Hepatitis B Virus–HIV Coinfection: Forgotten but Not Gone

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Abstract: Owing to shared routes of transmission and common risk factors, coinfection with hepatitis B virus (HBV) and HIV is common. As AIDS-related opportunistic infections have declined with successful antiretroviral therapy (ART), liver-related mortality has emerged as the second leading cause of death among patients infected with HIV. HIV infection negatively impacts the natural history of HBV, increasing the risks for cirrhosis, hepatocellular carcinoma, and liver-related mortality. With the availability of effective antiviral therapy active against both HIV and HBV and simplified treatment algorithms, it has become easier than ever to treat coinfected patients. However, the issues of suboptimal response, incomplete viral suppression, adverse effects of long-term antiviral treatment, and potential hepatotoxicity of ART remain major challenges.

It is estimated that almost one-third of the world’s population (nearly 2 billion people) have been infected with the hepatitis B virus (HBV), and at least 240 million have chronic HBV infection.1 Conversely, approximately 35.3 million people worldwide are currently estimated to be living with HIV infection.2 Because of shared routes of transmission, HBV coinfection among HIV-positive persons is common. In some settings, more than two-thirds of HIV-infected persons have markers of past exposure to HBV.3 Worldwide, an estimated 2 to 4 million people (~10% of HIV-infected individuals) are currently living with HBV-HIV coinfection (Figure).4,5 The prevalence of HBV-HIV coinfection, however, varies widely (5%-20%), depending on the local endemicity and mode of acquisition of HBV infection. In the United States, Europe, and Australia, where HBV endemicity is low, both HIV and HBV infections are usually acquired in adulthood, either by injection drug use or via sexual transmission. The prevalence of HBV coinfection in these populations is estimated to be approximately 5% to 7%.6 In Asia and sub-Saharan Africa, where HBV endemicity is intermediate to high, HBV is acquired primarily in the perinatal period and early childhood, and HBV infection usually precedes HIV infection. The prevalence of coinfection in these populations is approximately 10% to 20%.6,7

Keywords
Cirrhosis, hepatitis B, HIV, HIV-HBV coinfection
In the United States, it is estimated that half of all patients with HIV infection have been exposed to HBV, and the prevalence of HBV coinfection in these persons is approximately 8%, which is 20 times higher than in the general US population. Of the more than 4400 HIV-infected persons tested in HOPS (HIV Outpatient Study), 8.4% tested positive for hepatitis B surface antigen (HBsAg) or had detectable HBV DNA levels in the time period of 1996 to 2007. Similarly, MACS (Multicenter AIDS Cohort Study) reported in 2002 that of 2559 HIV-infected individuals, 8.3% were coinfected with HBV. A higher prevalence was noted among men who have sex with men than in intravenous drug users and heterosexuals. The prevalence of HBV-HIV coinfection was greater among men than women, among non-Hispanics than Hispanics, and among patients aged 35 to 44 years than younger or older patients.

Natural History of Hepatitis B Virus Infection

The chronicity of HBV infection typically depends on the timing of the acquisition of the infection. Typically, more than 90% of those who acquire the infection during infancy and early childhood become chronically infected, whereas fewer than 10% of adults who acquire the infection become chronically infected. Chronic HBV infection is a slowly progressive disease that develops over many years, during which patients pass through various clinical phases classically described as immune-tolerant, immune-active, and chronic inactive states (Table 1). Chronic HBV infection can lead to cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease, all of which can lead to liver-related death.

Impact of HIV Infection on the Natural History and Clinical Outcome of Hepatitis B Virus Infection

HIV coinfection adversely affects the natural history of HBV infection at every stage and accelerates the progression of HBV disease. HIV coinfection is associated with the increased replication of HBV and increased levels of HBV DNA. Higher HBV DNA levels are associated with an increased risk for HCC. HIV-coinfected individuals are more likely than HBV-monoinfected individuals to transmit HBV, less likely to have spontaneous clearance, and up to 6 times more likely to progress to chronicity. HIV-coinfected individuals are also more likely to lose protective hepatitis B surface antibody (HBsAb) and experience reactivation of HBV infection, particularly when their CD4 counts are low. The progression of fibrosis is accelerated, and cirrhosis is more common among HIV-coinfected individuals despite low alanine aminotransferase (ALT) levels. The risk for HCC is believed to be much higher among patients coinfected with HBV-HIV. These patients are more likely than HBV-monoinfected individuals to die of liver-related causes.

