# Research of Occult Hepatitis B Infection in HIV-infected Patients, Schindler Study

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**Abstract**

Research of Occult Hepatitis B Infection in HIV-infected Patients, Schindler Study ABSTRACT Objective: Occult hepatitis B infection seems to be more prevalent among subjects at high risk for HBV infection and with concomitant liver disease. The aim of this study was to assess the prevalence of OHBI in group of HIV-1+/HBsAg- Turkish patients. Methods: Ten centers in Turkey have been included in the study. Gender, age, occupation, place of residence, treatment status, clinic, immunodeficiency panel, eliza tests, hemogram, biochemistry and coagulation laboratory results of the patients were evaluated retrospectively. Results: The number of HIV-infected patients followed in these centers is 3172. The mean age of the patients was 37.2 ± 13.1, and they were 235 males (84.5%) and 43 (15.5%) females. 278 (99.6%) of the patients are patients who received antiretroviral treatment. included in the s Of the 279 patients included in the study, it was determined that HBsAg was negative in all of them, 169 were positive for Anti HBs and 125 were positive for Anti HBc IgG. HIV RNA (203/278) was detected in 203 of the patients. 4 (1.4%) of the patients were diagnosed with OHB. In our study, no significant difference was found in hemoglobin and bilirubin levels and complete blood count in patients with HIV-OHB co-infection. However, albumin values were found to be <3.5 in three OHD patients (p = 0.043). Conclusion: Reasearch the presence of OHB infection in HIV-infected patients is important in determining treatment options and predicting the survival of patient. Hypoalbuminemia could be showing hepatic failure and we can suggest the importance of treatment that diseases.

## INTRODUCTION

In the world, 245 million people are infected with Hepatitis B virus (HBV), 40 million people are infected with human immunodeficiency virus (HIV), and 7.4% of HIV-infected patients are co-infected with HBV. Acute

and chronic HBV infection causes approximately 887 thousand deaths annually. However, when compared with HBV monoinfection, the mortality and morbidity of HIV and HBV coexistence is higher (1).

HIV transmission routes (such as sexual intercourse, use of infected blood and blood products, infected stab injuries, unsafe injection, etc.) also increase the risk of developing HBV infection. Individuals with HIV infection should also be screened for HBV. However, in HIV-infected individuals, a situation called occult hepatitis B (OHB) can be encountered in HBsAg negativity, anti HBc IgG +/-, anti HBs +/-, and the HBV DNA level in serum or plasma is generally lower than 200 IU / ml. Two scenarios are mentioned in HBsAg-negative cases with suspected HIV / OHB coinfection. The first is that HBV infection is in the acute period after virus ingestion, when the surface antigen is not yet positive. The second is that although it is HBsAg, anti HBc, anti HBs negative, it is in the chronic period when there is cccDNA in the liver cell nucleus. OHB infection can also be detected by HBV DNA positivity in the patients serum or liver tissue in cases where cccDNA (covalently, closed, circuler DNA) persists in the liver cell nucleus even if HBsAg is found negative in HIV-infected individuals (2,3).

Immunosuppressive conditions such as HIV positivity, hematological malignancies, solid organ transplantations may cause hepatitis B reactivation. Among the mechanisms associated with the emergence of OHB infection, mutations in the PreS / S regions of HBV, the presence of HBV DNA molecules integrated into the HBV genome, HBV infection in mononuclear cells in peripheral blood, presence of HBV particles complexing with immunoglobulin (Ig) in the blood despite the formation of anti HBs, decrease in cellular humoral immune response and co-infection. HBsAg negativity can be associated with analytical sensitivity of laboratory methods and also viral genotypes (4). The border between healing HBV infection and occult HBV infection is not clear. In cases where HBV is eradicated and HBsAg loss occurs, in the presence of mechanisms that cause occult disease, the disease may flare up again. In a study in which 16 patients with occult HBV infection developing secondary to acute HBV infection were examined, anti HBc IgG positivity was found in all of the cases 30 years after the infection, and anti HBs positivity was found in 11 of them. In the same study, while HBV DNA was below the detectable level in the serum of the patients, it was found positive in the liver in two patients (5). Investigating the presence of OHB infection in HIV-infected patients is important in determining treatment options and predicting the survival of patients. It has been reported that the use of highly active antiretroviral therapy (HAART) reduces morbidity and mortality and delays the occurrence of complications in HIV-infected and HIV / HBV co-infected patients (6). In our study, we aimed to research the prevalence, demographic and clinical characteristics of occult HBV coinfection in a multicenter study in naive patients infected with HIV who received antiretroviral therapy and did not receive treatment.

