

## Prevalence of Occult Hepatitis B in HIV Positive Patients (Adolescents and Adults) in Kermanshah- Iran

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### Abstract

#### Background

Occult hepatitis B infection (OBI) is considered a risk factor for progression of liver disease in patients with hepatitis B virus (HBV) infection. This disease progression is reported to be more significant in those with concomitant HIV infection. We aimed to determine the prevalence rate of OBI in a sample of HIV-positive patients.

**Materials and Methods:** Sixty-six HIV-infected patients with positive Hepatitis B core antigen (HBcAb) and negative Hepatitis B surface antigen HBsAg were included. HBV DNA was measured by real time polymerase chain reaction PCR method. Those with positive HBV viral load were considered as seropositive OBI. Then, the patients were studied regarding age, gender, intravenous drug use (IVDU), CD4 count, and concomitant infection by hepatitis C virus (HCV), available in their medical records.

**Results:** Seventy-seven patients (38.5%) had positive HBc antibody (HBcAb). Of 66 patients who were positive for both HIV and HBc antibody, eight patients (12.12%) had OBI. About 3.7% in age group younger than 40 years and 5.3% in age group older than 40 years, OBI was detected. Forty-four patients (54.5%) were male. OBI rate was 22.2% in males and zero in females ( $P < 0.05$ ). In patients who received ART (anti-retroviral therapy) 11.3% and in those who did not receive ART, 12.4% had OBI. In patients with CD4 count of less than 350/mL, 20.1% and in those with CD4 count  $> 350$ /mL, 4.1% had OBI. In those who were IV drug user, 17.94% and in those who were not IV drug user, 3.57% had OBI.

#### Conclusion

The prevalence of OBI in the studied sample of HIV-infected patients is considerable. As we did not find any significant association between OBI and studied factors except for gender, we think that screening for OBI would be useful for HIV-infected patients, especially male patients.

**Key Words:** Adolescents, Hepatitis B virus, HIV, Occult Hepatitis B Infection.

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## 1- INTRODUCTION

Hepatitis B virus (HBV) infection is a major public health problem which affects 400 million persons worldwide. This infection can lead to several manifestations including acute hepatitis, chronic carrier state, fulminant hepatitis, liver cirrhosis, and ultimately hepatocellular carcinoma. It is likely that some patients are carrier of HBV without knowing that they are infected after resolution of an acute hepatitis B infection phase. This state may occur in patients without any apparent clinical symptoms or laboratory findings suggestive of underlying liver disease (1).

Occult HBV infection (OBI), which is known as one of the stages in natural evolution of chronic hepatitis B development, is defined as negative hepatitis B surface antigen (HBsAg) test despite presence of HBV DNA in the liver, serum, and mononuclear cells of the peripheral blood regardless of other serum biomarkers. OBI is regarded as a risk factor for blood and organ recipients, as screening using HBsAg and anti-HBc antibody (HBcAb), despite the presence of HBV DNA, may show negative results. About 20% of OBI patients are seronegative for all related serologic markers, despite positive for HBV-DNA even with very low titers. In such cases, a diagnostic challenge exists as HBV DNA level is very low (less than 200 IU/mL) (2). HBV DNA can be integrated to the host's cell genome, though this has no role in the viral replication cycle and only involves viral DNA segments. Integrated HBV can exist forever inside the hepatic cells of infected patients regardless of being seropositive or seronegative for HBsAg. The presence of integrated virus in seropositive patients for HBsAg does not indicate OBI per se, as OBI is related to the presence of hepatic complete genomes, episomal HBV, and genomes whose replication has finished (3).

In comparison to solitary HBV infection, concomitant infection by HBV and human immunodeficiency virus (HIV) increase the risk of fulminant hepatitis five-fold. This concomitant infection also raises morbidity and mortality 20 times as the result of advanced hepatic disease (4). Also, OBI increases the risk of acute liver failure, cirrhosis, and hepatocellular carcinoma (5, 6). The prevalence of OBI varies in different regions, but it is higher in high-risk patients for HBV and hepatic diseases compared to patients with lower risk for HBV infection and those without hepatic disease (7). Various studies have demonstrated the prevalence of OBI in HIV-positive patients to be 0-10% and using more sensitive methods as high as 35 to 84%. In a study from Iran, this rate was reported as 13.6% (8). In other high-risk groups, such as hemodialysis patients, this rate is about 1% (9). Nowadays, even patient groups such as those with hyperlipidemia can be considered at risk for OBI (10).

