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Research Article

Highly active antiretroviral therapy and changing spectrum of liver diseases in HIV infected patients

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ABSTRACT

Background: HIV is now considered as chronic disease than a fatal disease. HIV infected individual is having normal life expectancy post highly active antiretroviral therapy (HAART) era. Liver disease is the major cause of morbidity and mortality in HIV infected patients. The objective was to study the prevalence, clinical profile of various liver diseases in HIV infected individuals on HAART and also to study aetiologies of liver involvement in HIV patients.
Methods: It was a cross sectional observational study conducted from August 2014 to July 2015. 102 HIV positive individuals on HAART with liver involvement were included. Detailed history and clinical examination were noted. Baseline investigations (Hb, CBC, blood sugars, liver function tests, electrocardiogram, chest X-ray, urine routine and microscopy), special investigations (HBsAg, anti-HCV, CD4 count, ultrasonography, CT scan, ascitic fluid examination) were performed. The data was analyzed using descriptive statistics. Results are expressed as percentage.
Results: Out of the total 102 patients, 78 (76.5%) patients were male and 24 (23.5%) patients were female. The maximum number of patients belonged to the age group 41-50 years (38.2%). Hepatitis B (30.8%) was most common liver disease in males and AKT induced hepatitis (41.7%) most common liver disease in females. The most presenting symptom of patients with liver involvement in HIV was weakness and fatigue 82 (80.39%). The most common clinical sign was icterus 39 (38.23%), sonography finding was coarse echotexture of liver (46.07%) suggestive of cirrhosis.
Conclusions: Although hepatitis B and alcoholic liver disease are major causes of liver diseases in HIV patients in India, incidence of drug related hepato toxicities are increasing.

Keywords: HIV, HAART, Liver disease

INTRODUCTION

Human immunodeficiency virus (HIV) is probably the only pathogen with most diverse sites of affection in human body. Not a single organ system is particularly immune to its effects. Affections are caused either directly by the virus itself or more commonly by virtue of opportunistic infections and malignancies. Liver is not an exception either.[1-3] In the setting of highly active anti-retroviral therapy the clinical spectrum of HIV disease has dramatically changed. Prolonged survival leads to greater emphasis on gastrointestinal manifestations and liver diseases.

Most patients will experience hepatobilliary manifestations during the course of their HIV disease, with hepatomegaly and/or jaundice in 50% and abnormal liver function tests in over 80%. Liver is one of the most important organs to consider when treating HIV infected patients, as liver diseases are now the one of the commonest causes of death in HIV positive patients on antiretroviral therapy (ART).[4,5] The common causes

included opportunistic infections, liver abscess, malignancies and drug toxicities. Due to common modes of transmission and geographic patterns of disease, hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV frequently occurs as concomitant infections.[4-6] Most of the drugs in highly active antiretroviral therapies (HAART) can induce liver toxicity but the probability and extent of injury varies substantially with the individual agents. In addition to the antiretroviral drugs, other frequently prescribed medications for the management of opportunistic infections including Anti-tuberculosis drugs may cause hepatic injury.[4,5] HIV can involve liver directly, as demonstrated by presence of HIV p24 within kupffer cells and hepatic endothelial cells and HIV mRNA within hepatocytes.[7,8]

Since 2004 ART use expanded markedly coincided with the widespread availability of free ART in India under national aids control organization (NACO) programme (NACP III).[9] ART consisted of the generic fixed drug combination. In recent years widespread use of ART led to reduction in number of death related to AIDS. However, it has been accompanied by increase in liver related morbidity and mortality. Alcoholism, drug history, hepatitis B, hepatitis C, liver abscess, granulomatous hepatitis e.g. tuberculosis, AIDS cholangiopathy, hepatocellular carcinoma, schistosomiasis, haemangioma and hepatic adenoma are common causes of liver diseases in HIV infected individuals. One of cornerstone of prevention of progression of liver diseases in HIV is screening for liver diseases in HIV infected individual.[4,5] Therefore the present study was designed to study the prevalence, clinical and laboratory profile of various liver diseases in HIV infected individuals and also to study aetiologies of liver involvement in HIV patients.

METHODS

Study design

This was a cross sectional observational study conducted from August 2014 to July 2015 at tertiary care health centre, Mumbai, India. A total 102 HIV positive individuals with liver involvement who were fulfilling inclusion criteria and exclusion criteria were included. This study was conducted in compliance with the protocol, the institutional review board (IRB), and informed consent regulations. The study protocol was approved by local ethics committee. All patients provided written informed consent.

