

## Clinical impact of occult hepatitis B virus infection in immunosuppressed patients

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### Abstract

Occult hepatitis B infection (OBI), is characterized by low level hepatitis B virus (HBV) DNA in circulating blood and/or liver tissue. In clinical practice the presence of antibody to hepatitis B core antigen in hepatitis B surface antigen (HBsAg)-/anti-HBs-negative subjects is considered indicative of OBI. OBI is mostly observed in the window period of acute HBV infection in blood donors and in recipients of blood and blood products, in hepatitis C virus chronic carriers, in patients under pharmacological immunosuppression, and in those with immunodepression due to HIV infection or cancer. Reactivation of OBI mostly occurs in anti-HIV-positive subjects, in patients treated with immunosuppressive therapy in onco-hematological settings, in patients who undergo hematopoietic stem cell transplantation, in those treated with anti-CD20 or anti-CD52 monoclonal antibody, or anti-tumor necrosis factors antibody for rheumatological diseases, or chemotherapy for solid tumors. Under these conditions the mortality rate for hepatic failure or progression of the underlying dis-

ease due to discontinuation of specific treatment can reach 20%. For patients with OBI, prophylaxis with nucleot(s)ide analogues should be based on the HBV serological markers, the underlying diseases and the type of immunosuppressive treatment. Lamivudine prophylaxis is indicated in hemopoietic stem cell transplantation and in onco-hematological diseases when high dose corticosteroids and rituximab are used; monitoring may be indicated when rituximab-sparing schedules are used, but early treatment should be applied as soon as HBsAg becomes detectable. This review article presents an up-to-date evaluation of the current knowledge on OBI.

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**Key words:** Occult hepatitis B virus infection; Silent hepatitis B virus infection; Hepatitis C virus infection; Liver fibrosis

**Core tip:** In occult Hepatitis B infection (OBI), hepatitis B virus reactivation is more common in anti-HIV-positive subjects, in those in onco-hematological settings, in patients who undergo hemopoietic stem cell transplantation and in those treated with anti-CD20 or anti-CD52 monoclonal antibody. Reactivation may be severe and in nearly 20% of cases it may take a life-threatening course. The use of nucleot(s)ide analogues to prevent this reactivation is mandatory in hepatitis B surface antigen-negative/anti-hepatitis B core-positive patients in all conditions of strong and/or prolonged immunosuppression. We describe the characteristics of OBI in onco-hematological and rheumatological diseases, in solid cancers and in HIV infection.

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## INTRODUCTION

Hepatitis B virus (HBV) infection is a major health problem in most countries, with approximately 2 billion people worldwide with serological evidence of previous exposure to the virus, of whom nearly 300 million have HBV chronic infection and over 1 million deaths per year are due to HBV-related cirrhosis and/or hepatocellular carcinoma (HCC)<sup>[1-6]</sup>.

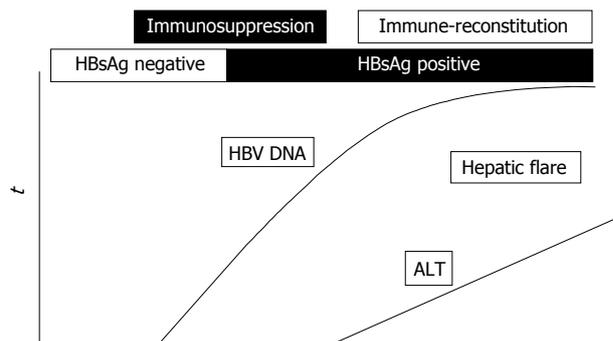
HBV infection is identified in most cases by the presence of circulating hepatitis B surface antigen (HBsAg), but an HBsAg-negative HBV infection has also been described [Occult B infection (OBI)]<sup>[7]</sup>, characterized by low levels of HBV DNA in circulating blood<sup>[8,9]</sup> and/or in liver tissue<sup>[10]</sup>. OBI has also been described as a serological condition characterized by the presence of hepatitis B core antigen (anti-HBc) in the absence of HBsAg and anti-HBs (isolated anti-HBc)<sup>[7,11-15]</sup>. OBI may be observed in the window period of acute HBV infection<sup>[16]</sup> in blood donors and in recipients of blood and blood products<sup>[9,17,18]</sup>, in patients with HCV chronic infection<sup>[7,19]</sup>, in cryptogenic chronic hepatitis, in patients under pharmacological suppression of the immune system<sup>[20,21]</sup> and in those with immunodepression due to HIV infection; it has also been associated to the development of hepatocellular carcinoma<sup>[22-30]</sup>.

