged liver functions due to hepatotropic virus infections, 11 had HBV infection, 6 had HCV infection while 2 had combined HBV and HCV co-infection. Two patients presented with acute hepatitis B with AST/ALT > 10 times ULN and were IgM anti HBc positive. The spectrum of baseline liver dysfunction in patients with HIV and their related etiologies is depicted in Table 3.

On serial follow up, of these 48 patients with abnormal baseline liver function, 10 patients worsened with increase in grading of transaminases, 34 of them continued to have the abnormal liver function in the same grade while 4 patients had improvement of liver functions (1 patient improved with decrease in transaminase to lower grade and 3 patients had returned to normal LFT). The cause for deterioration in LFT in patients with baseline abnormal LFT was starting of HAART in 7 patients, HAART with ATT in 2 patients and ATT in 1 patient.

Abnormalities in liver function tests on follow up in patients who had normal baseline liver function tests

Among the 272 patients who had normal LFT at baseline, 95/272 (34.9%) patients developed deranged LFT on follow up. The majority of these abnormalities were mild: grade I in 77 (81%), grade II in 11 (11.5%), grade III in 5 (5.2%) and grade IV in 2 (2%) and isolated elevation of SAP in 3 (3%). Significant hepatotoxicity (ALT/AST rise ≥ grade 3 or any symptoms of hepatitis) requiring treatment modification was seen in only 7 patients. Three patients on HAART and 4 patients on ATT with HAART required modification of their regimen.

The majority of the patients who had deranged liver function tests had more than one cause of liver involvement including HAART, alcohol intake and introduction of ATT. Of these 95 patients with deranged LFT, 88 (93%)

Table 3 Associations of Clinical Parameters with Abnormal Liver Function Tests on Baseline*

Parameter	Normal LFT (*n* = 272)	Abnormal LFT (*n* = 48)	*P* value
Age (years)	35.3 + 6.7	36.5 + 10.1	0.54
Sex (M:F)	237:35 (87.1%:12.5%)	45:3 (93.8%:6.2%)	0.91
BMI (kg/m^2)	21.8 ± 1.8	21.7 ± 2.7	0.88
Duration of HIV infection (months)	36 ± 50.3	38 ± 43.8	0.95
CD4 count (/mm^3)	280 ± 182	234 ± 212	0.12
Significant alcohol consumption	106 (38.9%)	24 (50%)	0.15
HBV & HCV Co-infection	47 (17.2%)	19 (39.6%)	**0.002**
HBsAg positive	26 (9.6%)	11 (22.9%)	**0.01**
Anti HCV positive	21 (7.7%)	06 (12.5%)	0.27
Combined HBV& HCV	0	02 (4.1%)	–
NAFLD	2 (1.2%)	1 (2.0%)	–
Disseminated TB	0	1 (2.0%)	–
No obvious cause	–	3 (6.25%)	–

ATT, anti-tubercular therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease; SAP, serum alkaline phosphatase.
*Values are Mean ± SD or percentages (%).

had been started on HAART. Besides HAART, the other major hepatotoxic etiologies were alcohol intake in 50 (52%) and ATT in 20 (21%). The other causes for the liver test abnormalities on follow up of the patients with baseline normal LFT were infections with hepatotropic viruses [*n* = 19; HBV-11, HCV-6, combined HBV & HCV-2], and other miscellaneous causes in 2 patients. The spectrum of liver dysfunction in patients with HIV who had normal LFT at baseline and the related associations are depicted in Table 3.

Comparison of HIV-infected persons with or without abnormal LFT

The selected characteristics of HIV-infected patients with or without abnormal LFT including HIV related factors, treatment with HAART and ATT, and HBV/HCV co-infection are depicted in Table 4.

