Profile and prevalence of HBV among HIV affected individuals attending the largest public HIV care center in India

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Abstract A large number of people living with HIV/AIDS residing in HBV endemic regions such as in India are highly susceptible to acquire co-infections like HBV but also transmit them to other due to their high risk behaviours. The present study aimed to estimate HBV prevalence and distribution of various HBV serological markers among HIV infected individuals. This cross sectional survey covered HIV infected individuals attending the largest HIV care center in India. Socio-demographic details and blood samples to screen for HBV seromarkers using commercial ELISA kits were collected. Among 1160 HIV infected patients, prevalence of HBcAb, HBsAb, HBsAg and HBeAg was 66, 29.4, 16.6 and 5.8 % respectively. Overall, 28.9 % individuals had no evidence of any of the four markers, indicating lack of previous exposure and future risk of acquiring HBV infection. Presence of anti-HBsAg in a mere 0.9 % of individuals reflected low levels HBV vaccine conferred immunity which could be due to poor HBV vaccine coverage in this high risk population. With high prevalence and evidence of exposure to HBV as well as considering the growing literature on increase in hepatic complications in HIV-HBV co-infected individuals, the need for mandatory HBV screening of all HIV infected individuals cannot be over-emphasised. The policy makers and HIV programme managers must consider HBV vaccination for newly detected HBV naive HIV infected individuals and also focus on creating public awareness on HBV and HIV prevention.

Keywords HIV · HBV co-infection · Seromarkers · Prevalence · Chennai · India

Introduction

Hepatitis B virus (HBV) is a circular, partially double stranded DNA virus of the Hepadnaviridae family that causes acute self-resolving hepatitis, asymptomatic chronic state or may lead to severe illness such as fulminant hepatitis, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). HBV infection continues to be a significant public health problem world over with about 400 million individuals chronically infected and about one million deaths occurring annually due to HBV related disease [1]. This is in spite of the availability of an effective vaccine against HBV. India, the second most populous country with an estimated population of about 1.21 billion (Census, 2011) accounts for over 40 million HBV carriers and about half a million deaths annually. HBsAg prevalence among general population in India ranges from 0.1 to 11.7 % [2].

The co-infection of HBV with HIV is common due to their similar routes of transmission. Underlying HIV infection increases the chance of HBV chronicity and antiretroviral treatment regimens have been shown to increase the risk of hepatotoxicity [3, 4]. With about 2.09 million (NACO, 2014) people living with HIV/AIDS in India, HBV co-infection is a cause for concern in the management of the HIV infected individuals (http://www.naco.gov.in/upload/2014%20mslms/NACO_English%202013-14.pdf). Previous studies from India have shown the prevalence of HBsAg in HIV seropositive patients to vary between 7 and 30 % [5–9].

Areas where HBV is highly endemic usually overlap with areas having high rates of HIV infection [10]. Being a

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moderate HBV endemic country having a large population of people living with HIV/AIDS, India presents an ideal setting for increased transmission and occurrence of HIV-HBV co-infections. The objectives of the present study was to determine the prevalence of the HBV co-infection and the distribution of serological markers of HBV infection among HIV infected individuals attending the largest public HIV care center in India.

Materials and methods

Study design and setting

This cross sectional study was conducted between March 2012 and September 2012 at the Government Hospital for Thoracic Medicine (GHTM), the largest public HIV care center in India located at Tambaram in Chennai metropolis.

Study population and participant recruitment

Individuals attending GHTM and confirmed to be HIV positive were enrolled consecutively in the study after obtaining written informed consent. A sample size of 1100 HIV positive patients was considered to be sufficient to detect HBV prevalence of 9 % with a precision of 20 and 95 % CI.

Data collection and testing

Demographic and laboratory data viz. blood counts, liver function tests, CD4 counts of the participants were collected from the GHTM records. Five ml blood was collected from the enrolled individuals for the HBV analyses. Analysis of HBV markers involved screening of Hepatitis B surface antigen (HBsAg) by HEPALISA (JMITRA Pvt. Ltd., India), Hepatitis B envelope antigen (HBeAg) by ETI-EBK PLUS (Diasorin, Italy), Hepatitis B total core antibody (HBcAb) by ETI-AB-COREK PLUS (Diasorin, Italy) and Hepatitis B surface antibody (HBsAb) by ETI-AB-AUK-3 (Diasorin, Italy). All commercial ELISAs were carried out strictly as per manufacturer's instructions.