The frequency and patterns of mutations in the HBV genome also differ between mono- and coinfected patients; however, the significance of these differences has not been well elucidated. One potential consequence of these mutations is incomplete viral suppression and the development of resistance, particularly under the selection pressure of long-term antiviral treatments. This issue is being addressed in ongoing studies. Additionally, antiretroviral therapy (ART) can lead to immune reconstitution syndrome, which can be both advantageous (increased seroconversion) and deleterious (increased liver injury and disease progression, also called immune reconstitution hepatitis), and the hepatotoxicity associated with ART can further accentuate HBV-associated liver disease among these individuals.

Impact of Hepatitis B Virus Infection on the Natural History and Clinical Outcome of HIV Infection

The impact of HBV on the natural history of HIV and AIDS, on the other hand, does not appear to be significant. Among patients receiving long-term ART, HBV status does not influence HIV suppression or CD4 counts. Before the era of ART, the morbidity and mortality associated with HIV infection dwarfed the complications of HBV infection. However, with major advances in ART, liver-related mortality has supplanted AIDS-related mortality as the second leading cause of death among HIV-infected persons.
All persons infected with HIV should be tested for evidence of HBV and hepatitis C virus (HCV) coinfection by serology and vice versa. As in HIV-negative individuals, the initial screening serologic test for HBV will include HBsAg, HBsAb, and hepatitis B core antibody (anti-HBc; total or immunoglobulin G). HBV coinfection is diagnosed by the detection of HBsAg or HBV DNA in the serum. The hepatitis B envelope antigen (HBeAg) may or may not be detectable and is not essential for diagnosis, but it is a valuable indicator of viral replication. Regardless, HBV DNA levels should be measured as a marker of viral replication independently of the patient’s HBeAg status. HBV genotyping is not essential in the management of these patients but may be useful.

Spontaneous seroreversion (disappearance of HBsAb and reappearance of HBsAg) has been reported among HIV-infected patients. This can occur especially if a patient’s CD4 cell count is very low (<200/mm³). Therefore, among HIV-infected individuals with prior positivity for HBsAb, HBV serologic tests should be repeated in the event of unexplained liver function abnormalities to rule out the reemergence of HBV infection. The various clinical stages of HBV infections are defined based on the patterns of HBV serologic test results (Table 2).

### Table 1. Clinical Phases of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT Level⁴</th>
<th>Serologic Markers</th>
<th>HBV DNA Level⁵</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant</td>
<td>Persistently normal</td>
<td>HBsAg+&lt;br&gt;HbsAb–&lt;br&gt;HBeAg+&lt;br&gt;Anti-HBe–</td>
<td>High</td>
<td>Asymptomatic&lt;br&gt;Usually young individuals</td>
</tr>
<tr>
<td>Immune active</td>
<td>Persistently high</td>
<td>HBsAg+&lt;br&gt;HbsAb–&lt;br&gt;HBeAg+/–&lt;br&gt;Anti-HBe+/–</td>
<td>Moderate to high</td>
<td>Symptomatic&lt;br&gt; Clinically diagnosed as chronic HBV</td>
</tr>
<tr>
<td>Chronic inactive</td>
<td>Normal to minimally elevated</td>
<td>HBsAg+&lt;br&gt;HbsAb–&lt;br&gt;HBeAg–&lt;br&gt;Anti-HBe–</td>
<td>Low to undetectable</td>
<td>Asymptomatic&lt;br&gt; Inactive histology but can have significant fibrosis</td>
</tr>
<tr>
<td>Reactivation</td>
<td>Elevated</td>
<td>HBsAg+&lt;br&gt;HbsAb–&lt;br&gt;HBeAg–&lt;br&gt;Anti-HBc IgM+</td>
<td>Elevated</td>
<td>Symptomatic&lt;br&gt; May behave like acute infection</td>
</tr>
</tbody>
</table>

⁴ Normal ALT level is <30 U/L for males and <20 U/L for females. ⁵ High HBV DNA level is >20,000 IU/mL, and low HBV DNA level is <2000 IU/mL.

ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B envelope antibody; HBeAg, hepatitis B envelope antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgM, immunoglobulin M.

### Diagnosis and Assessment of Hepatitis B Virus Coinfection in Patients With HIV Infection

All persons infected with HIV should be tested for evidence of HBV and hepatitis C virus (HCV) coinfection by serology and vice versa. As in HIV-negative individuals, the initial screening serologic test for HBV will include HBsAg, HBsAb, and hepatitis B core antibody (anti-HBc; total or immunoglobulin G). HBV coinfection is diagnosed by the detection of HBsAg or HBV DNA in the serum. The hepatitis B envelope antigen (HBeAg) may or may not be detectable and is not essential for diagnosis, but it is a valuable indicator of viral replication. Regardless, HBV DNA levels should be measured as a marker of viral replication independently of the patient’s HBeAg status. HBV genotyping is not essential in the management of these patients but may be useful.

Spontaneous seroreversion (disappearance of HBsAb and reappearance of HBsAg) has been reported among HIV-infected patients. This can occur especially if a patient’s CD4 cell count is very low (<200/mm³). Therefore, among HIV-infected individuals with prior positivity for HBsAb, HBV serologic tests should be repeated in the event of unexplained liver function abnormalities to rule out the reemergence of HBV infection. The various clinical stages of HBV infections are defined based on the patterns of HBV serologic test results (Table 2).

### Occult Hepatitis B Virus Infection

It is not uncommon among HIV patients to detect antibodies to the core protein (anti-HBc) in the absence of HBsAg or HBeAg or their antibodies. Although it is possible to have a false-positive core due to an anamnestic reaction to HBV vaccination, the presence of isolated core antibody among HIV-infected persons most likely results from past infection and should be further evaluated by measuring the HBV DNA level to rule out occult HBV infection. Occult HBV infection (the presence of HBV DNA in the absence of HBsAg) has been reported in 2% to 10% of HIV-infected persons. ALT and HBV DNA levels usually remain low in these patients. The clinical significance of occult HBV infection is not well understood, but accelerated disease progression has been reported. In addition, the role of vaccination remains unclear among such patients. However, many experts recommend vaccination for these individuals.

All HBV-infected individuals should be tested for HCV, hepatitis D or delta virus, and hepatitis A virus (HAV). Vaccination against HAV should be offered if the patient is not immune. All patients with newly diagnosed HBV infection should be asked about risk factors and evaluated for signs of underlying liver disease and cirrhosis. All persons coinfected with HBV-HIV should undergo serial liver ultrasound examinations and/or alpha-fetoprotein (AFP) serology every 6 months for HCC screening, irrespective of the presence of cirrhosis. Patients should be advised to abstain from alcohol and injection drug use completely as well as from high-risk sexual behavior. Patients should also be asked about any family history of HCC or other liver diseases. All household and sexual contacts should be screened for HBV seromarkers, and
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if the results are negative, vaccination should be offered. Lastly, because of the high morbidity of *Vibrio* infection, all those with chronic liver disease should be advised to avoid raw shellfish.

**Role of Liver Biopsy**
Histology is still the gold standard for the assessment of necroinflammatory activity and fibrosis. Liver biopsy will be particularly helpful in eliminating other causes of liver damage and for the diagnosis of cirrhosis. However, histologic evaluation by liver biopsy is not routinely recommended, although it should be considered in select cases. Noninvasive measures, such as serum fibrosis markers (eg, FibroSure) and transient elastography (FibroScan), can help determine the degree of underlying fibrosis and may be considered in lieu of liver biopsy. These tests have a high accuracy rate in detecting minimal fibrosis (F0-F2) and advanced fibrosis or cirrhosis, but not moderate fibrosis. Alternatively, fibrosis indices based on routine laboratory tests, such as FIB-4 and the AST-to-platelet ratio, can be used and may be as good as the above measures. Moreover, changes in the fibrosis score may be predictive of all-cause mortality among patients with HBV-HIV coinfection.