Using univariate analysis, it was seen that HIV-infected patients were more likely to have liver test abnormalities if they had lower CD4 counts (OR, 0.99; 95%CI, 0.92–0.99), significant alcohol consumption (OR, 1.77; 95%CI, 1.13–2.78), using HAART (OR, 5.41; 95%CI, 2.71–10.81) or ATT (OR, 2.6; 95%CI, 1.38–4.93). There was no co-relation of deranged LFT to age, BMI and HBV or HCV infection.

Using multivariate analysis, the only factors that were significantly associated with abnormal LFT were HAART (OR, 5.92; 95%CI, 2.83–12.37), ATT (OR, 2.06; 95%CI, 1.06–3.99) or HCV infection (OR, 2.54; 95%CI, 1.03–6.26).

Effect of HAART on LFT

Among the cohort of 320 patients, 254 were started on HAART. HAART was initiated at CD4 count less than 200 cells/ml. All the patients on HAART received 2 nucleoside reverse transcriptase inhibitor (NRTI) (zidovudine, stavudine, lamivudine or tenofovir) and one 1 non-nucleoside reverse transcriptase inhibitors (NNRTI) (nevirapine or efavirenz). Ten patients who were started on second line ART received protease inhibitor (PI) (lopinavir + ritonavir) in addition. LFT abnormalities were seen in 132 (74.6%) patients on ART. Majority of these abnormalities were mild [109/132 (82.5%)].

Overall seven patients developed severe hepatotoxicity on initiation of HAART requiring withdrawal of the incriminating drugs. The common drugs causing significant hepatotoxicity were nevirapine and stavudine in combination in 4 patients and nevirapine alone in 3 patients.

Effect of ATT on LFT

Forty-eight patients in the cohort of 320 patients were receiving ATT during the study period, 46 of whom were also on HAART. Of the patients on ATT, 31/48 (64.58%) patients had liver enzymes abnormalities. Grade I abnormalities were seen in 22 (71%), grade II in 6 (19%), grade III in 2 (6.5%) and grade IV in 1 (3.2%) patients. The mean time for development of deranged LFT in HIV patients with ATT was 2 months. Four patients on ATT developed hepatotoxicity severe enough to modify the ATT.

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Table 4 Univariate and Multivariate Associations of Various Clinical Parameters with Abnormal Liver Function Tests on Baseline and on Follow up*

Parameter	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age (years)	1.01 (0.98–1.04)	0.40	–	–
BMI (kg/m^2)	1.0 (0.43–1.08)	0.98	–	–
Duration of HIV infection (months)	1.2 (0.67–2.36)	0.95	–	–
CD4 Count (/mm^3)	0.99 (0.92–0.99)	**<0.001**	0.99 (0.99–1.00)	0.25
Significant alcohol consumption	1.77 (1.13–2.78)	**0.013**	1.21 (0.73–2.01)	0.45
HBV & HCV Co-infections	1.31 (0.77–2.2)	0.32	–	–
HBsAg positive	1.00 (0.51–1.98)	0.99	1.60 (0.75–3.44)	0.23
Anti-HCV positive	1.61 (0.73–3.56)	0.24	2.54 (1.03–6.26)	**0.04**
Combined HBV & HCV	1.3 (0.77–2.24)	0.32	–	–
Use of ART	5.41 (2.71–10.81)	**<0.001**	5.92 (2.83–12.37)	**<0.001**
NRTI	5.41 (2.71–10.81)	**<0.001**	5.92 (2.83–12.37)	**<0.001**
NNRTI	4.49 (2.41–8.33)	**<0.001**	4.52 (2.52–8.68)	**<0.001**
PI	0.82 (0.23–2.96)	0.76	-	–
Use of ATT	2.6 (1.38–4.93)	0.003	2.06 (1.06–3.99)	**0.032**

ATT, anti-tubercular therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NRTI, nucleoside reverse transcriptase inhibitor; non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SAP, serum alkaline phosphatase.
*Values are odds ratio (95% confidence interval).