It has been shown that the hepatitis B virus maintains its pro-oncogenic properties in OBI<sup>[31]</sup> and that its presence in patients with chronic hepatitis C is associated with a higher risk of disease progression and HCC development<sup>[32-36]</sup> and with a reduced response to alpha interferon treatment<sup>[37-39]</sup>. The clinical importance of OBI is also underscored by the need for nucleot(s)ide treatment to prevent the recurrence of HBV infection in HBsAg-negative/anti-HBc-positive patients in various immunosuppressive settings<sup>[40-42]</sup>.

This review article presents an up-to-date evaluation of the current knowledge on OBI, focusing in particular on the clinical approach in onco-hematological and rheumatological diseases, solid cancers and HIV infection.

## OCCULT HBV INFECTION AND IMMUNOSUPPRESSION

Reactivation of HBV infection in patients under immunosuppressive treatment is a well-known, life-threatening event described in HBsAg-positive patients (overt HBV infection) and in subjects with OBI<sup>[20,21,42-50]</sup>. The reactivation of HBV infection, overt or occult, is characterized by a marked enhancement of viral replication during immunosuppressive therapy, with a wide spread of HBV to uninfected hepatocytes and a substantial increase in the HBV DNA serum level followed by the restoration of the immune function after treatment withdrawal and consequent cytotoxic-T-cell-mediated necrosis of HBV-



**Figure 1** Virological and biochemical dynamics of reactivation of occult hepatitis B infection. HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen.

infected hepatocytes usually responsible for a hepatic flare and in some instances for liver failure and even death<sup>[42]</sup>. A schematic representation of the dynamics of serum HBV DNA and alanine aminotransferase (ALT) before and during the reactivation of OBI is shown in Figure 1.

Both in overt and occult infection the risk of HBV reactivation is estimated as high when immunosuppression is marked, particularly in onco-hematological patients (21%-67%), in those receiving hematopoietic stem cell transplantation and in those treated with the anti-CD20 monoclonal antibody rituximab or with the monoclonal anti-CD52 antibody alemtuzumab, both responsible for profound, long-lasting immunosuppression<sup>[20,21,43,51-59]</sup>. Under these conditions HBV reactivation has a mortality rate close to 20%, due to a hepatic failure or to the progression of the underlying disease due to the discontinuation of specific treatment<sup>[51,60,61]</sup>. Besides host factors, also some virological characteristics have been described as possibly associated with HBV reactivation. In 7 of 84 HBsAg-negative/anti-HBc-positive patients treated for hematological diseases or solid cancer, HBV reactivation was due to non-A HBV genotypes, core promoter and/or precore HBV mutants. In these 7 patients mutations known to impair HBsAg antigenicity were also detected<sup>[62]</sup>. A precore stop mutation (A1896) was detected in one patient with genotype B<sub>j</sub> who developed fulminant liver failure<sup>[63]</sup>. Also sub-genotype D1 has been described as possibly associated with HBV reactivation in two studies, one from Egypt and one from Italy<sup>[21,64]</sup>.

There is general agreement for the use of nucleos(t)ide analogues to prevent HBV reactivation in HBsAg-positive immunosuppressed patients, whereas it is still a matter of debate whether subjects with occult HBV infection should be treated or closely monitored for early treatment once HBsAg positivity has developed.

## PHARMACOLOGICAL PROPHYLAXIS OF OCCULT HBV INFECTION IN DIFFERENT CLINICAL SETTINGS

### Hematological diseases

A crucial role in the reactivation of OBI is played by the

severity and duration of immunosuppression, which in turn reflects the extent of immunodepression due to the hematological disease and of the degree of immunosuppression induced by chemotherapy. The drugs commonly responsible for HBV reactivation are those used in hematological malignancy, such as fludarabine, anthracyclines, high dose corticosteroids<sup>[51,52]</sup> and, more recently, rituximab (anti-CD20) and alemtuzumab (anti-CD52)<sup>[53]</sup>.