As the prevalence, risk factors, the effect of antiretroviral therapy (ART), and clinical importance of OBI in HIV-positive patients is still controversial and we have a high rate of HBV infection in our area, limited studies have been done. We intended to determine the prevalence, clinical importance, and the significance of screening for early diagnosis of OBI in HIV-positive patients in order to prevent the transmission of HBV to susceptible patients.

## 2- MATERIALS AND METHODS

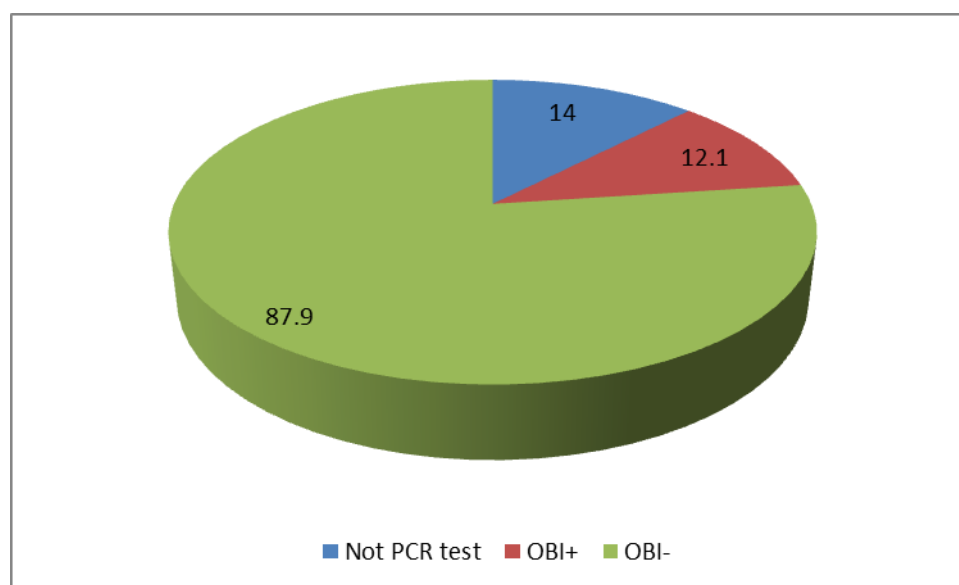
In this study, 200 HIV-positive and negative HBs-Ag patients with medical records at the Behavioral Diseases Consultation Center of Kermanshah, Iran were randomly selected. This center is the sole center for control and monitoring HIV infection in the city. For all patients, HBsAg, HBsAb, and hepatitis C virus (HCV) antibody tests had been done.

Those with negative HBsAg and HBsAb tests were included in the study. HBcAb test was performed for all patients. Then, based on HBcAb test results, the patients were divided into two groups: positive HBcAb and negative HBcAb. In order to diagnose OBI, HBV viral load should be measured for all patients with negative HBsAg and negative HBsAb test results. However, because of limitations in financial resources, this test was only done for those with positive HBcAb. Those with positive HBV viral load, which was done by polymerase chain reaction (PCR) method, result were considered as seropositive OBI. Then, the patients were studied regarding age, gender, intravenous drug use, CD4 count, and concomitant infection by HCV. HBcAB was measured

by ELISA method (Biokit, Spain). HBV viral load measurement was done in another center using real time PCR method (AB17500). The data were analyzed using the SPSS software for Windows (ver. 20.0) by descriptive indices, correlation coefficient, the Chi-squared test, and t-test.

### 3- RESULTS

Of 200 studied subjects, 77 subjects (38.5%) had positive HBcAb. Of 77 patients with positive HBcAb, 11 cases did not present for PCR test and were excluded. As a result, 66 patients remained for PCR test. Of 66 patients with positive HVI and HBcAb results, 8 subjects (12.1%) had OBI and 58 cases (87.9%) did not have OBI (**Figure.1**).



