

# Occult hepatitis B virus infection among human immunodeficiency virus-infected patients with isolated hepatitis B core antibody in Isfahan, Iran

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**Background:** Detection of hepatitis B virus (HBV) genomes without detectable hepatitis B surface antigen (HBs-Ag) is termed occult HBV infection (OHBV) that may be transmitted by blood transfusion or organ transplantation and has acute reactivation when an immunosuppressive status like human immunodeficiency virus (HIV) infection occurs. We aimed to evaluate OHBV in HIV-infected patients with isolated antibodies to hepatitis B core antigen (anti-HBc) in Isfahan, Iran. **Materials and Methods:** In a cross-sectional study during August-September 2011, serum samples from HIV-infected patients who attended Isfahan Consultation Center for Behavioral Diseases were tested for HBs-Ag and anti-HBc using ELISA method. HBV-deoxyribonucleic acid (DNA) was detected and quantified in plasma of HBs-Ag negative/anti-HBc positive subjects by real-time polymerase chain reaction. **Results:** From 64 HIV-positive individuals, 12 (18%) patients were HBs-Ag negative/anti-HBc positive, and from those 3 (25%) had detectable HBV-DNA in their plasma. **Conclusion:** It seems that occult HBV might be assessed and be treated in HIV-infected patients.

**Key words:** Hepatitis B, hepatitis B core antigen, human immunodeficiency virus

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## INTRODUCTION

Hepatitis B virus (HBV) is a serious global health problem with 2 billion people infected, from which 350 million suffer from chronic hepatitis B worldwide.<sup>[1]</sup> For the long time, hepatitis B surface antigen (HBs-Ag) positivity has been the classic carrier state; however, it is demonstrated that HBV replication may persist for years in the livers of HBs-Ag negative patients after they have recovered from acute HBV infection.<sup>[2,3]</sup> Occult HBV infection (OBI) is defined as the presence of HBV-deoxyribonucleic acid (DNA) in individuals who test negative for HBs-Ag and is more frequent in patients positive for the antibody to hepatitis B core antigen (anti-HBc).<sup>[4]</sup> The state of suppression of viral replication and gene expression typical of the occult HBV status, leads to a severe and sometimes even fulminant hepatitis B<sup>[5]</sup> which is an event is usually observed in immunosuppressed patients like human immunodeficiency virus (HIV)-infected ones. In fact, these patients may show a reaction of the viral replication because of the fault of the immunological control which leads to cytotoxic T lymphocytes-medical hepatocyte injury and development of hepatitis.<sup>[6]</sup> Exposure to HBV infection is common among HIV-infected patients

because of shared routes of transmission, and serologic markers of prior or active HBV infection are identified in up to 68% of HIV patients.<sup>[3]</sup>

Conflicting data are reported on the prevalence of occult HBV infection in HIV settings, and the published data for occult HBV prevalence in patients with HIV infection ranges from 0% to 89.5% in the world.<sup>[7]</sup> In a study by Neau *et al.*, it was recommended to test all HIV-infected persons for both HBs-Ag and anti-HBc and if either is positive, to test for HBV-DNA.<sup>[8]</sup> In a study in Iran 85% of HIV-infected patients with positive “anti-HBc alone” were reported to be HBV viremic.<sup>[9]</sup> As there was no more study in Iran, we aimed to determine the frequency of occult HBV infection among a sample of HBs-Ag-/anti-HBc+ HIV-infected subjects in Isfahan-Iran.

## MATERIALS AND METHODS

In a cross-sectional study during August-September 2011, all the HIV-infected patients who attended Isfahan Consultation Center for Behavioral Diseases on a voluntary basis after obtaining informed consent, enrolled in this study regardless of clinical stage of infection, sex or HIV transmission category. The

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project was approved by the Ethical Committee of Isfahan University of Medical Sciences (research project number: 389301).

The subjects had laboratory confirmed HIV by Western blot and completed a checklist that collected demographic data at enrollment. From each patient, a serum sample was obtained and was stored at  $-70^{\circ}\text{C}$ . Clinical and therapeutic data were retrieved from the database of Isfahan Consultation Center for Behavioral Diseases.

Immunologic evaluation for HBs-Ag was performed using enzyme immunoassay test kit (Diapro-Milano-Italy), in accordance with manufacture's specification. Those samples that were negative for HBs-Ag were tested for total anti-HBc by enzyme immunoassay (Diapro-Milano-Italy), and for those that were positive for anti-HBc, HBV-DNA test was done. DNA was extracted from 200  $\mu\text{l}$  of serum using high pure viral Nucleic Acid kit (Roche, Germany). For detection of HBV genomes, samples were assessed by Taqman real-time polymerase chain reaction in the Rotor-Gene Q (QIAGEN, Germany). Analytical studies yielded a limit of detection of 10 IU/ml.

