

Occult hepatitis B virus co-infection in human immunodeficiency virus-positive patients: A review of prevalence, diagnosis and clinical significance

Angelica Maldonado-Rodriguez, Ana Maria Cevallos, Othon Rojas-Montes, Karina Enriquez-Navarro, Ma Teresa Alvarez-Muñoz, Rosalia Lira

Angelica Maldonado-Rodriguez, Othon Rojas-Montes, Karina Enriquez-Navarro, Ma Teresa Alvarez-Muñoz, Rosalia Lira, Unidad de Investigacion Medica en Enfermedades Infecciosas y Parasitarias, Hospital de Pediatria, Centro Medico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, 06720 Mexico City, Mexico

Ana Maria Cevallos, Departamento de Biologia Molecular y Biotecnologia, Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico, 06720 Mexico City, Mexico

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Correspondence to: Rosalia Lira, PhD, Unidad de Investigacion Medica en Enfermedades Infecciosas y Parasitarias, Hospital de Pediatria, Centro Medico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Cuauhtemoc 330 Col. Doctores, 06720 Mexico City, Mexico. rolica36@yahoo.com

Telephone: +52-55-56276940

Fax: +52-55-56276949

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(HIV) and hepatitis B virus (HBV) co-infection is high as they share similar mechanisms of transmission. The development and widespread use of highly sensitive tests for HBV diagnosis has demonstrated that a significant proportion of apparently healthy individuals with evidence of exposure to HBV continue to carry fully functional HBV DNA in their hepatocytes, a situation that predisposes them to the development of progressive liver disease and hepatocellular carcinoma. The presence of co-infections frequently influences the natural evolution of each of the participating infections present by either facilitating their virulence or competing for resources. Furthermore, the drugs used to treat these infections may also contribute to changes in the natural course of these infections, making the analysis of the impact of co-infection more difficult. The majority of studies has examined the impact of HIV on overt chronic hepatitis B, finding that co-infection carries an increased risk of progressive liver disease and the development of hepatocellular carcinoma. Although the effect of HIV on the natural history of occult hepatitis B infection (OBI) has not been fully assessed, all available data suggest a persisting risk of repeated flares of hepatitis and progressive liver disease. We describe studies regarding the diagnosis, prevalence and clinical significance of OBI in HIV-positive patients in this short review. Discrepancies in worldwide prevalence show the urgent need for the standardization of diagnostic criteria, as established by the Taormina statements. Ideally, standardized protocols for testing should be employed to enable the comparison of data from different groups. Additional studies are needed to define the differences in risk for OBI without HIV and in HIV-HBV co-infected patients with or without overt disease.

Key words: Hepatitis B virus; Occult hepatitis B; Human immunodeficiency virus; Prevalence; Diagnosis; Clinical significance

Abstract

The prevalence of human immunodeficiency virus

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Core tip: The prevalence of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) co-infection is high. However, as HBV infection may be occult, its diagnosis requires the routine use of highly sensitive tests. Although viral load or replication in these patients is low, they still have an increased risk of viral reactivation, chronic liver disease and hepatocellular carcinoma development. The majority of our knowledge on occult hepatitis B infection is derived from studies performed in patients with mono-infection or with HIV co-infection. This review summarizes the latest contributions in the field, clearly revealing that more studies are needed to evaluate the full impact of HIV in patients with occult HBV disease.

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INTRODUCTION

The presence of co-infections frequently influences the natural evolution of each of the participating infections present, either by facilitating their virulence or competing for resources^[1]. Furthermore, the drugs used to treat these infections may also contribute to changes in the natural history of these infections^[2], complicating the analysis of the impact of co-infection.

For overt chronic hepatitis B virus (HBV) infection, it is known that the virus does not substantially alter the progression of human immunodeficiency virus (HIV) disease, nor does it influence HIV suppression or CD4 cell responses following the initiation of antiretroviral treatment^[3-5]. In contrast, it is clear that HIV infection has a negative effect on HBV disease, for both acute and chronic infections. In cases of acute hepatitis, progression to chronic infection is approximately 4 times more frequent in patients with HIV than in those without HIV infection (20% vs 5% and most likely higher if the CD4 count is low)^[5]. For chronic hepatitis, HIV infection results in a faster progression of fibrosis, a faster development of cirrhosis and hepatocellular carcinoma, and a lower rate of spontaneous hepatitis B e antigen (HBeAg) or hepatitis B surface antigen (HBsAg) seroconversion^[5]. There is also a greater risk of HBV reactivation in inactive carriers.