Human subject protection

The study was approved by the Institutional Review Board of the GHTM and the Institutional Human Ethics Committee of National Institute of Epidemiology (Protocol ID No. NIE/IEC/2011-003). All study participants received pre- and post HIV test counselling and treatment at GHTM as per the existing national guidelines.

Statistical analysis

Simple frequencies, cross tabulation and summary statistics were performed to understand the distribution patterns of variables. Associations between outcome variable (HBV biomarkers) and various exposure variables (socio-demographic, behavioural) were analyzed using T test for continuous variables and Chi square test for proportions. All statistical analysis was performed using SPSS version 15.0. A *p* value of < 0.05 was considered statistically significant.

Results

Patient characteristics and HBV infection

During the 7-month study period, 1160 HIV positive individuals consisting of 618 (53.3 %) males, 538 (46.4 %) females and 4 (0.3 %) transgenders were consecutively enrolled in the study.

HBsAg was detected in 192 (16.6 %; 95 % CI 14.4–18.7) individuals of which 107 (55.7 %) were males (including one transgender) (Table 1). HBcAb, HBsAb and HBeAg were present in 66, 29.4 and 5.8 % of participants respectively. The mean values of various liver enzymes among HBsAg positives were Aspartate aminotransferase

Table 1 Characteristics of study participants by HBsAg status

Baseline characteristics	HBsAg positive (%) n = 192	HBsAg negative (%) n = 968	<i>p</i> value
Gender			
Male	56	53	0.53
Age			
<20	4	4	0.72
20–39	52	49	0.480
>40	44	47	
Mean age (CI)	38.4 (36.9–39.9)	38.9 (38.3–9.5)	
Marital status			
Unmarried	13	12	0.78
Currently married	76	75	
Ever married	12	13	
Education			
Illiterate	24	20	0.46
Primary	63	65	
Above primary	14	15	
Smoking			
Yes	18	18	0.93
Alcoholism			
Yes	18	20	0.52

Table 2 Baseline biochemical profile of participants by HBsAg status

Variables	n	HBsAg positive Mean (95 % CI)	n	HBsAg negative Mean (95 % CI)	p value
Hb	161	12.92 (12.64–13.20)	823	12.95 (12.83–13.07)	0.840
Blood urea	143	23.25 (21.87–24.62)	712	25.77 (25.07–26.47)	0.003
S. Creatinine	139	1.11 (1.08–1.14)	703	1.10 (1.08–1.12)	0.638
SGOT (AST)	121	32.7 (29.5–35.8)	560	33.7 (31.67–35.88)	0.667
SGPT (ALT)	64	43.7 (34.9–52.4)	373	42.10 (39.73–44.48)	0.642
Alk. phosphatase	83	101.2 (88.6–113.8)	542	87.41 (83.55–91.27)	0.014
T. Bilirubin	141	0.618 (0.48–0.75)	710	0.628 (0.56–0.69)	0.900
Globulin	137	3.74 (3.61–3.89)	691	3.73 (3.68–3.80)	0.920
Albumin	23	1.30 (1.0–1.6)	94	1.38 (1.19–1.57)	0.702
T. Protein	137	8.21 (8.09–8.33)	691	8.09 (8.03–8.16)	0.144
CD4 count ^a	192	512 (470–558)	964	507 (487–528)	0.840
RBC ^a	160	3.72 (3.62–3.83)	823	3.71 (3.67–3.76)	0.870
WBC ^a	160	6.96 (6.63–7.31)	823	6.89 (6.74–7.04)	0.710
Platelet ^a	160	2.45 (2.32–2.60)	822	2.43 (2.37–2.49)	0.780

^a Geometric mean

(AST) 32.7U/L, Alanine aminotransferase (ALT) 43.7 U/L, and Alkaline phosphatase (ALP) 101.2 U/L. Level of bilirubin ranged from 0 to 9.9 mg/dl with 92.5 % individuals having bilirubin level below 1 mg/dl.