Subject selection criteria

Patients who were HIV-1 by ELISA more than 18 years of age and ready to give written informed consent were enrolled in the study. HIV positive individuals who were on HAAT or going to be initiated on HAART were selected. Patients with hepatic involvement in any one or more of following: clinical history suggestive of liver disease, clinical evidence of liver disease, deranged liver function tests, radiological evidence of liver disease were included. Child-pugh score was used to recruit patients. Pregnancy was an exclusion criterion for the study.

Procedure

Consecutive 102 HIV infected individuals with liver involvement on presenting to hospital were enrolled in this study. Detailed history including history of opportunistic infections like tuberculosis, blood transfusion, medications was recorded. The history related to liver diseases was noted. Each patient underwent detailed clinical examination. All laboratory, radiological parameters were noted. Baseline investigations like Hb, CBC, blood sugars, renal and liver function tests, electrocardiogram, chest X-ray, urine routine and microscopy were done and recorded. Special investigations like HBsAg, anti-HCV, CD4 count, ultrasonography, CTscan, ascitic fluid examination were noted.

Statistical analysis

The data was analyzed using descriptive statistics. Results are expressed as percentage.

RESULTS

Age and sex distributed is shown in Table 2 and 3. Etiological distribution of liver diseases in HIV patients is shown in Table 4.

Table 1: Child-Pugh score of liver diseases.

Parameter	Assign 1 point	Assign 2 points	Assign 3 points
Ascitis	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (second over control) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Encephalopathy	None	Grade 1-2 (Mild to moderate)	Grade 3-4 (Severe)

Class A-=5-6 points, Class B=7-9 points, Class C=10-15 points.

Table 2: Gender distribution.

Gender	Number of cases (n=102)	Percentage (%)
Male	78	76.5%
Female	24	23.5%

Gender wise distribution of etiologies of liver disease is shown in HIV patients in Table 5. Distribution of etiologies of liver diseases on the basis of use of ART is shown in Table 6. Distribution of patients on the basis of

CD4 count and etiologies of liver disease in HIV patients is shown in Table 7.

Table 3: Age group distribution.

Age group	No of patients (n=102)	Percentage (%)
18-30	15	14.7
31-40	43	42.5
41-50	39	38.2
51-60	5	4.9

Table 4: Etiological distribution of liver diseases in HIV patients (n=102).

Etiology	No of cases (n=102)	Percentage (%)
Hepatitis B	30	29.4
AKT Induced hepatitis	27	26.5
Alcoholic liver disease	15	14.6
Nevirapine induced hepatitis	10	9.8
Pyogenic liver abscess	10	9.8
Hepatitis C	3	2.9
Haemangioma	2	1.96
Hepatitis E	2	1.96
Amoebic liver abscesses	1	0.98
Hepatocellular carcinoma	1	0.98
Malaria with hepatic involvement	1	0.98

Table 5: Gender wise distribution of etiologies of liver disease in HIV patients (n=102).

Etiology	Sex	
	Male (n=78) No. of patients (%)	Female (n=24) No. of patients (%)
Hepatitis B	24 (30.8%)	6 (25.0%)
AKT induced hepatitis	17 (21.8%)	10 (41.7%)
Alcoholic liver disease	15 (19.2%)	0 (0.0%)
Pyogenic liver abscess	8 (10.3%)	2 (8.3%)
Nevirapine induced hepatitis	5 (6.2%)	5 (20.8%)
Hepatitis C	2 (2.6%)	1 (4.2%)
Hepatitis E	2 (2.6%)	0 (0.0%)
Haemangioma	2 (2.6%)	0 (0.0%)
Amoebic liver abscesses	1 (1.3%)	0 (0.0%)
Hepatocellular carcinoma	1 (1.3%)	0 (0.0%)
Malaria with hepatic involvement	1 (1.3%)	0 (0.0%)
Total	78 (100%)	24 (100%)

Table 6: Distribution of etiologies of liver diseases on the basis of useof ART.