Evidence has become available in hematological malignancy that the reactivation of occult HBV infection is frequent in patients treated with rituximab or fludarabine in the absence of lamivudine prophylaxis<sup>[21,60,61]</sup>. However, due to the retrospective nature of most studies published, the geographical differences in HBV epidemiology and the genetic differences in HBV and the host have not been investigated, and the prevalence of HBV reactivation varies widely (from 3% to 45%)<sup>[21,48,52,65-69]</sup>. The first prospective study<sup>[65]</sup> on 244 occult HBV carriers with malignant lymphoma showed a reactivation in 8 (3.3%) cases, with a higher risk of reactivation in patients receiving rituximab plus corticosteroids than in those under a rituximab-sparing schedule. In a prospective study on patients with diffuse large B-cell lymphoma (DLBCL), Yeo *et al.*<sup>[20]</sup> reported reactivation of HBV infection in 5 of 21 (23.8%) patients treated with rituximab plus cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) and in none of the 25 patients receiving only CHOP. Recently Fukushima *et al.*<sup>[48]</sup> observed reactivation in 2 (4.1%) of 48 HBsAg-negative/anti-HBc-positive patients. In addition, in 150 patients with lymphoma and a resolved HBV infection who received rituximab-based chemotherapy, Hsu *et al.*<sup>[70]</sup> described an incidence of HBV reactivation and of HBV hepatic flares of 10.4 and 6.4, respectively, per person per year. Matsui *et al.*<sup>[71]</sup> followed up for a median period of 20.5 mo 59 patients with isolated anti-HBc and lymphoma treated with rituximab-based chemotherapy and observed HBV reactivation in 4 (6.8%).

Lower prevalences of HBV reactivation in HBsAg-negative patients after rituximab-based therapy have been reported in two studies from eastern Asia, 1.5% and 4.2%, respectively<sup>[46,72]</sup>. In another Asian study only one (2.3%) of 43 DLBCL patients treated with an R-CHOP regimen showed reactivation of HBV replication<sup>[73]</sup>, for which a remission was obtained with antiviral therapy with no need to discontinue chemotherapy. Koo *et al.*<sup>[74]</sup> described HBV reactivation in two (3%) of 62 HBsAg-negative/anti-HBc-positive patients treated with rituximab-based chemotherapy who did not undergo anti-HBV prophylaxis. More recently, the Asia Lymphoma Study Group investigated for HBV reactivation HBsAg-positive patients and HBsAg-negative/HBcAb-positive patients who received rituximab-based chemotherapy; the study was retrospective and performed on 340 patients, with a reactivation rate of 2.4% in subjects with OBI and 27.8% in HBsAg-positive patients<sup>[75]</sup>.

The different frequency of cases with reactivation of occult HBV infection in different countries may explain, at least in part, the discordance in different national guidelines on lamivudine prophylaxis, some of which indicate the use of this nucleoside analogue for a pharmacologi-

cal prophylaxis of HBsAg-negative/anti-HBc-positive patients undergoing highly immunosuppressive treatment for onco-hematological diseases<sup>[76]</sup>, and others conclude that the information available does not allow any routine prophylaxis to be recommended for these patients<sup>[77]</sup>.

The data of a recent meta-analysis, however, suggest that rituximab-based chemotherapy increases the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients with non-Hodgkin lymphoma<sup>[78]</sup>, an observation of clinical importance to be taken into consideration for future guidelines.

### Rheumatological disease

Biological therapies targeting tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) have been used increasingly over the last decade to treat various immune-mediated inflammatory diseases such as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease<sup>[42]</sup>. Studies carried out over this period showed that monoclonal antibodies against TNF- $\alpha$  (anti-TNF- $\alpha$ ) and high doses of steroid treatment may induce HBV reactivation in patients with overt HBV infection<sup>[79-82]</sup>, thus suggesting the need for anti-HBV pharmacological prophylaxis for inactive HBsAg carriers<sup>[83]</sup> and treatment for patients with HBsAg-positive chronic hepatitis.