The overall mean age was 39 years (males 41 years; females 37 years). The lowest HBsAg positivity rate (4 %) was observed in participants aged less than 20 years whereas the highest (52 %) was seen in those aged 30–39 years. The prevalence of HBV among male participants was 56 % (Table 2). Highest HBcAb positivity was among males in 40–49 years age group and among females in 30–39 years age group. More than 70 % of the participants were currently married and nearly 90 % of the participants were illiterate or up to 5th grade of school education. Mode of acquisition of HIV infection among the HBV positive individuals was mainly heterosexual (87.5 %), followed by blood transfusion/surgery (3.1 %), homosexual (1.04 %) and bisexual (0.5 %) (Table 2).

The mean age of HBsAg positive individuals was 38.4 (95 % CI 36.9–39.9) years which was not significantly different from that of HBsAg negatives 38.9 (95 % CI 38.3–39.5) (Table 1). The mean CD4 count among HBsAg positive (512 cells/mm³) individuals was not significantly different from the HBsAg negative participants. Twenty-three of the co-infected patients had CD4 counts below 350. The mean values of Alkaline phosphatase (101.2 U/L) in the HBsAg positive group was found to be significantly higher as compared to the HBsAg negative group ($p = 0.014$) and the blood urea (23.25U/L) was significantly lower ($p = 0.003$) in the HBsAg positive group (Table 2).

Association of HBsAg with other HBV seromarkers

Among the HBsAg positive cases, 21.4 % (41/192) had HBeAg, 90.5 % (173/191) had HBcAb and 3.1 % (6/191) had HBsAb (probable cases of dual infection). Among the 5.8 % of participants positive for HBeAg, HBsAg was detected in only 61.2 % (41/67). Among the 38.8 % (26/67) of HBeAg positive individuals who were HBsAg negative, 12 individuals had detectable HBsAb. 'Isolated anti-HBs' (only HBsAb present) was found in 0.9 % (10/1132) individuals. In 28.9 % (335/1160) individuals there was no evidence of any of the four serological markers tested. There was no significant association of CD4 counts with any HBV markers (Data not shown).

HBV-TB co-infection

Sixty-five percent of HBsAg positive individuals had tuberculosis and were on Anti Tuberculosis Treatment (ATT). There was significant difference in proportion of TB cases among HBcAb positive individuals whereas no significance was observed with other HBV seromarkers (Table 3).

Discussion

The high prevalence of HBsAg (16.6 %), a marker of current HBV infection in HIV positive patients in the present study indicates that individuals with or at high risk of acquiring HIV infection are also at a higher risk of

Table 3 Association of HBV markers in HIV-TB coinfecting individuals

HBV marker status	Tuberculosis (n)		<i>p</i> value
	Positive	Negative	
HBsAg			
Positive	125	67	0.679
Negative	615	353	
HBeAg			
Positive	41	26	0.638
Negative	682	383	
HBcAb			
Positive	508	258	0.008
Negative	225	161	
HBsAb			
Positive	223	119	0.565
Negative	501	289	

acquiring HBV infection. The prevalence of HBV infection reported from India ranges from 0.1 to 11.7 % in general population, 2.3–6.3 % in pregnant women, and 2–69.2 % in association with transfusion of blood and blood products [2].

The prevalence of HIV-HBV co-infection seen in the present study was same as that reported from Hyderabad (15 %) in south India but was considerably higher than the 6.4 and 9 % prevalence reported previously from Chennai [6–8].

The proportion of male patients who were co-infected with HBV was more as compared to females (Table 1), which could be attributed to the higher rate of sexual promiscuity and other exposure risks among males. The percentage of HBcAb (marker of HBV exposure) positivity among females in the younger age groups was found to be higher than among males, indicating that exposure of women to the virus occurs at an early age.