## RESULTS

Of 64 HIV-infected patients evaluated in the study, we identified 58 HBs-Ag negative and of them, 12 (20.7%) were anti-HBc positive. HIV acquisition was unknown.

After testing for HBV-DNA, 3 (25%) subjects identified with occult HBV. The plasma HBV-DNA load in the three patients was 357, 536, and 267857 IU/ml. All of them were male and co-infected with hepatitis C virus (HCV). Subjects with and without occult HBV infections were similar with regard to age, use of antiretroviral therapy, CD4 count, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, co-infection with HCV, and routes of HIV transmission. Table 1 presents the clinical and demographic characteristics of these patients.

## DISCUSSION

In this study, isolated anti-HBc was detected in 18.75% of the HIV-infected subjects from whom 25% had occult HBV infection. The frequency of isolated anti-HBc in HIV-infected patients is not similar in different studies.<sup>[10,11]</sup> About 50% of cases with OHBV infection have been reported to be positive for anti-HBc.<sup>[12]</sup> The prevalence of occult HBV in HIV-infected patients in previous studies varies from 0% to 89.5% in the world which may be due to the diverse prevalence of hepatitis B and HIV infections in different geographical regions and the sensitivity of the technique used to detect the HBV-DNA.<sup>[6,7]</sup>

**Table 1: Baseline characteristics of HIV+ subjects with isolated hepatitis B core antibody (n= 12)**

Variable	Number (%)	Percentage
HCV infected		
Negative	4	33.3
Positive	8	66.6
Antiretroviral therapy		
No	6	50
Yes	6	50
Transmission		
IVDU	5	45.5
IDU and heterosexual	2	18.2
Prison	3	27.3
Heterosexual	1	9.1
Unknown	1	9.1
CD4 (mean $\pm$ SD)	413.55 $\pm$ 315.51 cells/mm	
AST (mean $\pm$ SD)	30.89 $\pm$ 24.17 IU/l	
ALT (mean $\pm$ SD)	39.22 $\pm$ 19.34 IU/l	
Age (mean $\pm$ SD) (year)	33.64 $\pm$ 8.15 years	

HIV = Human immunodeficiency virus; IVDU = Intravenous drug use; IDU = Injection drug user; SD = Standard deviation; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; HCV = Hepatitis C virus

There are some reports in Iran as well. In a study which was carried out in Tehran, Iran, 20.75% of HIV-infected patients had isolated anti-HBc, and HBV-DNA was detected in 13.6% of them.<sup>[13]</sup> In another study in Tehran, Iran, HBV-DNA was detected in 12 out of 40 (30%) high-risk patients, including HIV-infected and hemodialysis patients with anti-HBc alone.<sup>[14]</sup> It is demonstrated that, the mortality rate is 19 times higher in co-infected patients than in HIV mono-infected individuals and an increased risk of liver-related morbidity and mortality among HIV-HBV co-infected patients have been indicated.<sup>[15]</sup>

Prior studies among HIV-infected patients found that occult HBV increased the frequency of transaminitis and hepatic flares.<sup>[16]</sup> We evaluated ALT and AST levels, which are biochemical markers of liver injury. We did not find any correlation between HBV-DNA detection in the plasma and these parameters which may be due to small sample size.

In our study, all of the OHBV patients were HCV infected, which is important. Occult hepatitis B, particularly in HCV-infected subjects may play a role in accelerating the progression of liver disease.<sup>[17]</sup> Furthermore, patients with chronic hepatitis C and OHBV infection have more frequently lack of response to interferon treatment, and a higher risk of developing hepatocellular carcinoma than those with chronic HCV alone.<sup>[18]</sup>

On the other hand, in patients co-infected with hepatitis and HIV, more severe and end-stage liver disease is declared.<sup>[19]</sup> Approximately 20% of HIV-infected patients in the world have chronic hepatitis C infection and HCV has emerged as an important cause of morbidity and mortality in these patients.<sup>[15]</sup>

It is concluded that occult HBV might be regularly assessed in HIV-infected population. Our study limited by small sample size which is due to problems in HIV patient's selection.

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## AUTHORS' CONTRIBUTION

All authors have contributed in designing and conducting the study. KT and BA collected the data and AJ and FK did the analysis. All authors have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. All authors have read and approved the content of the manuscript and are accountable for all aspects of the work.

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