The reactivation of OBI during anti-TNF therapy has not been extensively investigated and the data available are anecdotal and mostly from case reports. In a recent evaluation of the literature data, HBV reactivation was found in only 8 (1.7%) of 468 HBsAg-negative/anti-HBc-positive patients with rheumatological diseases treated with anti-TNF<sup>[82]</sup>. In addition, none of 20 HBsAg-negative/HBV DNA-negative/anti-HBc-positive patients receiving anti-TNF- $\alpha$  for rheumatoid arthritis and spondyloarthropathy experienced reactivation of OBI during a 4-year follow up<sup>[84]</sup>.

### Solid cancers

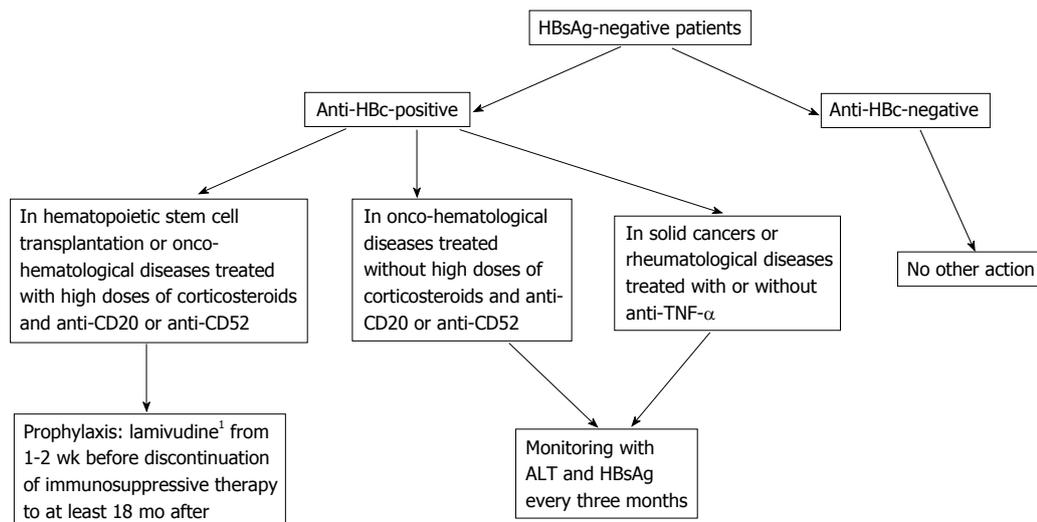
The literature data give evidence of HBV reactivation in HBsAg-positive patients treated with chemotherapy for solid tumors<sup>[85-87]</sup>, and, consequently, pharmacological prophylaxis for inactive HBsAg carriers and therapy for patients with HBsAg-positive chronic hepatitis is recommended. Instead, the studies on HBV reactivation in patients with OBI are not conclusive, but so far no evidence of reactivation of OBI in these patients has emerged. The longitudinal study by Saitta *et al.*<sup>[88]</sup> on 44 HBsAg-negative patients with solid tumors undergoing chemotherapy did not find cases with HBV reactivation. Further prospective studies are needed to improve our knowledge of the clinical importance of OBI in patients with solid cancers.

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## STRATEGIES TO PREVENT REACTIVATION OF OCCULT HBV INFECTION

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In patients with OBI, pharmacological prophylaxis with



**Figure 2** Management of occult hepatitis B infection in hematological and rheumatological diseases and in solid cancers. <sup>1</sup>Entecavir instead of Lamivudine, when appropriate. HBsAg: Hepatitis B surface antigen; ALT: Alanine aminotransferase; Anti-HBc: Hepatitis B core antigen; TNF- $\alpha$ : Tumor necrosis factors-alpha.

nucleot(s)ide analogues should be based on the HBV serological status (anti-HBc-positive or -negative), the underlying diseases (onco-hematological diseases, hematopoietic stem cell transplantation or others) and the type of immunosuppressive treatment (rituximab, high doses of corticosteroids, anthracyclines, or others). In anti-HBc-positive patients, the prophylaxis with anti-HBV nucleos(t)ide analogues is indicated in hematopoietic stem cell transplantation and in onco-hematological diseases when high doses of corticosteroids and rituximab are used, whereas monitoring is indicated in all other clinical conditions or when rituximab-sparing schedules are used (Figure 2). The literature data have shown the efficacy of lamivudine in preventing HBV reactivation in these subsets of patients<sup>[17,43,61]</sup>. Also entecavir has been proposed in the prophylaxis of reactivation of OBI. In a randomized controlled trial<sup>[89]</sup> 80 patients with CD20+ lymphoma and resolved hepatitis B were randomly assigned to a prophylactic schedule with entecavir, started before rituximab-based chemotherapy and stopped 3 mo after its discontinuation, or to be treated with entecavir once HBV reactivation and reversion to HBsAg positivity had occurred (control group). During an 18-mo follow up, HBV reactivation occurred in 2.4% of patients who underwent entecavir prophylaxis and in 17.9% of cases in the control group ( $P < 0.05$ ).