## MATERIAL METHOD

Ten centers in Turkey have been included in the study. The number of HIV-infected patients followed in these centers is 3172. In a study with a similar setup to our study, the prevalence of OHB was found to be 7.5% (7). In our study, the sample size was calculated as 255 people in a population of 3172 people at 7.5% prevalence, 5% error, 80% power, 95% confidence level. Among 3172 HIV-infected patients who were followed up until February 1, 2020 in the centers participating in the study, 279 patients who met the inclusion criteria were included in the study. Gender, age, occupation, place of residence, treatment status, clinic, immunodeficiency panel, eliza tests, hemogram, biochemistry and coagulation laboratory results of the patients were evaluated retrospectively.

### Statistical analysis

Our study is a cross-sectional study, and descriptive data are given together with number, percentage, mean and standard deviation values. In statistical analysis, analysis of categorical variables was done with the fisher exact test. A p value below 0.05 was considered statistically significant at a 95% confidence interval. SPSS v 21.0 program was used for statistical analysis.

## RESULTS

A total of 279 HIV-infected patients followed in ten centers were included in the study. The centers and distribution of patients included in the study are shown in (Table 1). The mean age of the patients was 37.2 ± 13.1, and they were 235 males (84.5%) and 43 (15.5%) females. 278 (99.6%) of the patients are patients who received antiretroviral treatment.

| **CENTERS** | **Total number of HIV-infected patients followed-up** |
|---|---|
| **Cukurova University** | 815 |
| **Akdeniz University** | 650 |
| **Antalya EAH** | 591 |
| **Gaziantep University** | 316 |
| **Dicle University** | 295 |
| **University of Kocaeli** | 200 |
| **Mustafa Kemal University** | 115 |
| **İnönü University** | 110 |
| **Scie nce of Health University, Kocaeli Derince EAH** | 56 |
| **Mardin State Hospital** | 24 |
| **TOTAL** | 3172 |

Table 1. Centers included in the study and distribution of patients

Of the 279 patients included in the study, it was determined that HBsAg was negative in all of them, 169 were positive for Anti HBs and 125 were positive for Anti HBc IgG. HIV RNA (203/278) was detected in 203 of the patients. 4 (1.4%) of the patients were diagnosed with OHB. Anti HCV positivity was detected in two patients (2/277). Delta antibody positivity was not found in any of the 121 patients whose delta antibody was tested (Table 2).

| | **Negative** | **Pozitive** |
|---|---|---|
| | **Number (%)** | **Number (%)** |
| **HBsAg** | 279 (100%) | 0 |
| **Anti HBs** | 110 (39.4%) | 169 (60,6%) |
| **Anti HBc IgG** | 93 (42.7%) | 125 (57.3%) |
| **HBV DNA (IU/ml)** | 275 (98.6%) | 4 (1.4%) |
| **OHB** | 275 (98.6%) | 4 (1.4%) |
| **HIV RNA (copies/ml)** | 75 (27%) | 203 (73%) |
| **Delta Antikoru** | 121 (100%) | 0 |
| **Anti HCV** | 275 (99.3%) | 2 (0.7%) |