Etiology	Sex	
	On ART patients (n=49) No. of patients (%)	ART Naïve patients (n=53) No of patients (%)
Hepatitis B	5 (10.20%)	25 (47.2%)
AKT induced hepatitis	21 (42.9%)	6 (11.3%)
Alcoholic liver disease	5 (10.2%)	10 (18.8%)
Pyogenic liver abscess	3 (6.1%)	7 (13.2%)
Nevirapine induced hepatitis	10 (20.4%)	0 (0.0%)
Hepatitis C	1 (2%)	2 (3.8%)
Hepatitis E	1 (2%)	1 (1.9%)
Haemangioma	2 (4%)	0 (0.0%)
Amoebic liver abscesses	0 (.0%)	1 (1.9%)
Hepatocellular carcinoma	1 (2%)	0 (.0%)
Malaria with hepatic involvement	0 (.0%)	1 (1.9%)
Total	78(100%)	24(100%)

Table 7: Distribution of patients on the basis of CD4 count and etiologies of liver disease in HIV patients: (n=102).

Diagnosis	CD4 <200 (n=60)	CD4 200-499 (n=35)	CD4>500 (n=7)
AKT induced hepatitis	25(41.67%)	2 (5.71%)	0
Hepatitis B 12	(20.0%)	16 (45.71%)	2 (28.57%)
NVP induced hepatitis	8 (13.33%)	2 (5.71%)	0
Alcoholic liver disease	8 (13.33%)	4 (11.42%)	3 (42.85%)
Pyogenic liver abscess	3 (5.0%)	7 (20.0%)	0
Haemangioma	2 (3.33%)	0	0
Hepatitis C	0	2 (5.71%)	1 (14.28%)
Amoebic liver abscess	1 (1.66%)	0	0
Hepatitis E	1 (1.66%)	1 (2.85%)	0
Malaria	0	1 (2.85%)	0
Hepatocellular carcinoma	0	0	1 (14.28%)

In this study the presenting symptoms of patients with liver involvement in HIV in descending order of frequency were Weakness and fatigue 82 (80.39%), loss of appetite and malaise 77 (75.49%), nausea 68 (66.66%), abdominal pain 53 (51.96%), vomiting 43 (42.15%), jaundice 39 (38.23%), loss of weight 23 (22.54%), fever 14 (13.72%) and distension of abdomen 2 (1.96%). The clinical signs of patients with liver involvement in HIV in descending order of frequency were icterus 39 (38.23%), pallor 32 (31.37%), hepatomegaly 13 (12.74%), oral candidiasis 12 (11.76%), ascites 11 (10.78%), herpes zoster 6 (5.88%), spleenomegaly, 5 (4.90%), hepatospleenomegaly 3 (2.94%).

In this study, serum albumin level was <3 g/dl in 49 (48.03%) patients, 3-3.5 g/dl in 28 (27.45%) patients and >3.5 g/dl in 25 (24.50%) patients. Serum alkaline phosphatase level was abnormal in 86 (84.31%) patients and normal in 16 (15.68%) patients. Patients with INR <1.7 were 85 (83.33%), 1.7-2.3 were 12 (11.76%) and >2.3 were 5 (4.90%).

In this study patients having different USG findings were as follows coarse echotexture 47 (46.07%), bright echotexture 36 (35.29%), liver abscess with hepatomegaly 8 (7.84%), bright echotexture with hepatomegaly 5 (4.90%), liver abscess 3 (2.94%), haemangioma with hepatomegaly 2 (1.96%), lobulated hepatomegaly suggestive of hepatocellular carcinoma 1 (0.98%) patients.

DISCUSSION

Indian data on evaluation of the liver diseases in HIV infected patients is lacking. The present study differs from most evaluations of liver disease in HIV infected populations, because symptomatic as well as asymptomatic patients with liver diseases were included. Most studies have described patients with asymptomatic liver test abnormalities found as incidental findings during screening or investigations for other conditions. This study is giving data post HAART era.

Overall there was male preponderance in this study and other studies also, this could be because either male are predominantly affected or male HIV patients predominantly seek healthcare facility help than female patients in India. In similar study done by Ponsiano Ocama et al in Africa, males were 47% and females were 33%.[1] Another study by Rathi PM et al, in India included 77% male and 33% female patients.[2] In the present study forth decade was the commonest age group affected. In similar study done by Rathi PM et al in India mean age was 34 years.

In this study hepatitis B was most common cause of liver involvement in HIV patients followed by AKT induced hepatitis, followed by alcoholic liver disease, nevirapine induced hepatitis and pyogenic liver abscess in that order. In another study conducted by Ocamaet P et al, 30% patients were having drug induced hepatotoxicity as most common cause of liver disease.[1] Ocamaet P et al study is conducted after the era of easy availability and use of HAART started. In this study 27 (26.5%) had AKT induced hepatitis, 10 (9.8%) had nevirapine induced hepatitis that is drug induced hepatotoxicity as the major cause of liver disease in HIV patients in HAART based therapy era. In similar study by Rathi PM et al HBsAg positive were 16%, hepatitis B core/surface antibody was present in 64%, anti-HCV antibody was positive in 30% patients.[2] As this study was done in 1997, before the widespread use of HAART in HIV patients reflecting that drug related toxicities were not seen during that era. But in present study, 27 (26.5%) patients of AKT induced hepatitis and 10 (9.8%) patients of nevirapine induced hepatitis, so drug related toxicities forms the major disease burden in this study.