Occult HBV infection (OBI) occurs when viral DNA persists in the liver (with detectable or undetectable HBV DNA in serum, with or without HBV antibodies)

in individuals testing negative for HBsAg^[6]. By convention, OBI has been defined as the persistence of isolated anti-HBc in patients who may or may not have detectable serum HBV DNA. However, OBI may also occur in patients without anti-HBc antibodies. Thus, in a workshop of the European Association for the Study of Liver held in Taormina (Italy) in 2008, experts joined together to re-define and standardize diagnostic criteria, which resulted in a series of new criteria known as the Taormina statements^[7]. It is expected that the universal use of these criteria will allow the comparison and proper evaluation of studies by different research groups.

In patients with HBV infection, the absence of HBsAg can occur in two main scenarios: firstly, in the early phases of acute infection prior to the development of antibodies and the detection of HBsAg in serum; secondly, during chronic HBV infection following the decline of HBsAg to an undetectable level, which is sometimes associated with the appearance of anti-HBs^[8]. In chronic occult infections, viral covalently closed circular DNA (cccDNA) persists as a stable chromatinized episome in the nucleus of infected cells. This viral genome remains competent for replication and able to synthesize minute amounts of antigens, which are undetectable by the available technical approaches but sufficient to maintain an HBV-specific T cell response^[6]. Fragments of the HBV genome may integrate into the host hepatic cell genome but this integration does not have a role in the replicative cycle of HBV and should not be strictly considered as occult infection^[6]. In addition, chronic occult infection may be associated with the presence of one or more specific antibodies in serum; therefore, individuals with occult infections are conventionally divided into seropositive [anti-hepatitis B core antigen (anti-HBcAg) and/or anti-hepatitis B surface antigen (anti-HBsAg) positive] and seronegative (anti-HBc and anti-HBs negative) groups^[6,7]. More than 20% of occult-infected individuals are negative for all HBV serum markers^[9]. The development of occult infections is mainly determined by host factors, such as the immune response, and the status of the infection can be modified by the presence of co-infections, such as with hepatitis C virus (HCV) or HIV, or the administration of drugs, including immune suppressors and/or antiretrovirals^[10]. Multiple viral variants have been identified in the liver of occult HBV-infected patients and it is believed that viral factors are not major determinants for the development of occult infections^[6,11].

We describe the diagnosis, prevalence and clinical significance of OBI in HIV-positive patients in this short review.

OBI DIAGNOSIS

The presence or absence of full infective virions is not assessed in clinical practice. Surrogate markers

for the detection of circulating virus are either the presence of HBV DNA or HBV proteins (HBsAg, HBeAg and HBeAg). Typically, the presence of anti-HBs antibodies and the absence of HBsAg suggests a resolved infection; however, the persistence of only anti-HBc may be associated with OBI^[12]. Overt HBV infection (acute or chronic) is defined as the presence of circulating HBsAg; according to the Taormina statements, OBI is defined as the absence of circulating HBsAg and the presence of HBV DNA^[7]. However, the sensitivity and specificity of diagnosis strongly depend on the sensitivity of the assays used; indeed, for many years, HBV DNA tests were not very sensitive. Thus, the presence of anti-HBc was used as a surrogate marker and according to the Taormina statements, it still can be used in regions where modern molecular assays are not available^[13,14]. The gold standard for OBI diagnosis is the demonstration of the presence of HBV DNA in the liver. To rule out the possibility that amplified fragments correspond to partial regions of the viral genome integrated into the host genome, several regions of the genome must be identified to suggest that full-length cccDNA is present. It is accepted that the diagnosis is frequently underestimated as liver biopsies are only rarely available and therefore diagnosis is usually based on blood samples. There is no evidence to date that HIV infection modifies the sensitivity or specificity of these tests.