**Treatment**
The decision to treat chronic HBV infection in a patient with HIV coinfection must be based on a careful consideration of several factors, including the status of the underlying liver disease, the likelihood of response to antiviral therapy, the risks for adverse events, and the need for ART against HIV. Until recently, HBV treatment was recommended only for those with cirrhosis, low CD4 cell counts (<500/µL), high HBV DNA levels (>2000 IU/mL), and/or elevated liver enzyme levels. Because HIV infection can accelerate the progression of HBV-related liver disease, with adverse outcomes, and because the response to HBV therapy may diminish as immunodeficiency progresses, the current standard of care is to offer HBV treatment to all coinfectected patients irrespective of their need for ART. Furthermore, it is recommended that all HBV-coinfected patients start ART when their CD4 cell count is below 500/µL or regardless of their CD4 cell count in the presence of severe chronic liver disease, including cirrhosis and end-stage liver disease. This strategy has simplified once complex and often confusing treatment algorithms.

**Goals of Therapy**
The primary goal of HBV therapy among HIV-coinfected individuals is to prevent liver-related complications by sustained suppression of HBV replication to the lowest achievable level. The ideal treatment endpoint is a sustained loss of HBsAg while the patient is off therapy. Failing that, or in the case of HBeAg-negative patients, the next most desirable endpoint is a sustained virologic remission (HBV DNA levels that are undetectable by a sensitive polymerase chain reaction assay). However, treatment should generally be continued even after seroconversion because seroreversion and reactivation are possible. Other important goals are to minimize hepatotoxicity from antiretroviral agents and to avoid interference with HIV therapy.

**Antiviral Agents**
Several antiviral agents are approved for the treatment of HBV mono-infection. Of these, tenofovir (Viread, Gilead), emtricitabine (Emtriva, Gilead), and lamivudine also have antiretroviral activity against HIV and are approved
for the treatment of HIV infection. Entecavir appears to have weak antiretroviral activity. The others (interferon alfa, adefovir, and telbivudine [Tyzeka, Novartis]) do not have significant anti-HIV effects.\(^{30-33}\)

The choice of agents will largely depend on whether concurrent ART is to be used and whether the patients have had prior exposure to lamivudine. Monotherapy with tenofovir or entecavir is the treatment of choice for HBV-monoinfected patients. However, to prevent the emergence of resistant HBV strains, none of these agents should be used as the only agent with anti-HBV activity in coinfected patients.\(^{30-33}\)

The preferred regimen is tenofovir in combination with either emtricitabine or lamivudine (each of which will also act as the nucleoside reverse transcriptase inhibitor backbone of ART), along with a third agent, a nonnucleoside reverse transcriptase inhibitor such as efavirenz (Sustiva, Bristol-Myers Squibb).\(^{32-33}\) In the event of prior lamivudine exposure or resistance, tenofovir plus emtricitabine should be used. This combination comes as a single pill (Truvada, Gilead) and is the preferred agent for most of these patients.

In case tenofovir cannot be used (eg, because of bone or renal toxicity), entecavir can be used as a substitute. Because entecavir displays weak antiretroviral activity and can select resistant HIV mutations, it should be used only in the context of fully suppressive ART. In persons with prior exposure to lamivudine, the dose of entecavir should be increased to 1 mg/kg. However, because entecavir resistance can develop rapidly, such patients should be closely monitored, with HBV DNA levels measured every 3 months.\(^{32}\) Other alternate regimens include peginterferon monotherapy and adefovir in combination with emtricitabine or lamivudine in addition to a fully suppressive ART regimen; however, data regarding these approaches are limited.

When there is no indication for ART and only HBV therapy is to be started, agents with no antiretroviral activity should be used. Low-dose adefovir and telbivudine can be used, but they are not considered first-line agents against HBV. Peginterferon alfa may be used in this setting as long as there are no contraindications, such as cirrhosis. Peginterferon alfa is best suited for patients who are HBeAg positive, have low HBV DNA levels and high ALT levels, are infected with HBV genotype A, and have CD4 cell counts above 500/µL.\(^{30-32}\) Agents with antiretroviral activity (tenofovir, emtricitabine, lamivudine, and entecavir) should be avoided in this setting because they can lead to the selection of resistant HIV strains.