Infection with hepatotropic viruses in HIV

Among the 320 subjects who participated in study, infection with hepatotropic viruses occurred in 68 (21.25%). Co-infection was seen with HBV in 37 (11.5%), HCV in 28 (9%), HBV + HCV in 2 (0.6%) and HEV in 1 (0.3%). Occult HBV occult infection was seen in 1 patient (0.3%) and occult HCV infection was seen in 3 patients (0.9%).

HBV infection in HIV

Co-infection with HBV was seen in 37 (11.6%) patients with HIV; 18/37 (48.6%) were HBeAg positive. Active viral replication with raised HBVDNA was seen in 83%. Two of these patients had dual co infection with HCV. Two patients presented as acute viral hepatitis with significant rise in AST/ALT and a positive IgM Anti-HBc and subsequently had normalization of LFT though the HBsAg continued to be positive. Besides this, 16 patients had isolated IgG Anti HBc positivity. Out of the 37 patients of HBV co-infection, LFT was deranged in 16 patients (43%) with grade I LFT dysfunction in 11 patients (68%), grade II in 3 patients (18%) and grade IV in 2 patients (12%) respectively.

Liver biopsy was done on 28 patients who had chronic HBV and HIV co-infection with evidence of replicating HBV (including one patient with both HBV-HCV co-infection). Eleven patients (including one with triple co-infection) showed evidence of fibrosis on biopsy out of which 4 patients had $\geq$ stage 2 fibrosis; whereas 17-patients did not show any evidence of fibrosis.

The AST and ALT levels prior to introduction of HAART in HBV/HIV co infection were 43.66 $\pm$ 121.4 IU/L and 33.88 $\pm$ 121.8 IU/L respectively while those after introduction of HAART were 52.52 $\pm$ 21.8 IU/L and 56.43 $\pm$ 27.4 IU/L respectively.

HCV infection in HIV

HCV and HIV co infection was seen in 28 patients (8.8%). Nine patients who were anti-HCV positive were HCV RNA negative by PCR. LFT abnormalities were seen in 15 patients (53.5%). The AST and ALT levels prior to introduction of HAART in HCV and HIV co infection were 38.45 $\pm$ 40.2 IU/L and 38.65 $\pm$ 43.2 IU/L respectively while those after introduction of HAART were 87.2 $\pm$ 47.4 IU/L and 88.1 $\pm$ 34.5 IU/L, respectively.

Liver biopsy was done in 15 patients which showed fibrosis in 8 cases, 6 of them $\geq$ stage 2. HCV genotype were tested in 8 patients: genotype 1 was seen in 3, genotype 2 in 1 and genotype 3 in 4 patients.

Combined HBV + HCV infection in HIV

Two patients had co-infection with both HBV and HCV. Of these, one patient had both anti-HCV reactivity and detectable HCV RNA by PCR method. He was on HAART as well as ATT. The other patient was anti-HCV negative but HCVRNA was detectable by PCR. The LFT abnormalities seen in these patients were grade IV and grade I respectively.

DISCUSSION

In this study, we sought to determine the prevalence of LFT abnormalities and their causes amongst HIV-infected persons and the prevalence of HBV and HCV co-infection. The prevalence of baseline LFT abnormalities prior to introduction of HAART in our HIV population was 15%. This is similar to that seen in other studies among HIV-infected persons.[18–20] Only significant association of deranged LFT at the baseline has been attributed to concurrent HBV with or without HCV infection. On follow up of these patients, LFT derangement increased significantly owing to initiation of HAART and ATT, advanced stage of HIV infection and significant alcohol consumption on univariate analysis. On follow up of patients with normal baseline LFT 35% developed abnormality in LFT. The overall prevalence of LFT abnormalities in our patients was 44.6%.

