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Original Research Article

HIV and hepatitis B co-infection - prevalence and clinical spectrum in a rural tertiary care centre of Northern India

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ABSTRACT

Background: HBV and HIV are both endemic in India. Currently, it is not well established what proportion of HIV-positive patients harbours HBV infection in India. No study was done to know the epidemiology of HBV HIV Co infection in rural population of Northern India. So, this study was done to explore the impact of HBV in HIV patients.
Methods: Prospective cohort study was conducted on HIV-HBV co infected patients who attended the ART Clinic at ART centre, Department of Medicine, UPUMS, Saifai, Etawah, after obtaining informed consent.
Results: Out of these 1751 HIV patients 919 were eligible for start on ART and the remaining were treatment naïve patients. Out of these 1751 HIV positive patients 79 patients were HBS Ag positive. Thus, the prevalence of HBV-HIV co infection at our ART centre was found to be around 4.5%. 68 patients were found to be eligible for start of ART drugs. Out of these 68 patients on ART, 46 (67.6%) patients were alive, 9 (13.2%) were transferred out, 5 (7.4%) patients were lost to follow up (LFU) and 8 (11.8%) expired till the end of the study.
Conclusions: HBV co infection is common in HIV serology positive and can cause significant morbidity and mortality especially in the presence of other concurrent cause of liver injury. HBV co infection might associate with severe hepatotoxicity during intake of HAART regimen. For these reasons, prevention and treatment of HBV infection is mandatory in HIV serology positive.

Keywords: HIV, HBV, HAART

INTRODUCTION

HBV and HIV are both endemic in India. The Indian government has introduced a large-scale supply of antiretroviral (ARV) drugs for the treatment of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in public hospitals since 2004. Despite this development, research programmes to monitor the efficacy of these ARV drugs in HIV/AIDS patients co-infected with hepatitis B virus (HBV), do not exist. Both of these viruses are endemic and frequently detected as co-infections. Nevertheless, screening of HBV serological markers in HIV patients initiating highly active antiretroviral therapy (HAART) in India is currently not yet a standard practice, due to financial constraints. HAART is defined as the use of severeal ARV drugs, typically comprising of three ARV drugs, usually two nucleoside analogues and either a protease inhibitor or a non-nucleoside reverse-transcriptase inhibitor, and are taken in combination. The

ARV drugs target HIV at multiple stages of its lifecycle, minimising the development of resistant strains, and slowing the progression of the disease by lowering the viral load.[1] Many of the antiretroviral drugs like lamivudine, Tenofovir are also active against HBV.

Currently, it is not well established what proportion of HIV-positive patients harbours HBV infection in India. Of the significant concern is that a number of ARV drugs for HIV have dual activity against HIV and HBV, and have not been extensively studied in co-infected individuals worldwide. This is despite reports of the detection of naturally and drug -induced occurring mutants which are associated with drug -resistant strains in naïve/treatment -experienced patients, both mono/co-infected HBV and HIV patients.[2-4] Therefore, baseline studies are needed for monitoring patients before and during HAART, especially with anti-HBV-containing HAART regimens.

The rate of progression and complications from viral hepatitis are accelerated in patient with HIV coinfection.[5] After acquiring HBV infection, HIV infected individuals are 6 times more likely to develop chronic hepatitis B than normal HIV negative individuals.[6] Following initiating ART, IRIS may occur which can lead to worsening liver disease including hepatic decompensation. Reactivation of hepatitis B is common in patient who left ART. HIV also hasten the progression of HBV related liver disease especially in patient with low CD_4 count (despite of low ALT level).[7] For individuals on ART, co infection with chronic hepatitis B increase the risk of hepatotoxicity from 3 to 5 times.[8]

So this study was done to explore the impact of HBV in HIV Patients and to investigate the clinical spectrum and follow up in HBV HIV Co infected patients.