In the present study, positivity of HBeAg, the marker of active HBV infection was seen in only 21.3 % individuals indicating the clearance of 'e' antigen in majority of the co-infected. Interestingly 38.8 % of HBeAg positive individuals were HBsAg negative and possible explanation for this could be that these individuals had undetectable low levels of HBsAg or due to presence of surface mutants that have evaded detection by conventional HBsAg assay. Spontaneous or treatment-induced seroconversion from HBsAg positive to negative is associated with undetectable HBV DNA but in patients who convert from HBeAg positive to negative (HBeAg seroconversion), HBV DNA may still be detectable at low levels [11]. This however could not be ascertained in the present cross-sectional study as HBV DNA level was not measured. The absence of any of the four serological markers in 28.9 % individuals is indicative

of the lack of exposure to HBV or absence of HBV infection. Lack of antibodies against HBV in these susceptible individuals renders them to be at risk of acquiring HBV infection.

There are reports of patients clearing chronic HBV infection with the recovery of CD4 cell count responses following ART [12]. HBV reactivation and re-infection can also occur and patients who appear to have cleared HBV infection can present with a further episode of acute or chronic hepatitis [12]. The risk of reactivation is higher in patients who are positive for HBcAb but negative for other markers of HBV infection [13]. In the present study, 252 (21.72 %) co-infected individuals showed the presence of 'isolated' core antibody, indicating previous exposure to HBV. These individuals possess a high risk of HBV reactivation. Presence of core antibody and DNA, in the absence of surface antibody is an indication of 'Occult infection' [14]. Further analysis of HBV DNA levels in these individuals would provide more information on the level of occult HBV infection in this population.

ALT elevation is less sensitive as an indicator of disease severity in HBV-HIV co-infection [11]. In the present study, ALT levels among HBsAg carriers were not significantly different from HBsAg negative individuals. Elevated ALT levels has been previously reported in individuals on anti-tuberculosis therapy (ATT) and with several of the participants (64 %) in the present study being co-infected with TB, the observed elevated ALT levels could be attributed to the concurrent ATT [15]. In contrast, alkaline phosphatase ($p = 0.040$), was found to be significantly higher and blood urea ($p = 0.003$) significantly lower in the HBsAg positive group. HIV infection is known to cause a rise in alkaline phosphatase levels, and this has been linked to HIV progression [16].

Alcohol use is as common in individuals infected with HIV as in the general population ($p = 0.52$) (Table 1). Excessive alcohol consumption is also an important risk factor for progressive liver disease, particularly in HIV-positive patients who are not infected with HBV [17]. This emphasizes the need for routine screening of HBV in HIV infected individuals and management of liver disease and its sequelae in the co-infected individuals as in the case of HBV mono-infection.

Despite widespread use of HAART, studies have shown increased number of deaths attributed to liver disease among HIV patients, possibly due to prolonged survival and time for development of cirrhosis [18]. The treatment of HBV in HIV co-infected patients is complex because the drugs are associated with emergence of drug resistance, hepatotoxicity and unresponsiveness. Another major concern is reactivation of HBV replication after withdrawal of dually active antiviral drugs leading to emergence of resistant strains [18]. Thus early diagnosis and appropriate

management of HBV infection in HIV co-infected individuals is of critical importance.

The limitations of the present study include its cross-sectional design that makes it difficult to establish temporality, lack of control group, information on the HBV vaccination status of the participants, lack of clinical workup (Liver USG, biopsy etc.) and inability to estimate viral loads/DNA PCR for suspected occult infection (non-availability of testing facility). HCV co-infection in HIV patients is well associated with intravenous drug use (IDU). In the present study only eight individuals (0.7 %) gave history of IDU and therefore HCV was not analyzed. Since it is known that HBV-HCV interaction could suppress HBV replication, it would be useful to perform HCV testing for anti-HBc +ve and HBsAg -ve individuals. Nevertheless, the study provides important demographic and serological insights on HBV prevalence among HIV infected patients. The findings also highlight the need for prospective studies to determine the influence of HBV genotypes on liver disease progression and HIV drug resistance.

The HBV prevalence of 16.5 % in the HIV infected individuals constitutes one of the few such reports with large sample size from India. The high seroprevalence of HBV in HIV infected individuals, has clinical relevance and the finding that only <1 % of participants had evidence of HBV vaccine-induced immunity, constitutes important information for policy makers and program managers to consider administering HBV vaccination to HBV negative HIV diagnosed individuals. The HBV infection among women of child bearing age seen in this study is a threat not only to their health but also the next generation who are at risk of HBV transmission.

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