### Monitoring of Response

All patients on antiviral therapy should be closely monitored for treatment response and for potential adverse events. Ideally, treatment should be closely coordinated by an infectious disease specialist and a hepatologist experienced in managing coinfected patients. All patients on antiviral therapy should have their liver function tests and HBV DNA levels monitored frequently. Serum ALT levels and HBV DNA levels should be tested at least every 3 to 6 months. For patients who are HBeAg positive, both HBeAg and hepatitis B envelope antibody (anti-HBe) should be tested every 6 months to monitor for seroconversion.\(^{30-33}\) Long-term HBV therapy is recommended for HIV-coinfected patients regardless of HBeAg seroconversion. Knowledge of seroconversion, nonetheless, may be helpful in predicting HBsAg loss/seroconversion and HBV DNA suppression. Although uncommon, HBsAg seroclearance is confined mostly to patients who achieve HBeAg seroconversion. On the other hand, persistent HBeAg seropositivity and low CD4 cell counts are associated with the detection of persistent HBV DNA and are predictors of a poor response to tenofovir.\(^{51,52}\) For HBeAg-negative patients, monitoring of HBeAg or anti-HBe is not necessary. Annual testing of HBsAg to evaluate for HBsAg seroconversion is recommended. Quantitative serum levels of HBsAg have been shown to correlate with hepatic HBV DNA levels\(^{33}\) and may be useful in monitoring response to HBV therapy. However, more data are needed before recommendations for routinely monitoring HBsAg levels can be made.

Discontinuation of agents with anti-HBV activity can result in the reactivation of HBV, leading to serious hepatocellular injury. Patients should be advised against discontinuing medications on their own and should be monitored closely during any interruptions in HBV therapy. If an ART modification is needed because of intolerance or lack of efficacy, the anti-HBV component should be continued to prevent the reactivation of HBV, even if this will not be part of the subsequent anti-HIV regimen.

Immune reconstitution can occur following the initiation of ART against HIV. This usually occurs within 4 to 8 weeks of the start of ART, is characterized by a rapid decline in HIV RNA levels and a rise in CD4 cell counts, and can lead to an exacerbation of HBV-related liver disease. Some experts recommend initiating HBV therapy before ART, especially if HBV DNA levels are very high; however, there are no data to support this notion.

### Outcome of Antiviral Treatment

The virologic outcomes of tenofovir treatment against HBV are defined by various terminologies (Table 3).\(^{31}\) Patients with HBV-HIV coinfection generally have higher baseline HBV DNA levels and generally take longer to achieve a virologic response (delayed response). Although earlier studies showed that a majority (~90%) of patients on tenofovir-based ART achieve complete sup-
pression of HBV DNA to undetectable levels after 3 to 5 years of therapy, more recent and larger multicenter prospective studies suggest that up to 50% of patients with HBV-HIV coinfection may have detectable HBV DNA levels despite ART that includes tenofovir (21% at 2.8 years; 52% at 28 months). The exact reason for this suboptimal response is not clear. Prior exposure to lamivudine, poor adherence to therapy, high HBV DNA levels, HBeAg seropositivity, and low CD4 cell counts are among the factors associated with incomplete HBV DNA suppression. To date, tenofovir resistance leading to a suboptimal response has not been reported.

Likewise, HBeAg seroconversion and HBsAg loss may not be as common as they are in monoinfected patients. HBeAg seroconversion and HBsAg loss have been reported in 15% to 57% and 8% to 29%, respectively, of coinfected patients over 5 years of tenofovir treatment, mostly confined to HBeAg-positive patients with high CD4 cell counts. This finding suggests the importance of immune restoration in HBV clearance.