Table 2.Virical serological and molecular test results of the patients

In the study, analysis of risk factors associated with occult hepatitis B was performed. Accordingly, 4 patients diagnosed with OHD are male, 3 of them are homosexual; It was determined that 1 was heterosexual, 2 was Anti HBS positive, 4 was Anti HBc IgG positive, 4 was HIV RNA positive, 2 had a CD4 count of 200 / mm3 (Table 3).

| | **OHB negative Number (percent)** | **OHB pozitive Number (percent)** | **p*** |
|---|---|---|---|
| **Gender** | | | |
| Male | 231 (84.3%) | 4 (100%) | 1 |

| | **OHB negative Number (percent)** | **OHB pozitive Number (percent)** | **p*** |
|---|---|---|---|
| Female | 43 (15.7%) | 0 | |
| **Drug addiction** | | | |
| Negative | 258 (97.4%) | 4 (100%) | 1 |
| Pozitive | 7 (2.6%) | 0 | |
| **Alcohol addiction** | | | |
| Negative | 248 (93.2%) | 4 (100%) | 1 |
| Pozitive | 18 (6.8%) | 0 | |
| **IV drug addiction** | | | |
| Negative | 263 (98.6%) | 4 (100%) | 1 |
| Pozitive | 3 (1.1) | 0 | |
| **Sexual preference** | | | |
| Homosexual | 88 (35.3%) | 3 (75%) | 0,268 |
| Heterosexual | 156 (62.7%) | 1 (25%) | |
| Other | 5 (2.0%) | 0 | |
| **Hepatitis C coinfection** | | | |
| Negative | 275 (100%) | 4 (100%) | N/A |
| Pozitive | 0 | 0 | |
| **Anti HBs** | | | |
| Negative | 108 (39.3%) | 2 (50%) | 0,648 |
| Pozitive | 167 (60,7%) | 2 (50%) | |
| **Anti HBcIgG** | | | |
| Negative | 93 (43,5%) | 0 | 0,138 |
| Pozitive | 121 (56,5%) | 4 (100%) | |
| **HIV RNA (copies/ml)** | | | |
| Negative | 75 (27,4%) | 0 | 0,577 |
| Pozitive | 199 (72,6%) | 4 (100%) | |
| **CD4 number** (cell/$mm^3$) | | | |
| 200 and below | 79 (30,4%) | 2 (50%) | 0,231 |
| 201-499 | 102 (39,2%) | 2(50%) | |
| 500 and above | 79 (30,4%) | 0 | |

Table 3. Analysis of risk factors associated with occult hepatitis B

The data of patients who are not diagnosed with OHD are as follows: 231 of the patients are male (84%), 7 of them (2.6%) have drug addiction. Homosexuality rate is 35.3%. In addition, 167 (60.7%) patients were Anti HBs positive, 121 (56.5%) patients were Anti HBcIgG positive, 199 (72.6%) patients were HIV RNA positive. In 30.4% of the patients, the CD4 count is '200 / mm3' (Table 3).

When the laboratory findings of patients with and without OHB were evaluated, no significant difference was found in terms of hemoglobin, leukocyte, thrombocyte, ALT, AST, GGT, ALP, and total bilirubin levels. However, albumin values were found to be <3.5 in three patients with OHB (p = 0.043) (Table 4).

| | **OHB negative Number (percent)** | **OHB pozitive Number (percent)** | **p*** |
|---|---|---|---|
| **Hemoglobin (g/dL)** | | | |
| <12 | 34 (12,4%) | 0 | 0,536 |