We had 30 (29.4%) HBsAg positive and 3 (2.9%) had anti-HCV antibody positive patients in this study. This reflects that still hepatitis B co-infection is commonly associated with HIV due to similar route of transmission for both the diseases. Also lack of awareness about availability of hepatitis vaccine and incomplete vaccination schedule may be the cause of increased hepatitis B infection. Rai et al, found prevalence hepatitis B and hepatitis C co-infection, 29.3% and 17.2 % demonstrated reactivity for any marker of past or current HBV and HCV infection respectively.[10] In the Ocama P et al 2005 study 15% patients were associated with hepatitis B co-infection.[1] This study had 29.4% patients HBV co-infection. Hepatitis B remains one of the major cause of liver disease in HIV patients. The first line ART regimens usually include lamivudine and if HBV co-infection is present then acquisition of HBV resistance to lamivudine is high. Because of this all HIV infected individuals are screened for hepatitis B co-infection before starting ART to help guide therapeutic decision making. After comparison with the Rathiet PM et al, study 30% anti-HCV antibody positive patients, there is significant decline in HCV co-infection in recent decades as seen in this study only 3 (2.9%) patients were positive, reflecting better blood donor screening and decreased occupational risks may be due to literacy regarding disease transmission and advanced laboratory equipments in comparison to past.[2] In recent Ocamaet P et al study only 2.6% patients were having HCV co-infection reflecting the similar results as present study that is decreased HCV transmission in recent decade.[1]

In HIV Infected male patients, most common cause of liver involvement was hepatitis B co-infection and in female patients AKT induced hepatitis was most common cause. Overall male and female populations are at equal risk of developing drug related hepatotoxicity as per result of present study.

In this study, most common etiologies of liver disease in HIV patients was hepatitis B co-infection (25) in ART naive patients and AKT induced Hepatitis(21) in patients

taking ART. Patients who were on ART most common cause of liver disease was drug related hepatotoxicity either AKT or ART. So, in recent decade as there is increase in widespread use of ART by HIV patients. Drug related hepatotoxicity is also increasing. The ART naïve patients were recently diagnosed and presented for the first time to hospital. Most common cause of liver disease in these patients was hepatitis B co-infection followed by alcoholic liver disease. Despite widespread use of ART these diseases liver involvement remains major cause concern. Prevalence of these liver diseases does not depend upon ART use. To decrease the prevalence of alcoholic liver disease in resource poor country like India will require political will and motivation.

In this study it was observed that the patients with low CD4 count are more prone to develop AKT induced hepatotoxicity than the patients with high CD4 count. In similar study by Ocamaet P et al in Africa 81% patients were having CD4 <200, 14% had CD4 200-350 and 5% had CD4 >350.[1] Drug related hepatotoxicity seen in 82% patients with CD4 <200 and 18% in whom CD4count 200-350. No hepatotoxicity seen in patients with CD4 >350. This African study shows similar results as present study. The common radiological (USG) finding in current study was coarse echotexture of liver in 47 (46.07%) followed by bright echotexture in 36 (35.29%). In a series of 103 patients with chronic liver disease it has been shown that liver parenchymal texture (graded as fine echotexture, mildly coarse, coarse and highly coarse) has a statistically significant correlation (rs=0.8853) with the degree of fibrosis.[12]

As it was cross sectional study, no follow up was done. It will be useful to do a prospective study with follow up, which will give an idea regarding prognosis of the disease and will help in future therapeutic decisions. Also in the present study the sample size was small. Larger sample size will give more idea regarding disease burden, various etiologies of liver disease in HIV population. It will be better if we can get comparison cohort of general population with liver disease. This will delineate the differences of liver diseases in HIV and general population.

In conclusion, in today's HAART based therapy era drug related hepatotoxicity is increasing in HIV infected patients. Patients with low CD4 count are more prone to develop drug induced hepatotoxicity. Hepatitis B and alcoholic liver disease are still major causes of liver diseases in HIV patients in India, incidence of drug related hepatotoxicities are increasing.

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