METHODS

This study was conducted on HIV-HBV co infected patients who attended the ART Clinic at ART centre, Department of Medicine, UPUMS, Saifai, Etawah.

Design of the study

Prospective cohort study for HIV-HBV co infected patients enrolled between May 2016 to March 2017.

Inclusion criteria

- All HIV positive patients (conformed by ICTC, UPUMS Saifai) between the year May 2016 to March 2017
- All HIV patients with HBsAg positive who were enrolled at ART centre.

Exclusion criteria

- HIV negative patient
- Pregnant females
- Patients who were receiving ARV drugs therapy from other centres
- Patient not giving consent for the study.

Study follow up

Eligible patients were included in the study after they were counselled regarding the study, its nature and the relevance. After the informed consent was obtained, they were subjected to a detailed evaluation of history, clinical examination, and investigations at the time of first visit. Baseline investigation like CBC, fasting blood sugar, S.Urea, S.creatinine, ALT (SGPT), VDRL, Urine R/M, Chest X-ray were done in all patients registered in ART centre. For Hepatitis B screening, HBsAg detection was done by using rapid card method.

- Baseline CD4 was done in all patients
- Those patients whose HBsAg had come positive were included in the study and were followed
- Of 6 Hepatitis B-HIV coinfected patients:
  (i) HBeAg and Anti HbeAb were detected by using ELISA method.
  (ii) Viral load of HBV was also assessed by REAL Time PCR method using COBAS TAQMAN kit.

ART was started as per NACO guidelines, and patients were followed up every month to look for the response to the treatment. In accordance with ART program guidelines, the CD4 was measured once in 6 months.

Monitoring of patients

All patients were monitored for the following:

- Clinical monitoring and staging at each visit as per NACO guidelines: Clinical staging is done using the T staging for clinical events.
- Immunological monitoring: CD4 count every 6 months.
- Adherence support and monitoring to ensure >95% adherence.

Data source

Data were extracted from the available computer record and white card of HIV patients on which information regarding, HIV risk behaviour, weight, clinical stage, functional status, drug toxicity, adherence to ART medication, newly diagnosed OI, and laboratory test results were documented. Statistical analysis was done by using SSPS version 22.0.

RESULTS

During the study period between May 2016 to April 2017 a total of 1751 HIV positive patients had been enrolled. Out of

these 1751 HIV patients 919 were eligible for start on ART and the remaining were treatment naïve patients. Out of these 1751 HIV positive patients 79 patients were HBsAg positive. Thus, the prevalence of HBV-HIV co infection at our ART centre was found to be around 4.5%. These 79 patients were then followed. Now out of these 79 patients, 68 patients were found to be eligible for start of ART drugs according to newer guideline of NACO regarding treatment. Out of these 68 patients on ART, 46 (67.6%) patients were alive, 9 (13.2%) were transferred out, 5 (7.4%) patients were lost to follow up (LFU) and 8 (11.8%) expired till the end of the study.

11 patients were not found eligible for start of ART according to NACO guideline regarding treatment and designated as "Pre-ART patients". Among 11 Pre-ART patients, 5 (45.5%) were alive, 4 were LFU (36.4%) and 2 (18.2%) were expired (Figure 1).

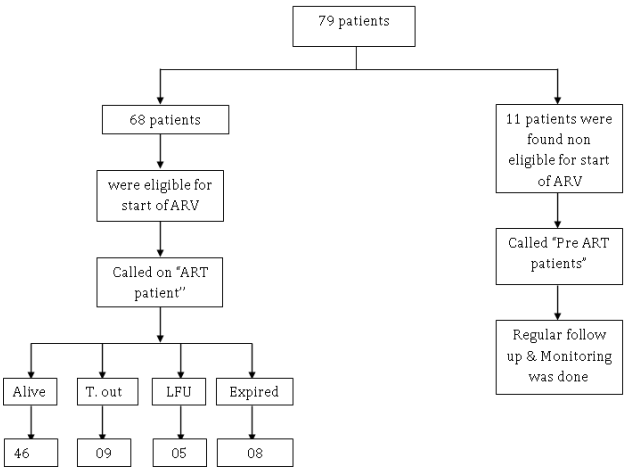

Figure 1: Study design.