| | **OHB negative Number (percent)** | **OHB pozitive Number (percent)** | **p*** |
|---|---|---|---|
| 12-16,8 | 235(85,5%) | 4(100%) | |
| >16,8 | 6(2,2%) | 0 | |
| **Leukocyte ($10^8$ / µL)** | | | |
| <4000 | 13(4,7%) | 0 | 0,707 |
| 4000-10600 | 252(91,6%) | 4(100%) | |
| >10600 | 10(3,6%) | 0 | |
| **Platelet($10^8$/µl)** | | | |
| <139 | 29(10,5%) | 2 (50%) | 0,129 |
| 139-346 | 229(83,3%) | 2 (50%) | |
| >346 | 17(6,2%) | 0 | |
| **ALT ( U/L)** | | | |
| 45 ve altı | 254(92,4%) | 4(100%) | 1 |
| >45 | 21(7,6%) | 0 | |
| **AST (U/L)** | | | |
| 35 ve altı | 202(73,5% | 1 (25%) | 0,063 |
| >35 | 73(26,5% | 3(75%) | |
| **GGT (U/L)** | | | |
| 65 ve altı | 153(90,0% | 3(100%) | 1 |
| >65 | 17(10,0% | 0 | |
| **ALP (U/L)** | | | |
| <40 | 6(2,2% | 0 | 0,164 |
| 40-150 | 233(86,3% | 2(50%) | |
| >150 | 31(11,5% | 2(50%) | |
| **Total bilirübin (mg/dl)** | | | |
| 1,2 ve altı | 162(90,0% | 4(100%) | 1 |
| >1,2 | 18(10,0% | 0 | |
| **Albümin (g/dl)** | | | |
| <3,5 | 91(34,6% | 3(100%) | 0,043 |
| 3,5 -5 | 172(65,4% | 0 | |

Table 4.Analysis of the laboratory results of the patients

* Fisher's exact test result OHB: Occult Hepatitis B ALT: Alanine aminotransferase AST: Aspartate aminotransferase GGT: Gamma glutamyl transferase ALP: Alkaline phosphatase

Detailed analysis of demographic, clinical data, laboratory results and radiological findings of HIV / OHB co-infected patients, 4 male patients diagnosed with HIV / OHB ranged from 23 to 56 years of age, patients received antiretroviral therapy for 2-8 years, 2 patients with tenofovir disoproxil / emtristabine. / dolutegravir treatment, the other 2 patients received tenofovir alafenamide / emtristabine / cobicistat / elvitegravir treatment, HBV DNA levels between 60-1128 IU / mL, ALT levels 18-34 U/L, AST levels 22-54 U/L, total bilirubin level was found to be 0.4 -1.2 mg/dl, and albumin levels to be 2.9-3.2 g/dl. USG (ultrasonography) findings of HIV / OHB co-infected patients were found to be normal (Table 5).

| | **OHB 1** | **OHB 2** | **OHB 3** | **OHB 4** |
|---|---|---|---|---|
| **Gender / Age (years)** | Male/56 | Male /33 | Male /23 | Male /37 |
| **ART regimen** | TDF/FTC+DTG | TAF/FTC+ COBİSİSTAT+EVG | TDF/FTC+DTG | TAF/FTC+ C |
| **ART usage period (years)** | 8 | 2 | 4 | 3 |

| | | | | |
|---|---|---|---|---|
| **HBsAg** | NEGATİF | NEGATİF | NEGATİF | NEGATİF |
| **Anti HBs** | NEGATİF | POZİTİF | NEGATİF | POZİTİF |
| **Anti HBc IgG** | POZİTİF | POZİTİF | | POZİTİF |
| **HBV DNA (IU/ml)** | 60 | 924 | 1128 | 932 |
| **HIV RNA (copies / ml)** | 285000 | 14000 | 2090 | 1287 |
| **Delta Antibody** | Normal | Normal | Normal | Normal |
| **CD4 count (cell/ mm3)** | 433 | 199 | 200 | 235 |
| **Hemoglobin (g/dL)** | 14,8 | 13 | 13 | 15 |
| **Leukocyte ($10^8$ / µL)** | 7500 | 7200 | 5100 | 5300 |
| **Platelet ($10^8$ / µL)** | 287000 | 119 | 121 | 231 |
| **ALT (U/L)** | 18 | 34 | 34 | 34 |
| **AST (U/L)** | 22 | 44 | 54 | 44 |
| **ALP (U/L)** | 69 | 56 | 181 | 220 |
| **Total bilüribin (mg/dl)** | 0,4 | 1,2 | 1,2 | 1,2 |
| **Albümin (g/dl)** | N/A | 3,2 | 2,9 | 2,9 |
| **USG** | Normal | Normal | Normal | Normal |