Although the efficacy of lamivudine and entecavir in preventing the reactivation of OBI has never been compared in published studies, we can conclude, in agreement with current international guidelines<sup>[2,76]</sup>, that lamivudine, despite of its low genetic barrier, remains the nucleos(t)ide analogue of choice for the prophylaxis of reactivation of OBI because of its low cost and of the low or absent HBV viremia in OBI. Instead, entecavir should replace lamivudine for patients with advanced liver diseases for whom reactivation of OBI might be life threatening.

Monitoring of pharmacological prophylaxis is not

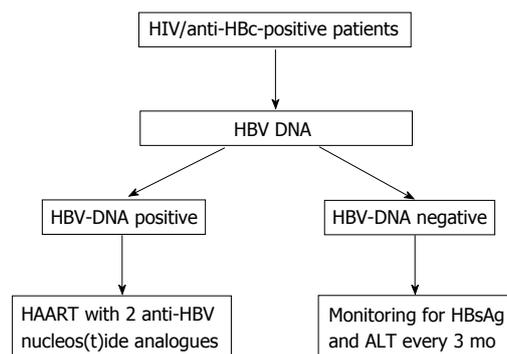
standardized and the widespread habit of determining HBsAg at three-monthly intervals is not the optimal strategy in all clinical conditions. In addition, it is not fully understood how long the pharmacological prophylaxis should last in order to prevent the reactivation of HBV infection. Observational studies suggest extending the prophylaxis to the 12<sup>th</sup> month after the discontinuation of immunosuppressive treatment, but in some case reports HBV reactivation occurred later, especially in patients treated with rituximab<sup>[39,90]</sup>. Recently, Tonziello *et al*<sup>[39]</sup> described a reactivation of OBI in an HBsAg-negative/anti-HBc-positive woman with non-Hodgkin lymphoma occurring 20 mo after rituximab discontinuation despite lamivudine prophylaxis covering the 4 mo of rituximab administration and the 12 mo after its discontinuation. Concluding on this point, prospective studies are needed to ascertain whether the pharmacological prophylaxis should be extended to the 18<sup>th</sup> month after the discontinuation of immunosuppressive treatment in patients receiving rituximab-based chemotherapy.

## MANAGEMENT OF REACTIVATION OF OCCULT HBV INFECTION

Once reactivation has occurred, effective antiviral treatment should be immediately administered. Lamivudine monotherapy has been demonstrated to be ineffective in reducing mortality<sup>[21]</sup>. Consequently, patients should be treated with drugs of high potency and high genetic barrier such as entecavir or tenofovir.

## OCCULT HBV INFECTION IN HIV-POSITIVE SUBJECTS

As a consequence of the availability of highly active antiretroviral therapy (HAART), which has determined a substantial improvement in the patients' survival, vi-



**Figure 3** Management of occult hepatitis B infection in anti-human immunodeficiency virus-positive subjects. HCV: Hepatitis C virus; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HAART: Highly active antiretroviral therapy; HBsAg: Hepatitis B surface antigen.

ral hepatitis has become the leading cause of morbidity and mortality in HIV-infected subjects. In these patients particular attention should be paid to OBI since it may have a strong clinical impact because of damage to the immune system and its frequent occurrence in HIV-HCV coinfecting patients.

## EPIDEMIOLOGY OF OBI IN HIV-POSITIVE SUBJECTS

The prevalence of OBI in HIV-infected patients is controversial, and the associated risk factors and the effect of HAART undefined. Also controversial is the role of the immune system in the genesis of OBI in HIV-positive patients. Some investigators never observed OBI in patients with CD4 counts > 500 cells/ $\mu$ L and concluded for a significant association of OBI with lower CD4 counts<sup>[91]</sup>. Other investigators, however, described no association of OBI with the CD4 count<sup>[92]</sup>.