### Resistance to Treatment

All nucleoside reverse transcriptase inhibitors may select resistant mutations in the HBV polymerase, leading to a loss of response and cross-resistance to other, closely related antiviral agents. Lamivudine has the lowest barrier to resistance, and the emergence of resistant mutations is noted in up to 90% of patients with HIV coinfection at 4 years of monotherapy, a rate much higher than that among patients with HBV monoinfection. This increased resistance among HIV-coinfected patients is likely due to higher serum HBV DNA levels. The rates are approximately 20% in 2 years for telbivudine and 29% in 5 years for adefovir. Entecavir and tenofovir exhibit the highest barriers to resistance. To date, no clinically significant mutations resistant to tenofovir have been demonstrated in vivo. The antiviral efficacy of tenofovir does not seem to be affected by prior lamivudine exposure and lamivudine resistance. Although entecavir resistance is very rare in naive individuals, it may develop in nearly half of patients with previous lamivudine failure after 5 years of treatment.

### Adverse Events

Although generally well tolerated, tenofovir may be associated with renal tubular abnormalities, including Fanconi syndrome and overt renal failure. Among HIV-infected patients, the long-term use of tenofovir has also been associated with bone demineralization, osteopenia, and increased risk for fractures.

### Renal Toxicity

Increases in serum creatinine levels have been reported with the use of tenofovir. In a multicenter prospective cohort study of 102 patients coinfected with HBV-HIV and treated with tenofovir, a modest decrease in renal function (9.8 mL/min/1.73 m²) was observed over 5 years, which occurred early in the course and was nonprogressive. Significant events necessitating discontinuation of the drug occurred only rarely (3%). In a meta-analysis of 17 studies, Cooper and colleagues found a significantly greater loss of kidney function among the tenofovir recipients in comparison with control subjects (mean difference in calculated creatinine clearance, 3.92 mL/min; 95% CI, 2.13-5.70 mL/min). The effect of tenofovir on renal function was greater in patients coinfected with HBV-HIV who had advanced fibrosis. Very rarely (~0.4%), tenofovir has been associated with Fanconi syndrome (amino aciduria, tubular proteinuria, phosphaturia, glycosuria, and bicarbonate wasting), particularly when used concomitantly with HIV protease inhibitors. The mechanism of renal tubular dysfunction is unclear but may be related to specific mitochondrial DNA toxicity, gene polymorphisms, and/or drug interactions affecting the transport of tenofovir across the renal proximal tubule. Although the optimal test for the evaluation of tenofovir-related renal toxicity remains to be defined, the close monitoring of serum creatinine is important, especially early in the course of treatment.
**Bone Toxicity**
Exposure to tenofovir has been associated with decreased bone density and increased osteoporotic fractures among both HIV-infected persons on tenofovir therapy and HIV-uninfected persons receiving tenofovir for pre-exposure prophylaxis.64,65 These effects on bone are believed to be due to renal phosphate wasting secondary to proximal renal tubulopathy; however, the exact mechanisms underlying the effect of tenofovir on bone mineralization remain unclear. Of note, tenofovir has been shown to alter gene expression in both osteoclasts and osteoblasts in vitro.66 The management of skeletal health should follow the standard guidelines. Important parts of management include adequate nutrition and repletion of deficient micronutrients.

**Hepatotoxicity of Antiretroviral Therapy**
The incidence of hepatotoxicity in patients taking ART is approximately 4.5% to 11%.67 The risk is generally low but can be significant among HBV- or HCV-coinfected patients, particularly if they have high baseline ALT levels and/or underlying liver dysfunction. Almost all ART agents are associated with hepatotoxicity. The most common ones include ritonavir (Norvir, AbbVie), tipranavir (Aptivus, Boehringer Ingelheim), darunavir (Prezista, Janssen), nevirapine, zidovudine, stavudine, and didanosine. The effect is usually modest but at times can lead to severe microvesicular steatosis and lactic acidosis. If the liver injury is mild to moderate (eg, ALT level <5 times the upper limit of normal), the same ART regimen may be continued with close monitoring of liver enzymes. When hepatotoxicity is severe, the ART regimen should be switched to one with a lower risk for hepatotoxicity.68