**Fig.1:** The prevalence of OBI in patients with HIV+ (percentage).

In terms of age, none of the subjects younger than 18 years had OBI. In age range of 18 to 40 years, 3.7% and in those older than 40 years, 5.3% had OBI ( $P < 0.05$ ) (**Table.1**). Forty-four patients were male (54.5%), and 22 were female (45.5%). Of 36 male patients, 8 (6.5%) had OBI. No female were found to have positive HBV PCR result. Therefore, a

significant association was found between gender and OBI ( $P < 0.05$ ). Of 58 OBI patients 57 were city dwellers and one patient was residing in rural areas. In 27 subjects, less than 5 years had passed from the time their HIV disease was diagnosed. In this group two patients (2.4%) had OBI. Of 39 patients whose HIV diagnosis was made more than 5 years earlier, 6 cases

had OBI (5.7%). No significant difference was seen regarding the time of HIV diagnosis and OBI ( $P > 0.05$ ). In those who were receiving ART (49 subjects), five patients (11.3%) had OBI. In those who were not receiving ART (17 subjects), 3 cases (12.4%) had OBI. No significant association was detected between receiving ART and OBI ( $P = 0.41$ ). In 41 patients, CD4 count was lower than 350/ml. In this group, seven patients (23.3%) had OBI. In 25 patients, CD4 counts were higher than 350. In this group, only one patient (4.1%) had OBI. There was no significant association between CD4 count and the presence of OBI ( $P > 0.05$ ).

Of 66 subjects, 37 cases had positive HCV tests. In this group, 7 cases (23.3%) had OBI. In 29 patients with negative HCV result, only one patient had OBI (3.57%). There was no significant association between positive HCV result and OBI ( $P = 0.06$ ). Of 66 studied patients, 39 were intravenous drug users. In this group, 7 subjects (17.94%), had OBI.

Among 27 patients who were not drug users, one patient (3.57%) had OBI ( $P > 0.05$ ). Twenty-six patients (39.3%) had hepatic disease. In this group, five patients (19.23%) had OBI. Among 40 patients without hepatic disease, three (7.5%) had OBI ( $P = 0.26$ ); **Table.2**.

**Table-1:** Frequency distribution of OBI in different age groups

Group years	Occult hepatitis B infection		Total
	Yes	No	
< 18 years	0	4 (100%)	4
18 to 40 years	4 (16%)	21 (84%)	25
> 40 years	4 (10.8%)	33 (99.2%)	37
Total	8 (26.8%)	58 (77.2%)	66

**Table-2:** Frequency distribution of OBI according to different studied variables

Variables	Sub-group	Positive OBI	Negative OBI	P-value
CD4 count	< 350	7 (20.1%)	24 (79.9%)	> 0.05
	> 350	(4.1%)	24 (95.9%)	
Hepatitis C virus	Positive	7 (23.3%)	30 (76.7%)	0.066
	Negative	1 (3.57%)	28 (96.43%)	
Intravenous drug user	Yes	7 (17.94%)	32 (82.06%)	> 0.05
	No	1 (3.57%)	26 (96.43%)	
Hepatic disease	Yes	5 (19.33%)	21 (80.76%)	0.23
	No	3 (7.5%)	37 (92.5%)	
Antiretroviral therapy	Yes	5 (11.3%)	44 (88.7%)	0.41
	No	3 (12.4%)	14 (87.6%)	

OBI: Occult hepatitis B infection.

#### 4- DISCUSSION

Identifying patients with OBI is important as this state predisposes patients to more advanced stages of liver disease

such as liver cirrhosis and hepatocellular carcinoma. Follow-up and treatment of such patients can prevent transmission of HBV to other persons. Globally, 7 to 10% of HIV-positive patients have chronic

HBV infection. HIV infection can increase HBV replication and raise HBV DNA titer and decrease HBcAg seroconversion in the evolution of HBV infection. These result in more severe liver disease and acceleration of fibrosis formation in the liver and higher rate of decompensated cirrhosis and advanced hepatocellular carcinoma (11). The prevalence rate of isolated positive HBcAb varies in different studies. Ramezani reported this rate as 20.75% (8) and in another report from India this rate was 33.9% (12). In our study, this rate was 34.9%. In addition, we found that positive HBV DNA regardless of HBcAb was about 4.2%. High rate of positive HBcAb can be the result of high HBV infection (8.28%) in our region (13). We found that the prevalence of OBI among HIV-positive patients was 12.1%. This rate in Iran has been reported as 63% (14) and 13.6% (8) earlier. This rate has been reported as 8.7% in a study from Colombia (15), 29.6% (16), and 24.5% in India (17).