The prevalence of OBI in HIV-HCV coinfecting patients varies in different studies from less than 1% to 40%<sup>[22,93-102]</sup>.

OBI may also be observed in anti-HIV-positive patients with chronic HBV/HCV coinfection, due to an HBsAg serum clearance consequent to a strong inhibitory effect of the HCV genome on HBV replication<sup>[103]</sup>.

In HIV subjects a strong association between OBI and HCV infection has been observed in several studies<sup>[28,101,104-106]</sup>. In contrast, Jardim *et al.*<sup>[107]</sup> reported no significant difference in the rate of OBI in HIV-positive patients with or without HCV coinfection.

The discrepancies in the rate of OBI in the different studies most probably reflect differences in HBV, HCV and HIV epidemiology in different countries, a variation in the sensitivity of the assays used to detect HBV DNA and the retrospective nature of some of the studies.

Cassini *et al.*<sup>[108]</sup> proposed a new approach to the detection of HBV DNA. By the genomic amplification of the partial S, X and precore/core regions, these Authors analyzed for the presence of HBV DNA the circulating blood, liver tissue and peripheral blood mononuclear cells

(PBMC). HBV DNA was never found in serum samples of the 24 HBsAg-negative patients investigated, but was detected in the liver tissue in 7 (29%) and in PBMC in 6 (86%) of these 7. The clinical value of these data should be confirmed in larger studies, but they suggest that the detection of HBV DNA in PBMC offers a useful tool to identify OBI. Morsica *et al.*<sup>[104]</sup> analyzed 1593 anti-HIV-positive patients enrolled in the Italian Cohort of Anti-retroviral Naïve patients and found 175 (11%) HBsAg-negative/anti-HBc-positive patients: 27 of these 175 (15%) patients had detectable HBV DNA in plasma. This prevalence was significantly higher (21%) in the 101 anti-HCV-positive than in the 74 (8%) anti-HCV-negative, regardless of the immune status, HIV load, or ART regimen.

## CLINICAL SIGNIFICANCE OF OBI IN HIV-POSITIVE SUBJECTS

The impact of OBI on the prognosis of HIV-positive patients is still unclear. In our previous study<sup>[22]</sup> on the clinical and virological impact of OBI in HIV-positive patients, we analyzed 115 HBsAg-negative patients, 86 of whom were observed in a long-term follow-up. A hepatic flare occurred more frequently in the 17 patients with occult HBV infection than in the 69 without (64.7% *vs* 24.6%;  $P < 0.005$ ). These preliminary data still await confirmation in larger studies.

Lamivudine-based HAART is effective in suppressing HBV replication even in anti-HIV-positive patients with OBI, as most of these cases clear HBV DNA during treatment. However, in approximately half of the lamivudine-treated patients, occult HBV replication became detectable again after 12-40 mo of lamivudine treatment, always associated with a hepatic flare. Although the presence of YMDD mutants in patients who became HBV-DNA-positive under lamivudine was not detected, most probably because of the low levels of plasma HBV DNA, the hypothesis that lamivudine induced the selection of YMDD mutants in these anti-HIV-positive subjects with OBI cannot be ruled out. In another study the ALT and aspartate aminotransferase levels showed a tendency to increase more frequently in patients with OBI than in those without<sup>[104]</sup>.

Concluding on this point, OBI seems relatively frequent in anti-HIV-positive patients, particularly in cases with HIV/HCV co-infection. This makes the clinical condition of HIV/HCV co-infection more complex since OBI may unfavorably affect the outcome of the liver disease. Lamivudine seems inadequate for a long-term prevention of hepatic flares in anti-HIV-positive patients with OBI and possibly in reducing the risk of HBV oncogenicity. Therefore, for these patients a high potency, high genetic barrier nucleos(t)ide analogue should be preferred (Figure 3).

## CONCLUSION

Clinicians should pay careful attention to OBI since it has

been demonstrated that it occurs with some frequency and may have clinical consequences.

Further studies are needed to better define the biological and clinical role of OBI and to identify new measures to prevent or limit its unfavorable clinical action. It would be of particular benefit to investigate the oncogenicity of OBI, particularly in anti-HIV-positive subjects, in order to devise new strategies for the prevention of HCC.

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