Table 5. Detailed analysis of demographic, clinical data, laboratory results and radiological findings of HIV / OHB co-infected patients

## DISCUSSION

In HBsAg negativity, OHB infection defined by anti HBc IgG +/-, anti HBs +/- serological table, presence of HBV DNA in serum or plasma is frequently reported in HIV-infected patients, especially those who have not received treatment. The mechanisms responsible for HBsAg negativity in occult infection are controversial. Among the causes of HBsAg negativity, decrease or absence of HBsAg expression, decrease of HBsAg secretion from hepatocytes, change of HBsAg antigenicity can be counted. The presence of mutations in the HBV genome, particularly the envelope gene, is an important cause of HBsAg negativity (1,8).

OHB infection has been investigated in many patient groups such as blood donors, pregnant women, those receiving immunosuppressive therapy, and hemodialysis patients, and OHB infection is encountered in HIV-infected patients, especially those who have not received treatment. In the literature, it has been reported that the prevalence of OHB infection in HIV-infected individuals varies between 0% and 89.5% (9). In our study, the frequency of OHB in 279 patients was found to be 1.4%. One of the reasons for the difference in the prevalence of OHB infection is the use of diagnostic methods with different sensitivity and specificity (1).

In HIV / OHB co-infected individuals, although antibody (anti-HBc) positivity against HBV core antigen is a marker of HBV exposure, OHB and HIV / OHB co-infected cases have been reported in regions with high endemicity where anti-HBc is negative (2). Recent studies show that approximately 20% of OHB infections are serologically negative, and anti-HBc positivity, which was used as a marker for the detection of OHB, is not sufficient in the diagnosis of OHB infection. In a study, serological evidence of HBV infection could not be shown in 2.2% of OHB patients (2). In studies conducted in South Africa (2.2%) and the USA (0.55%), HBV DNA positivity was reported in 2.2% and 0.55% of seronegative individuals, respectively (8). In our study, it was determined that 169 (60.6%) of the included HBsAg negative patients were positive for Anti HBs and 125 (57.3%) of them were positive for Anti HBc IgG. It was found that 2 out of four patients diagnosed with OHB were Anti HBS positive, 4 were Anti HBc IgG positive, and the HBV DNA levels of these patients were between 60-1128 IU / mL. These results show that routine HBV antibody tests are not sufficient for OHB screening. It is emphasized in the literature that the gold standard test for the diagnosis of OHB is the demonstration of the presence of HBV DNA in the liver. Since routine liver biopsy is not performed in HIV-infected patients, blood samples are generally used in the diagnosis of OHB infection. No evidence has been shown that HIV infection changes the sensitivity or specificity of these tests (10).

Some studies have reported a trend towards elevated ALT and AST levels in HIV / OHB co-infected individuals. In a study investigating the prevalence of OHB and the long-term effects of OHB in HIV-infected women, OHB infection was detected in 2% of HIV-infected women who were anti-HBc positive, and it was observed that the increases in aminotransferase levels were not associated with detectable HBV DNA (17). In our study, no significant relationship was found between OHB and liver enzyme elevation.

On the other hand, the clinical effect of OHB in HIV-infected patients is still controversial. There is evidence that OHB is associated with hepatic exacerbations, advanced liver fibrosis, decreased response to interferon therapy, and hepatocellular carcinoma (HCC) (12). In patients with HIV / OHB co-infection, HIV-induced immunodeficiency may accelerate the progression to cirrhosis and hepatocellular carcinoma. Literature data report that the fibrosis score is higher in patients with OHB (13). However, since fibrosis scoring was not routinely performed in HIV / OHB co-infected patients in centers participating in our study, no comment could be made on this issue. These data indicate that large-scale studies are needed regarding the clinical course, status of liver enzyme levels, and fibrosis scoring in patients with suspected HIV / OHB.