OBI can even be seen in those who have received vaccination during neonatal period. In a previous study in Egypt, two cases of 7 patients with OBI among 132 patients were health-care workers (18). Generally speaking, the prevalence of OBI in HIV infected patients is very heterogeneous and ranges from 0 to 89.5%. This heterogeneity can be due to variable prevalence of HIV and HBV infections in different parts of the world as well as different methods and sensitivities of these methods in identifying OBI and measuring HBV DNA titer.

Basically, OBI is seen in two forms namely seropositive and seronegative forms. Seropositive form which is seen in 80% of cases is seen when HBsAg is negative, and HBsAb and HBcAb results are positive. This state is usually seen after resolution of an acute episode several months after being carrier for HBsAg or years after a positive HBsAg chronic

infection where HbsAg is negative. In seronegative form, which is seen in 20% of patients with OBI, HBV DNA titer is very low and is mostly seen in window period when this is the time between HBsAg is becoming negative and HBsAb is becoming positive (HBsAb clearance time). This form of OBI (i.e., seronegative form) should always be considered as patients without HBV antigens or antibodies can have potential seronegative OBI. Especially, OBI can be transmitted via blood transfusion or organ transplantation and can be activated in immunocompromised states (19). HBV reactivation has been reported in patients with OBI who were receiving immunosuppressive agents (20).

Recently, reports have been published regarding the reactivation of HBV following use of agents such as sofosbuvir, ribavirin, and ledipasvir among patients with chronic HCV/OBI (21, 22). Mean age of the studied patients was 35 ( $\pm 3.2$ ) years. Four patients were younger than 18 years. None of these patients had OBI. Of remaining 62 cases, eight had OBI. We did not find any significant relationship between age and OBI which is compatible with former studies (16). Also, we did not detect any significant associations between residence place and the time elapsed from HIV diagnosis to OBI.

Five patients (11.3%) who were receiving ART (lamivudine, zidovudine, and efavirenz) had OBI. There was no significant association between ART and OBI. However, it seems that taking ART which have no effect on HBV (i.e., lamivudine and tenofovir) may have role in decreasing the prevalence of OBI (15, 23). However, in some studies the effect of medication on decreasing OBI rate has not been demonstrated (24). In a previous study, 11 patients of 13 cases with positive HBV-PCR who were receiving HAART including lamivudine it was reported that during the follow-up, their HBV-PCR

became negative. But two patients experienced flair up and their PCR became positive (25). This topic needs further studies for better elucidation. Here, seven cases had CD4 counts lower than 350. In this group 6.1% had OBI. Of patients with CD4 counts higher than 350, 1.3% had OBI. It seems that CD4 count and as a result, HIV severity have no impact on OBI prevalence. In similar studies, likewise, such relationship has not been reported (24). However, in one study, the prevalence rate of OBI was higher in patients with CD4 counts lower than 200 (15). Thirty-seven patients had HCV infection. In this group, 7 patients had OBI (23.3%). Among those who were free from HCV infection, one patient (1.1%) had OBI. There was no significant association between HCV state and OBI. The minimum CD4 count was 571 and the highest CD4 count was 70,339 with average count of 18,314/mL. This count in comparison to other studies (26) which reported an average of 10.5 copies is higher. In OBI, serum HBV DNA titers are usually very low and are not recognized by many quantitative methods (1). However, this titer may be high as in one study, DNA titer range of 103 to 106 mL has been reported (27).

## 5- CONCLUSION

The prevalence of OBI in the studied sample of HIV-infected patients was 12.1%. As these patients can potentially transmit HBV to others and they can experience disease aggravation and flair up and HBV-related complications, it is suggested that in management of HIV positive patients, serum assays for HBcAb and HBV-PCR be performed.

**6- CONFLICT OF INTEREST:** None.

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