On evaluation, for possible associations of the abnormal LFT in these patients it was found that majority of the cases had multiple causes responsible for deranged LFT. On multivariate analysis, drug-related LFT abnormalities were significantly more frequent as 74% and 21% patients who had abnormal LFT were on HAART and ATT, respectively. The major anti-retroviral drugs, which we found associated with hepatotoxicity, were nevirapine and stavudine in combination. Very few (07) patients had severe hepatotoxicity, which necessitated stopping ART, which is reassuring, given the increasing use of HAART among HIV patients. Drug induced liver injury can occur with almost all the classes of HAART, of which NNRTIs are commonly implicated to cause significant liver toxicity.[21] The latest guidelines for management of HIV infection recommend starting HAART even in HIV-positive persons with CD4 count $\geq$350 or at any CD4 count in symptomatic HIV disease. Guidelines recommend considering initiation of ART irrespective of CD4 count in all with the possible exception of elite controls with high and stable CD4 count with the rationale of preventing long-term complications.[22,23] As a higher threshold of CD4 count is being advocated for initiation of HAART, cases of drug related hepatotoxicity are expected to rise in near future.

It is often difficult to establish causality between liver damage and the medications in HIV patients because they may be under treatment with many potentially hepatotoxic medications.[24] With a high prevalence of tuberculosis in India, increased need for ATT among the HIV-infected population further compounds the problem of drug related hepatotoxicity. In our study, 48/320 patients were receiving ATT during the study period, 46 of whom were also on HAART. Of these, 31/48 (64.58%) patients had abnormal LFT. Fortunately, severe hepatotoxicity requiring ATT modification was seen only in four patients. The mild nature of LFT abnormalities in our cohort may also be due to a close follow up of these patients and early withdrawal of hepatotoxic drugs.

Significant alcohol consumption was seen in 46% of the persons who were studied. While alcohol intake was associated with LFT abnormalities on univariate analysis, this was not significant on multivariate analysis. Drug interactions between HAART and ATT, need to be kept in mind. Rifampicin is not recommended with many HAART drugs including PIs, elvitegravir and rilpevirine. In these cases, rifampicin should be substituted for rifabutin. In patients on neveripine, neither Rifampicin nor rifabutin are recommended.[23]

It is surprising to find very low incidence of non-alcoholic fatty liver disease (NAFLD) in our study group. In contrast, Crum–Cianflone et al.[25] found that NAFLD was the most common cause of deranged liver function tests in patients with HIV. A possible explanation may be that a large number of patients in this study were consuming significant quantity of alcohol and hence, the finding of fatty liver on ultrasound could not be attributed to NAFLD.

Worldwide, it is estimated that the prevalence of HBV infection in HIV-infected patients is high with around 80–90% of patients infected with HIV having serologic markers of past HBV infection (anti-HBc positive).[26–28] The prevalence of HBV varies markedly among different HIV-infected populations.[29] In India, where the HBV carrier rate in the general population is 3%, the prevalence of HBV infection in HIV-infected persons has reported between 2.25 and 29.7%.[30] The prevalence of HBV co-infection in this study was 11.6%. Only 5% patients tested positive for isolated IgG anti-HBc suggesting past infection with HBV.

Occult HBV is defined by the presence of HBV DNA in the serum or liver of individuals with negative test results for HBsAg. Gandhi et al. found that 10 percent of patients with anti-HBc without HBsAg in serum were detected to be HBVDNA positive by PCR.[31] In our study, occult HBV co-infection was low and was seen in only one patient. In this study only 5% patients tested positive for isolated IgG anti-HBc suggesting past infection with HBV; hence, the prevalence of occult HBV co-infection is likely to be low. Occult HBV is uncommonly described in HIV-infected patients without any serological markers of HBV infection.[32] Another reason for low prevalence of occult HBV infection may be because we tested HBVDNA only once. However, studies have suggested that the best capturing modality for occult HBV infection is by serial testing of HBV DNA as these patients may have transient viremia.[32]

Globally, the overall prevalence of HCV infection in HIV is approximately 30%.[33–35] However, the prevalence of HCV in HIV-infected persons in India is reported between 1.3 and 8.3%.[36] The prevalence of HCV co-infection varies markedly among various risk groups and route of transmission of HIV. The prevalence of HCV co-infection in our study group was around 8%.