In a study conducted with HIV-1 infected pregnant women, it was reported that low CD4 count, cases over 35 years of age and HCV co-infection were independent risk factors for isolated anti-HBc positivity (11). Suppression of the immune system has been associated with a CD4 T cell count of <100 cells / μL, birth in northern Thailand, loss of anti-HBs and isolated anti-HBc in HIV-infected patients. It has been argued that anti-HBs production decreases against HBV infection as the age gets older (11). In the study conducted by Walz et al., It was reported that 7 out of 105 babies born from isolated anti-HBc positive women were infected with HBV. In the study of Khamduang et al., 47 women with occult HBV infection had HBV DNA levels (> 15 IU / mL). It was found that none of their babies were infected with HBV (11).

In our study, a significant correlation was found between OHB and CD4 count. Our data suggest that the possibility of OHB should be kept in mind in cases with low CD4 cell count. Viremia is suppressed in OHB patients due to the strong host defense that occurs during acute or chronic infection (12). Similarly, in our study, HBV DNA levels in patients with OHB are between 60-1128 IU / mL.

In our study, no significant difference was found in hemoglobin and bilirubin levels and complete blood count in patients with HIV-OHB co-infection. However, albumin values were found to be <3.5 in three OHD patients ($p = 0.043$) (18).

Pooled HBV nucleic acid test (NAT) can be used to detect HIV / OHB coinfection. In a study conducted in India, OHB infection was detected in 10% of HIV-infected participants; It has been argued that the pooled HBV NAT test used in the detection of HIV / OHB coinfection is a cost-effective and highly specific test. It has been reported that the sensitivity of this method is low in patients with low HBV DNA levels (14). In a study conducted in Cameroon, anti-HBc positivity was detected in more than 50% of blood donors; The presence of OHB has been shown in 1% of the patients with HBsAg negative and antiHBc positive. This study reports that performing HBsAg test alone is not sufficient in eliminating the risk of HBV transmission through transfusion and screening potential donors; recommends the use of HBV NAT test in addition to anti-HBc screening (16).

In our study, patients diagnosed with OHB were those under ART treatment for 2-8 years. It was determined that 2 patients with a diagnosis of OHB received tenofovir disoproxil / emtristabine / dolutegravir treatment, and the other 2 patients received tenofovir alafenamide / emtristabine / cobicistat / elvitegravir treatment. This shows that OHB can develop in HIV patients under ART treatment (19).

Routine serological markers and especially isolated Anti-HBc positivity may be insufficient in the diagnosis of OHB in HBsAg negative patients. The most reliable method in the diagnosis of OHB in these patients is HBV DNA detection. HBV DNA levels in these patients are usually low (<1000 IU / mL). A low CD4 count and age> 35 are among the independent risk factors for OHB. In our study, no significant difference was found in patients with HIV-OHB co-infection in terms of liver enzyme levels, hemoglobin and bilirubin levels, and complete blood count, but a significant correlation was found between OHB and CD4 count. In addition, in our study, it was found that albumin values in patients with OHB were significantly low.

Hypoalbuminemia could be showing hepatic failure and we can suggest the importance of treatment that diseases. There was no significant relationship between transmission routes, sexual preferences and OHB. It has been determined that all patients with OHB are under ART treatment. The outputs we obtained from our study clearly show that HIV-infected patients should be evaluated in terms of OHB co-infection. For the diagnosis of OHB infection, the HBV DNA test should be used, the test should be performed before starting HAART, and accordingly, it should be decided to use drugs effective against HBV in the treatment of patients. There is a need for large-scale studies investigating the clinical course, liver enzyme levels, histopathology, and treatment options of HIV-OHB co-infected patients.

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`Table 5.pdf` available at https://authorea.com/users/399661/articles/512157-research-of-occult-hepatitis-b-infection-in-hiv-infected-patients-schindler-study