Baseline characteristics of HBsAg positive patients on ART

Among 68 patients on ART, 56 (82.4%) were males and 12 (17.6%) were female. Average age of the patients was 38.2±11.2 years. 48% of the patients were in stage III and stage IV (33/68). Average baseline CD4 count was 103 (IQR-61.5-271) (Table 1).

Opportunistic infections

40% (28/68) patients had tuberculosis. The incidence of pulmonary Koch's was surprisingly less as compared to extra pulmonary Koch's. Out of these 40% patients, 30% have extra pulmonary Koch's and 10% have pulmonary Koch's. 13% patients have pneumocystis carinii pneumonitis and 10% patient had oral candidiasis (Table 2). Among expired patients, the most common opportunistic infection was Tuberculosis which was 62.5% (5/8), 1 patient died due to ATT induced hepatitis and cause of death of 2 patients was unknown.

Table 1: Baseline characteristics of HIV-HBV co infected patients on ART.

Variable		Number (n=68)
Age (years)	Mean±SD	38.25±11.20
	Minimum	6 months
	Maximum	61 years
Sex	Male	56 (82.4)
	Female	12 (17.6)
Weight (kg)	Mean±SD	45.39±11.10
	Minimum	5.3
	Maximum	65
CD4 count	Median	103.0
	IQR	61.50-271.0
Clinical Stage	I	27 (39.7)
	II	8 (11.8)
	III	15 (22.1)
	IV	18 (26.5)
Duration of ART	Median (months)	5.50
	IQR	4.0-10.50
Baseline Regimen	SLN	5 (7.4)
	ZLN	21 (30.9)
	ZLE	22 (32.4)
	TLN	4 (5.9)
	TLE	16 (23.5)
Functional status	Working	65 (95.6)
	Ambulatory	3 (4.4)
Baseline SGPT	Median	43
	IQR	32.0-54.75

Table 2: Opportunistic infection.

OI	No. of cases	Percentage
Koch's		
Pulmonary	7	10.3
Extrapulmonary	21	30.9
Diarrhoea	5	7.4
PCP	9	13.2
PUO	4	5.9
URTI	3	4.4
Oral candidiasis	7	10.3

The baseline CD4 count was 164.5 (77.5-34.25) which was raised to 257 (169.75-475.75) at the end of the study with significant $p<0.001$. The initial average weight of the patient was 43.8kg which was also raised to 46.99kg at the end of the study with p value of 0.024. The liver enzyme (SGPT) was 42 (27.5-55.75) in the beginning of the study and was 40 (27-54) at the end of the study with p value of 0.652. In the beginning of the study 59% patients were in stage I and stage II and 41% patients belongs to stage III and stage IV. But at the end of the study, almost 80% patients come in stage I and II while 20% patients were in stage III and stage IV (Table 3).

Table 3: Comparison of baseline characteristics with that at the end of the study.

Variable	Baseline (n=46)	At the end (n=46)	p-value
Weight (mean±SD)	43.88±15.35	46.99±16.86	0.024
Clinical stage			
I	24 (52.2)	35 (76.09)	
II	3 (6.5)	2 (4.35)	
III	9 (19.6)	4 (8.70)	
IV	10 (21.7)	5 (10.87)	
SGPT, Median (IQR)	42.0 (27.75-55.75)	40.0 (27.0-54.0)	0.652
CD4, Median (IQR)	164.50 (77.50-342.25)	257.0 (169.75-475.75)	<0.001

Table 4: Comparison of characteristics at baseline and end of study in therapy change group (n=15).