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Though HBV-HCV co-infection was a significant factor associated with baseline LFT abnormality in HIV infected patients but on follow up, because majority of the patients were exposed to HAART with or without ATT the effect of this co-infection became insignificant, statistically. However co-infection with HCV was still a significant cause for LFT derangements on follow up of HIV infected patients.

This is the largest study looking at LFT abnormalities in HIV patients from India. Previous studies from India looked at only 74 and 198 patients, respectively. Rathi et al.[37] evaluated 74 patients with HIV and found bilirubin, transaminases and alkaline phosphatase to be elevated in 13%, 13% and 24% respectively. Shammana et al.[38] screened 198 patients with HIV and found that 51 (26%) had either abnormal LFT or had HBsAg or anti-HCV positivity.

LFT abnormalities are common among HIV-infected persons on ART with almost half of the patients showing abnormal liver function tests. In most of these cases, multiple factors are involved. Use of HAART, ATT, significant alcohol consumption and co-infection with hepatotropic viruses were the most common associated factors responsible for liver function tests abnormalities but on multivariate analysis only use of HAART, ATT and co infection with HCV were the significant associations with abnormal LFT. HBV co-infection was seen in 11.6% but unlike reports from the west, isolated IgG Anti-HBc positivity was much less common. HCV co-infection was seen in 8.8% and is much lower than the reports from the west which may reflects the difference in the mode of transmission with possibly lower intravenous drug use and homosexuality in our population. Occult HBV and HCV infection in HIV infected patients was uncommon in our study.

In conclusion, while abnormalities in the LFT were seen in a large number of the patients with HIV, these abnormalities were usually mild in this closely monitored cohort of HIV-infected patients and modification of HAART and ATT were required only in a small number of cases. The presence of HBV and HCV co-infection was low and occult HBV and HCV were rare in our study.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. WHO fact sheet on HIV/AIDS. Updated Nov 2016. Available from http://www.who.int/mediacentre/factsheets/fs360/en/ [Accessed 1.12.16].
2. UNAIDS. How AIDS changed everything; 2015. http://www.unaids.org/en/resources/documents/2015/MDG6_15years-15lessonsfromtheAIDSresponse [Accessed 1.12.16].
3. National AIDS control organization. Ministry of Health and Family Welfare. India HIV estimates 2015, Technical Report. Available from http://naco.gov.in/upload/2015 MSLNS/HSS/India HIV Estimations 2015.pdf [Accessed 1.12.16].
4. Sherman KE, Soriano V, Chung RT. Human immunodeficiency virus and liver disease: conference proceedings. *Hepatology.* 2010;51(3):1046–1054.
5. Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study. *HIV Med.* 2004;5:174–179.
6. Weber R, Sabin CA, Friis-Moller N, et al. Liver related deaths in the human immunodeficiency virus: D:A:D study. *Arch Intern Med.* 2006;166(15):1632–1641.
7. Costa-Mattioli M, Allavena C, Poirier AS, Billaudel S, Raffi F, Ferre V. Prolonged hepatitis A infection in an HIV-seropositive patient. *J Med Virol.* 2002;68:7–11.
8. Ida S, Tachikawa N, Nakajima A, et al. Influence of human immunodeficiency virus type infection on acute hepatitis A virus infection. *Clin Infect Dis.* 2002;34:379–385.
9. Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. *J Infect Dis.* 1991;163:1138–1140.
10. Gilson RJ, Hawkins AE, Beecham MR, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS.* 1997;11:597–606.
11. Di Martino V, Thevenot T, Colin JF, et al. Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B. *Gastroenterology.* 2002;123:1812–1822.
12. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology.* 1999;30:1054–1058.
13. Mohsen AH, Easterbrook PJ, Taylor C, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. *Gut.* 2003;52:1035–1040.
14. Chaudhry AA, Sulkowski MS, Chander G, Moore RD. Hazardous drinking is associated with an elevated aspartate aminotransferase to platelet ratio index in an urban HIV-infected clinical cohort. *HIV Med.* 2009;10:133–142.
15. Guarda LA, Luna MA, Smith Jr JL, Mansell PW, Gyorkey F, Roca AN. Acquired immunodeficiency syndrome: postmortem findings. *Am J Clin Pathol.* 1984;81:549–557.
16. Price JC, Thio CL. Liver disease in the HIV-infected individual. *Clin Gastroenterol Hepatol.* 2010;8:1002–1012.
17. AIDS Clinical Trial Group. *Table of Grading Severity of Adult Adverse Experiences*. Rockville MD: Division of AIDS, National Institute of Allergy and Infectious Diseases; 1996.
18. Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002. *Am J Gastroenterol.* 2006;101:76–82.
19. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms. *Clin Infect Dis.* 2004;38:S65–S72.
20. Sterling RK, Chiu S, Snider K, Nixon D. The prevalence and risk factors for abnormal liver enzymes in HIV-positive patients without hepatitis B or C coinfections. *Dig Dis Sci.* 2008;53:1375–1382.
21. Nunez M. Clinical syndromes and consequences of antiretroviral related hepatotoxicity. *Hepatology.* 2010;52:1143–1155.
22. WHO early release guidelines on when to start antiretroviral therapy and on pre exposure prophylaxis for HIV; September 2015. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/ [Accessed 1.12.16].
23. European AIDS Clinical Society guidelines, Version 8.0; October 2015. Available from http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html [Accessed 1.12.16].
24. Splengler U, Licherfeld M, Rockstroh JK. Antiviral drug toxicity-a challenge for hepatologist? *J Hepatol.* 2002;36:283–294.