Markers for screening OBI

HBsAg: It is of crucial importance to define the best methodology to test HBsAg to prevent false positive results, which is dependent on the HBsAg assay sensitivity. Several problems of this aspect are associated with the virus, the host or the test kits employed in practice. The quantification of HBsAg should be performed by comparing the sample with a standard curve generated with the second International Standard for HBsAg (World Health Organization code number 00/588, document WHO/BS/03.1987); 1 international unit is equivalent to 5.6 Abbott ng, 1.9 French ng and 0.43 PEI units^[8]. Unfortunately, some HBV variants have mutations in the *HBs* gene and the encoded proteins are not detected with conventional commercial kits. Accordingly, alternative methods should be tested to detect common mutants^[15].

HBV DNA: It has been established that HBV-DNA is the only reliable diagnostic marker for OBI. The experts meeting at Taormina recommended that new generation assays with detection limits of less than 10 copies of HBV DNA per reaction should be employed^[7]. The estimated viral load in OBI is usually below 200 IU/mL.

New generation assays for DNA detection include nested-polymerase chain reaction (PCR), real-time PCR and transcription-based mediated amplification.

Indeed, advances in the development of these DNA detection technologies has allowed a decrease in the lower detection limit (< 5 IU/mL of HBV DNA), which is particularly important in OBI because DNA levels vary at -5-10 IU/mL (range < 10 to 425 copies/mL)^[8].

HBV genome regions for diagnosis: According to the Taormina statements^[7], the primers used must be specific for different HBV genomic regions and be complementary to highly conserved nucleotide sequences. The *S* and *X* genes are the regions most commonly amplified by PCR for diagnosis; it has been found that the *X* gene is the most sensitive for the liver, whereas the *S* gene is better for serum samples^[9]. To avoid the problems of cross-contamination, appropriate controls in each PCR assay as well as amplicon sequencing are recommended.

PREVALENCE

The prevalence of infections in open populations is frequently estimated using data obtained from serological testing performed using blood donor samples; however, HBV tests can detect either overt infections or previous exposure to the virus in blood donors. Therefore, the available data reflect only the prevalence of overt HBV infections. OBI is only screened in specific scenarios, such as in areas of high endemicity of HBV, intravenous drug users, organ transplant patients, patients on maintenance hemodialysis or patients with HIV and/or HCV. For this review, we analyzed 34 papers that examined the prevalence of OBI in HIV patients during the period 2003-2014 (Table 1). The range of reported prevalence in these studies varied from 0.63% to 88.4%, which is similar to the prevalence reported in a previous review (0%-89.5%)^[16]. This extremely wide range of prevalence reflects the diverse nature of published studies. Some of the differences are explained by the individual prevalence of HIV and HBV in the different populations studied. Although there are reports from central and south America^[17-22], the majority of the studies are from regions of Africa, India and the Far East, regions where the prevalence of both HIV and HBV is high^[23-27]. Differences also arise from the type of high-risk group to which the co-infection patients studied belong (*e.g.*, hemodialysis patients, homosexuals, intravenous drug users). Another source of variability depends on differences in the sensitivity of the diagnostic test used, with more recent studies using more sensitive HBV DNA detection assays than earlier studies^[28]. Clearly, prospective, longitudinal studies in well-defined populations are needed to fully evaluate the prevalence and impact of HIV in the natural history of OBI. These studies should contain detailed clinical and demographic data, including age, sex, risk group liver function tests and, whenever possible, the evaluation

Table 1 Reported prevalence of occult hepatitis B virus infection in HIV-infected subjects *n* (%)