**Prevention of Coinfection**
The HBV status of all HIV-infected patients should be screened by serology. If the patient is not immune, vaccination should be offered. Despite the wide availability of the HBV vaccine, the immunization status of HIV-infected individuals is not satisfactory. According to HOPS, only 5.8%, 23.4%, and 31.6% of eligible patients had received at least 1 dose of HBV vaccine by the years 1996, 2002, and 2007, respectively. HBV vaccination is recommended for all patients with HIV infection who are negative for HBsAg and HBsAb. Response to the vaccine depends on CD4 cell counts, with a response rate of approximately 25% in patients with CD4 cell counts below 200/µL.69 An HBsAb level above 10 IU/L is considered protective. In case of an insufficient response, repeated vaccination with a double dose and/or an extra dose at 1 year may improve response.70 Patients who fail to achieve immunity should have annual tests for HBV serology because they remain at risk for HBV infection. All household and sexual contacts of HBV-infected persons should be screened for HBV seromarkers, and if the results are negative, vaccination should be offered.

**Monitoring for Hepatocellular Carcinoma**
HBV-infected persons are at risk for the development of HCC, even in the absence of cirrhosis.30 The risk depends on the duration of infection and the presence of advanced fibrosis, and it is higher in those with elevated HBV DNA levels,12 particularly Asians and Africans. Society guidelines recommend surveillance for HCC among all Asian men older than 40 years, all Asian women older than 50 years, and all Africans older than 20 years with chronic HBV infection.30,31 Although the evidence characterizing the course and progress of HCC among patients coinfected with HIV is limited, HIV coinfection is believed to increase the risk for HCC and accelerate the course of advanced liver disease among patients with chronic HBV infection.19,20 Patients with HIV coinfection and HCC tend to be younger and to become symptomatic earlier in the course than their HIV-uninfected counterparts.71 However, these patients will have a comparable survival if HCC is recognized at an early stage with the institution of potentially curative therapy.71 Therefore, the institution of an HCC screening protocol in all patients with HBV-HIV coinfection should be stressed irrespective of their age or the presence of cirrhosis. In the absence of guidelines specific to patients with HBV-HIV coinfection, these patients should be screened and should undergo surveillance at least as frequently as any other patients with chronic hepatitis and/or cirrhosis. Accordingly, they should undergo HCC surveillance with liver ultrasound at least every 6 months with or without the concurrent measurement of serum AFP.2 In the event of suspicious sonographic findings, the ultrasound should be followed by multiphase contrast computed tomography (CT) or magnetic resonance imaging (MRI) dedicated to rule out HCC. Enhanced surveillance with ultrasound every 3 months is often performed for patients with nodules smaller than 10 mm, which are too small to be well characterized by contrast CT or MRI.2 Although the sustained suppression of viral DNA by antiviral therapy is reported to reduce the risk for HCC,12 the risk is not completely eliminated. All patients, therefore, should undergo HCC surveillance with the same intensity, irrespective of the extent and duration of antiviral suppression.

**Conclusion**
Despite significant improvement in the diagnostics and therapeutics of both HIV and HBV infections in the past
2 decades, HBV-HIV coinfection remains a unique challenge to clinicians and scientists. Treatment algorithms have evolved and have simplified this once complex and confusing territory. Because most coinfected patients are on tenofovir-based ART with suppressed HBV and normal ALT levels, HIV providers may fail to keep in mind that these patients still have chronic HBV infection, may have acquired significant fibrosis during the period when their HBV was not controlled, and are still at risk for HCC and liver-related morbidity and mortality. Furthermore, several issues remain unresolved and require ongoing research and refinement. The role of emerging noninvasive biomarkers in the assessment of liver fibrosis and cirrhosis is evolving, but it is yet to be seen if they will obviate the need for liver biopsy among coinfected patients. Likewise, despite highly active antiviral therapy, incomplete viral suppression remains a concern, and the factors leading to suboptimal response warrant further research. The need for long-term treatment poses unique challenges related to adherence to therapy and raises safety concerns. Another unsettled issue includes the clinical significance and management of occult HBV coinfection. The role of liver transplant for HIV-coinfected patients with end-stage liver disease continues to evolve, but studies show excellent outcomes for these patients.73,74

The authors have no relevant conflicts of interest to disclose.

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