25. Crum-Cianflone N, Collins G, Medina S, et al. Prevalence and factors associated with liver test abnormalities among human Immunodeficiency virus-infected persons. *Clin Gastroenterol Hepatol.* 2010;8:183–191.
26. Gordon SC, Reddy KR, Gould EE, et al. The spectrum of liver disease in the acquired immunodeficiency syndrome. *J Hepatol.* 1986;2:475–484.
27. Francisci D, Baldelli F, Papili R, Stagni G, Pauluzzi S. Prevalence of HBV, HCV, HDV markers in HIV-positive patients. *Eur J Epidemiol.* 1995;11:123–126.
28. Lebovics E, Dworkin BM, Heier SK, Rosenthal WS. The hepatobiliary manifestations of human immunodeficiency virus infection. *Am J Gastroenterol.* 1988;83:1–7.
29. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology.* 2010;49:S138–S145.
30. Puri P. Tackling the hepatitis B disease burden in India. *J Clin Exp Hepatol.* 2014;4:312–319.
31. Gandhi RT, Wurcel A, Lee H, et al. Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1-infected individuals. *Clin Infect Dis.* 2003;36:1602–1605.
32. Shire NJ, Rouster SD, Stanford SD, et al. The prevalence and significance of occult hepatitis B virus in a prospective cohort of HIV-infected patients. *J Acquir Immune Defic Syndr.* 2007;44:309–314.
33. Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palu G, et al. Short statement of the first European consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol.* 2005;42:615–624.
34. Cotler SJ, Jensen DM. Treatment of hepatitis C virus and HIV coinfections. *Clin Liver Dis.* 2001;5:1045–1061.
35. Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology.* 2002;36(5 Suppl 1):S201–S209.
36. Puri P, Kumar S. Liver involvement in human immunodeficiency virus infection. *Ind J Gastroenterol.* 2016;35:260–273.
37. Rathi PM, Amarapurkar DN, Borges NE, Koppikar GV, Kairo RH. Spectrum of liver diseases in HIV infection. *Indian J Gastroenterol.* 1997;16:94–95.
38. Shamanna SB, Naik RR, Hamide A. Causes of liver disease and its outcome in HIV-infected individuals. *Indian J Gastroenterol.* 2016;35:310–314.

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