Ref.	Country	OBI prevalence			
		Overall	Anti-HBsAg-/anti-HBcAg+	Anti-HBsAg+/anti-HBcAg+	Anti-HBsAg-/anti-HBcAg-
Alvarez-Muñoz <i>et al</i> ^[17]	Mexico	24 (49.0)	5 (10.2)	8 (16.3)	11 (22.4)
Araujo <i>et al</i> ^[18]	Brazil	6 (14.0)	1 (2.3)	5 (10.2)	ND
Attia <i>et al</i> ^[45]	Africa	40 (21.3)	40 (21.3)	ND	ND
Azadmanesh <i>et al</i> ^[46]	Iran	3 (13.6)	2 (9.1)	ND	1 (4.5)
Bagaglio <i>et al</i> ^[47]	Italy	9 (31.0)	9 (31.0)	ND	ND
Bell <i>et al</i> ^[48]	Africa	45 (15.1)	16 (5.4)	17 (5.7)	12 (4.0)
Bloquel <i>et al</i> ^[38]	France	3 (0.8)	2 (0.5)	ND	1 (0.3)
Chadwick <i>et al</i> ^[49]	England	15 (4.5)	5 (1.5)	10 ¹ (3.0)	ND
Coffin <i>et al</i> ^[50]	Canada	19 (42.0)	ND	19 (42.2)	ND
Dapena <i>et al</i> ^[51]	Spain	6 (2.4)	2 (0.8)	4 (1.6)	ND
Filippini <i>et al</i> ^[13]	Italy	17 (20.0)	11 (12.8)	3 (3.5)	3 (3.5)
Firnhaber <i>et al</i> ^[23]	Africa	38 (88.4)	38 (88.4)	ND	ND
Gupta <i>et al</i> ^[30]	India	24 (45.3)	13 (24.5)	11 (20.8)	ND
Hakeem <i>et al</i> ^[52]	Scotland	2 (2.8)	2 (2.9)	ND	ND
Jardim <i>et al</i> ^[19]	Brazil	8 (5.0)	2 (1.3)	6 (3.8)	ND
Khamduang <i>et al</i> ^[35]	Thailand	47 (23.5)	47 (23.5)	ND	ND
Liang <i>et al</i> ^[53]	Taiwan	3 (2.3)	3 (2.3)	ND	ND
Lo Re <i>et al</i> ^[54]	United States	17 (10.0)	10 (5.6)	7 (3.9)	ND
Loustaud-Ratti <i>et al</i> ^[55]	France	31 (44.3)	20 (28.6)	11 (15.7)	ND
Morsica <i>et al</i> ^[56]	Italy	27 (15.4)	9 (5.1)	18 (10.3)	ND
Mphahlele <i>et al</i> ^[57]	Africa	31 (18.6) ²	5 (3.0)	26 (15.6)	ND
N'Dri-Yoman <i>et al</i> ^[24]	Africa	51 (10.0)	51 (11.8)	ND	ND
Neau <i>et al</i> ^[58]	France	1 (0.6)	1 (0.6)	ND	ND
Nebbia <i>et al</i> ^[59]	England	48 (14.0)	48 (14.0)	ND	ND
Opaleye <i>et al</i> ^[25]	Nigeria	21 (11.2)	8 (4.3)	9 (4.8)	2 (1.1)
Panigrahi <i>et al</i> ^[26]	India	12 (10.7)	9 (8.0)	3 (2.7)	ND
Santos <i>et al</i> ^[20]	Brazil	16 (15.8) ²	4 (4.0)	12 (11.9)	ND
Sen <i>et al</i> ^[27]	India	1 (5.6) ²	1 (5.6)	ND	ND
Shire <i>et al</i> ^[60]	United States	4 (10.5)	4 (10.5)	ND	ND
Shire <i>et al</i> ^[61]	United States	12 (30.2)	3 (7.0)	5 ¹ (11.6)	5 (11.6)
Sucupira <i>et al</i> ^[21]	Brazil	6 (18.8) ²	3 (9.4)	3 (9.4)	ND
Torres Barranda <i>et al</i> ^[22]	Mexico	7 (18.4)	1 (2.6)	1 (2.6)	5 (13.2)
Tramuto <i>et al</i> ^[62]	Italy	24 (5.9)	8 (2.0)	7 ¹ (1.7)	9 (2.2)
Tsui <i>et al</i> ^[63]	United States	8 (2.0)	8 (2.0)	ND	ND

¹In some studies the anti-HBsAg positive group was also included; ²Prevalence calculated using the reported data; anti-HBsAg+, antibodies against hepatitis B surface antigen positive; anti-HBcAg+ antibodies against hepatitis B core antigen positive. Prevalence (%) were included for each group of patients studied according the HBV serological markers (Anti-HBsAg-/anti-HBcAg+, Anti-HBsAg+/anti-HBcAg+, Anti-HBsAg-/anti-HBcAg-). ND: Not determined because this group was not included in the study; OBI: Occult hepatitis B infection; anti-HBsAg: Anti-hepatitis B surface antigen; anti-HBcAg: Anti-hepatitis B core antigen.

of liver damage by biopsy. Ideally, standardized protocols for testing should be employed so that studies from different groups can be compared.