Variable	Baseline	At the end	p-value
Weight	45.69±8.34	47.75±9.46	0.068
Stage			
I	4	10	
II	1	1	0.089
III	5	1	
IV	5	2	
CD4 count	114 (49-161)	259 (187-541)	0.001
SGPT	52 (39-86)	45 (15-58)	0.109

Table 5: Comparison of characteristics at baseline and end of study in no therapy change group (n=31).

Variable	Baseline	At the end	p-value
Weight	45.789±14.69	46.12±23.61	0.197
Stage			
I	20	25	
II	2	1	0.678
III	4	3	
IV	5	3	
CD4 count	213 (91-368)	253 (157-469)	0.018
SGPT	39 (26-47)	42.50 (29.75-63.0)	0.099

Table 6: Comparison of change therapy group to non-change therapy group.

Variable	Change (n=15)	Not change (n=31)	p-value
Weight			
Baseline	45.69±8.34	45.789±14.69	0.963
Last weight	47.75±9.46	46.12±23.61	0.861
CD4 count			
Baseline	114 (49-161)	213 (91-368)	0.049
Last CD4	259 (187-541)	253 (157-469)	0.897
SGPT			
Baseline	52 (39-86)	39 (26-47)	0.041
Last SGPT	45 (15-58)	42.50 (29.75-63.0)	0.885

Effects of change of therapy

The baseline therapy was changed in 15 patients either due to any drug induced reactions or due to the introduction of newer guideline of NACO regarding treatment of HBV HIV patients or patient developed tuberculosis during the study period. Out of 15 patients, 12 patients needed change of therapy due to drug induced adverse event. The most common drug induced adverse event was Zidovudine induced anaemia 86% (10/12).

NVP induced hepatitis in 1 patient (1/ 12) and one patient had ATT induced hepatitis (1/12) (Table 4 to 7).

Table 7: Comparison of clinical stage with change of therapy.

Stage	Baseline		At the end	
	Change (n=15)	Not change (n=31)	Change (n=15)	Not change (n=31)
I	4	20	10	25
II	1	2	1	1
III	5	4	1	3
IV	5	5	2	3

Table 8: Hepatitis B profile and other characteristics (n=6).

Patient No.	Viral load	HBeAg antigen	Anti-HBe	Baseline CD4	CD4 at the end	Baseline regimen	Last regimen	Duration of therapy
1	64.6	-ve	+ve	298	582	TLN	TLN	11 months
2	299	+ve	-ve	73	285	TLE	TLE	8 months
3	<6.0	-ve	+ve	368	746	TLE	TLE	6 months
4	TND	Invalid	Invalid	91	183	TLN	TLN	8 months
5	<6.0	-ve	+ve	49	120	ZLE	TLE	9.5 months
6	<6.0	-ve	+ve	93	153	ZLN	TLE	4.5 months

***Serological profile of hepatitis* B**

We had done HBeAg, anti HBe and viral load of the 6 HBV-HIV Co infected patients and the results were as follows: Out of the 6 patients 2 patients have detectable viral load, 4 patients have viral load below detectable target. HBeAg was positive in 1 patient while it was negative in 4 patients and invalid in 1 patient. Anti HBe antibody was positive in 4 out of 6 patients, negative in 1 patient and invalid in 1 patient. At the baseline 4 out of 6 patients were on tenofovir based therapy while 2 patients were on zidovudine based therapy. Average duration of therapy was 8.6 months. At the end of the study all 6 patients were on tenofovir based therapy. The CD4 count was also increased in all 6 patients when compared to baseline value (Table 8).

DISCUSSION

The prevalence of HBV-HIV co infection in our study was found to be 4.5% (79/1751) which was comparable to the prevalence rate found in other studies.