In general, OBI prevalence appears to be higher among patients at high risk for HBV infection and with liver disease than among individuals at low risk of infection and without liver disease^[9,29-31]. As mentioned above, patients with OBI may be negative for all HBV serum markers and there is also evidence that levels of viremia are correlated with levels of anti-HBc and/or anti-HBs^[8]. Unfortunately, the majority of studies have been performed in seropositive patients (usually isolated anti-HBc), whereas seronegative patients who are more difficult to identify have not been fully assessed. Furthermore, the available data suggest seronegative patients have a different clinical evolution and should therefore be evaluated separately. Another factor that is common in HIV patients and that is known to affect

the evolution of HBV infection is HCV co-infection; the presence of HCV should always be screened and those with OBI/HCV should be analyzed separately.

CLINICAL SIGNIFICANCE

The significance of chronic OBI relates to the risk of transmission, reactivation, progression to chronic liver disease and development of hepatocellular cancer^[6,8,32,33]. The rate of transmission is directly proportional to the number of viable virions in blood. Unfortunately, the true level of viremia, *i.e.*, the number of infectious HBV particles within 1 mL of serum or plasma, is difficult to measure in a bioassay^[34]. Therefore, surrogate markers of HBV infectivity are being used to measure the risk of transmission. The best available marker for the presence and number of infectious HBV particles is the number of HBV DNA molecules. However, it is

important to note that the detection of HBV DNA in serum does not always correspond to infectivity or to the number of HBV progeny viruses released from hepatocytes. Indeed, in the majority of viral infections, the number of physical virus particles is much larger than the number of fully infectious virions^[34]. There also appears to be a correlation between levels of HBV DNA and serological status among patients with OBI: HBV DNA levels are lowest in seronegative patients, intermediate in anti-HBc negative and anti-HBs positive patients, and highest in subjects who are anti-HBc-positive but anti-HBs negative^[8]. This last group is more likely to be infectious. The possibility of transmission is crucial for non-immunocompromised individuals who are potential donors of blood or other organs, for health care providers who can infect their patients, and for pregnant women *via* vertical transmission. Although known HIV patients are not candidates for organ donation, there remains a risk of HIV/HBV transmission either through sexual encounters, needle sharing or other risky behaviors. The potential risk of vertical transmission in pregnant HIV/OBI women is clear but the prevalence rate has not been fully evaluated. In a recent study of 1682 HIV-infected pregnant women in Thailand who were fully evaluated for HBV infection, 216 were HBsAg negative and anti-HBc positive (14%). It was also possible to assess the levels of HBV DNA in 200 of these women with OBI; all 200 women had HBV DNA < 1000 IU/mL, with 153 showing HBV DNA below the limit of detection (15 IU/mL), 44 with an HBV DNA level between 15-100 IU/mL, and 3 showing HBV DNA between 101 and 1000 IU/mL. However, none of these women transmitted the disease to their infants^[35]. Based on the available information, a group of experts in the United States has provided guidelines to manage pregnant women with HIV-HBV co-infection; the full guidelines have been published at the AidsInfo site of the National Institute of Health (<http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/159/hiv-hepatitis-b-virus-coinfection>). It is recommended that all pregnant women should have full screens for both HBV and HCV; these tests would identify most cases of OBI in HIV patients. They also strongly recommend that the management of HIV/HBV co-infection in pregnancy should be performed with the advice of an expert in HIV and HBV, with close monitoring of the viral activities in pregnant woman. In their review, the experts conclude that women who screen negative for HBV (*i.e.*, HBsAg-negative, anti-HBc-negative and anti-HBs-negative) should be vaccinated for HBV, stating that the presence of isolated anti-HBc can represent a false-positive case or can indicate a previous exposure and a posterior loss of anti-HBs or most likely an "occult" HBV infection. The possibility of OBI needs to be confirmed by HBV DNA detection. These experts also

recognize that the clinical significance of isolated anti-HBc is still unknown. For that, they recommend, with the panel of their peers on opportunistic infections in HIV-infected adults and adolescents, to test for HBV DNA in HIV+/anti-HBc+ patients before HBV vaccination and treatment initiation or prophylaxis to avoid the risk of a paradoxical exacerbation of HBV infection and the incidence of immune reconstitution inflammatory syndrome (http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). The risk of vertical HBV transmission in mothers with OBI is most likely small due to the low levels of HBV viremia. Clearly, the decision to treat a pregnant woman with OBI should be made by an expert.