A study done at AIIMS, New Delhi for a period of 6 years between Jan 2002 to Dec 2007, 837 HIV Positive patients (631 males and 206 females (M: F: 3:1) were enrolled in the study. Amongst them 7.28% of HIV positive patients have showed presence of HBsAg as compared to 1.4% in the HIV negative control group.[9]

Another study was done at a referral Hospital in Northern India. Total 620 HIV positive patients were studied, HBV co-infection was detected in 2.25% patients and HCV co-infection was 1.61% patients.[10]

Data of 9802 patients in 72 European HIV centres were analysed. HBsAg was found in 498 (8.7%) patients and the incidence of all causes and liver related mortalities were significantly higher in HBsAg positive subjects (3.7%). Among HIV positive patients studied from America and West Europe, prevalence of HBV was 6-14%.[11]

Among patients with chronic liver disease in Amritsar 3% of sample were positive for HIV HBV infection.[12]

HIV positive patients were studied at tertiary care hospital in New Delhi, India serum samples from 451 HIV positive patients were analysed for HBsAg and HCV antibodies during 3 year, control group comprises of apparently healthy bone marrow and renal donors. The prevalence of HbsAg in this population was 5.3% as compared to 1.4% in apparently healthy.[13]

In our study, 82.4% patients were male in the study cohort and around 50% were in stage III and stage IV. The average baseline CD4 count was low i.e. 103/mm^3 in the beginning. It means that most of the patient visiting ART centre in the study cohort were in stage III and IV and had low CD4 count. So, it suggests that rate of progression and complication are accelerated in patient with HBV-HIV co infection.[14]

The opportunistic infections were common in HBV-HIV co infected individuals. Among the opportunistic infections the most common was tuberculosis followed by PCP and then oral candidiasis which was more or less similar to other studies.[15]

Among the total on ART patients of 68, 8 were expired and 5 had left from follow up. Among the expired patients, the most common opportunistic infection was tuberculosis followed by PCP and then oral candidiasis.[14]

When the baseline characteristics like weight, clinical stage of the patient, CD4 count and liver enzyme were compared at the end of the study, then it was found that all were improved at the end of the study. So the patients who were taking ART and were in regular follow up then there was improvement in the clinical, biochemical and immunological parameters of the patients.[16]

The baseline therapy was changed in 15 patients either due to the development of drug induced adverse event or a patient develop tuberculosis during the treatment phase or introduction of newer guidelines of NACO regarding treatment of HBV-HIV co infected patients. The most common cause of change of therapy was adverse drug reaction among which the most common adverse reaction was zidovudine induced anaemia followed by NVP induced rash, NVP induced hepatitis. This finding was contrary to the other studies in which the most common adverse drug reaction was hepatotoxicity reflected by elevated liver enzymes.[17]

HBeAg, Anti HBe antibody and HBV viral load was done in 6 ART patients. Viral load for HBV was detectable in 2 patients only and it was not detectable in most of the patients. Further most of the patients were in non-replicative phase. All these patients had received tenofovir based regimen for average duration of 8.5 months.[18]

CD4 count was also improved with the above regimen. So, it means that tenofovir based therapy have dual activity against the HBV and HIV virus and shows overall improvement in the patient clinical, biochemical, immunological and molecular level.[19]

CONCLUSION

India is endemic for both HBV and HIV co infection because both virus shares a common transmission route. The prevalence of HBV in HIV patients in India is not clear because it is different in different regions. Further it is more in high risk groups. There is unfavourable impact of HIV on the natural history of hepatitis B virus.

HBV co infection is common in HIV sero positive and can cause significant morbidity and mortality especially in the presence of other concurrent cause of liver injury.

Even if there are some in vitro data suggesting an adjuvant action of HBV genes on HIV replication, there are not convincing results to support an unfavourable impact of HBV co infection on HIV disease progression. On the contrary, HIV heavily modifies the course of HBV infection, inducing higher rates of chronicity, viral replication and lower rates of HBeAg and HBsAg clearance.

The impact of HIV on hepatitis B evolution towards, cirrhosis is still unclear. HBV co infection might associate with severe hepatotoxicity during intake of HAART regimen.

For these reasons, prevention and treatment of HBV infection is mandatory in HIV serology positive patients.

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