The natural history of chronic hepatitis B is highlighted by spontaneous flares of the disease. The reasons for HBV reactivation are not clear but most likely can be explained by subtle modifications in virus replicative fitness due to host immunological control, such as that which occurs with herpes virus^[36]. The flares are potentially important clinically because they can have severe or even fatal consequences. Most frequently, the reactivation of HBV replication occurs in patients with overt chronic HBV infection (HBsAg-positive) who receive cytotoxic or immunosuppressive therapy^[10,33]. In contrast, HBV reactivation occurs more rarely in patients with OBI. Both in overt and occult infection, the risk of HBV reactivation is high, particularly in patients with hematological malignancies, in those receiving hematopoietic stem cell transplantation and in those treated with either anti-CD20 (rituximab, which destroys B-cells) or anti-CD52 (alemtuzumab, which targets mature lymphocytes) monoclonal antibodies (reviewed in^[10]). In these cases, HBV reactivation is associated with a mortality rate of approximately 20% due to hepatic failure or to progression of the underlying disease owing to the discontinuation of treatment.

There are multiple anecdotal reports of the reactivation of OBI in HIV-patients, with the majority of cases being identified in seropositive patients. Many factors, similar to those demonstrated for overt infection, have been implicated in the recurrence of HBV replication in HIV/OBI-co-infected patients, including the interruption of HAART^[37-39], recovery of immune responses after HIV-treatment^[14], development of resistance to lamivudine therapy^[13], and appearance of HBV immune-escape^[40].

The overall prevalence of OBI reactivation in HIV patients and the frequency of the specific triggers of reactivation need to be assessed in prospective longitudinal studies^[14]. In an effort to evaluate the full impact of HIV-infection in OBI, a multicenter prospective study on 115 consecutive anti-HIV+, HBsAg-negative, treatment-naïve patients was performed^[13]. Of the 86 patients with at least 6 mo of follow-up, 13 were HBV DNA positive on

admission and four in the subsequent testing. The HBV DNA+ frequency for the anti-HBs-negative/anti-HBc-positive group was 36% and 21% for the anti-HBs-positive/anti-HBc-positive group; the lowest frequency was reported in the anti-HBs-negative/anti-HBc-negative group (9%). Episodes of reactivation were detected in 32% of the patients and were more common in patients with detectable HBV DNA than in those without it (65% vs 25%). These preliminary data await confirmation in larger studies^[10].

HBV infection causes liver inflammation and hepatocellular carcinoma. The lifetime risk of developing HBV-related cirrhosis or hepatocellular carcinoma has been estimated to be between 15% and 40% for males who acquire infection during early life^[36]. There is evidence to suggest that the risk of progression of liver disease from inflammation, to fibrosis, to cirrhosis and to cancer is directly related to the level of transcription of HBV DNA^[41-43]. However, the prevalence and rate of progression to cirrhosis are also related to differences in the clinical and serological features of the disease, such as repeated flares, age and HBV genotype^[36]. There is an increased risk of hepatocellular carcinoma even in patients with inactive HBV infection^[44]. It is widely accepted that the risk of progression is particularly high in patients with OBI/HCV co-infection^[8]. However, the impact of HIV infection in the oncogenicity of OBI HIV patients has not been studied and requires specific evaluation^[10].

CONCLUSION

The real impact of co-infection can only be fully established when the presence of OBI is routinely assessed in all patients with HIV. As routine liver biopsy of all HIV patients is not possible, at least all HIV patients should be screened initially with a complete panel of HBV tests. As both the reactivation of hepatitis (with or without the emergence of drug resistance) and an increase in the risk of transmission are associated with higher levels of HBV DNA, the monitoring of OBI should always include regular highly sensitive measurements of circulating HBV DNA. More studies are needed to define when to repeat the full set of HBV tests and when a liver biopsy is indicated in these patients.

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