

## Case Report

# Hepatitis B Virus and HIV Coinfection

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## Abstract and Introduction

### Abstract

Coinfection with HIV and hepatitis B virus (HBV) is more common than that with HIV and hepatitis C virus (HCV), although more attention has been given to HCV coinfection as a result of its higher frequency of chronic disease. Natural history studies with HIV-HCV coinfection have also shown more rapid progression of liver disease, and end-stage liver disease due to hepatitis C is now a leading cause of death in HIV-infected patients. Like HCV infection, HBV infection can also be associated with significant morbidity and mortality in patients with HIV infection. Fortunately, treatment options for hepatitis B are expanding and may have a clinical impact on slowing disease progression. A case study of a patient with severe HBV-HIV coinfection is presented to illustrate what is known about this increasingly problematic disease state.

### Introduction

Much attention has been given to HIV and hepatitis C virus (HCV) coinfection because of its strong association with excess mortality in the HAART era.<sup>[1]</sup> However, chronic coinfection with HIV and hepatitis B virus (HBV) is also likely to become an important cause of end-stage liver disease and mortality. The following case study and review of the literature examines this problematic coinfection in patients with HIV/AIDS.

### Case Summary

A 48-year-old incarcerated white male former injection drug user with chronic HBV (serum hepatitis B surface antigen [HBsAg]-positive) and HIV coinfection presented to the emergency department with a 10-day history of increasing abdominal girth and a 3- to 4-day history of right upper quadrant and midepigastic abdominal pain. He noted a 10- to 15-lb (4.5- to 6.8-kg) weight loss in the past year but denied nausea, vomiting, diarrhea, and jaundice. His most recent CD4<sup>+</sup> cell count was 379/ $\mu$ L with a viral load of less than 400 HIV RNA copies/mL while he was taking zidovudine, stavudine, lamivudine (3TC), and saquinavir soft-gel capsules for the past 4 years. His CD4<sup>+</sup> cell count nadir was 300/ $\mu$ L, and he had no history of opportunistic infections. His medical history was notable for a positive HCV antibody test and confirmatory radioimmunoblot assay but an undetectable HCV viral load by polymerase chain reaction. He had not had a previous evaluation for liver disease.

On physical examination, his abdomen was moderately distended, with marked tenderness in the right upper quadrant, and both his liver and spleen were 5 cm below the costal margin. Laboratory assessment showed the following: platelet count, 92,000/ $\mu$ L (normal, greater than 130,000/ $\mu$ L); prothrombin time, 14.1 seconds (normal, 10.3 to 12.3 seconds); serum albumin, 1.7 g/dL (normal, 3.5 to 5.2 g/dL); total and direct bilirubin, 1.5 and 0.6 mg/dL, respectively (normal, 0.1 to 1.2 mg/dL and less than 0.3 mg/dL); serum alkaline phosphatase, 134 IU/L (normal, 30 to 115 IU/L); serum aspartate and alanine transaminases, 70 and 39 IU/L, respectively (normal, 5 to 45 IU/L and 5 to 60 IU/L); and normal pancreatic enzyme and serum lactate levels.

The presumptive diagnosis was end-stage liver disease and cirrhosis. An abdominal ultrasonographic

examination revealed a large, right hepatic lobe mass and adjacent malignant portal vein thrombosis consistent with hepatocellular carcinoma (HCC), splenomegaly, and marked ascites. The patient's antiretroviral therapy was stopped, and diuretics and narcotic analgesics were started. A serum  $\alpha$ -fetoprotein test revealed a markedly elevated level of 4700 ng/mL (normal, 0 to 9 ng/mL), confirming the diagnosis of HCC secondary to chronic HBV infection. Oncologic consultation recommended palliative care. The patient died 2 months later.

## Discussion

More than 1.25 million people in the United States (0.3%) have chronic hepatitis B, with approximately 335,000 new infections reported each year.<sup>[2]</sup> Among the African American population, 12% have been exposed to HBV, while 3% of whites have been. HBV is primarily transmitted via blood exposure (injection drug use, needle stick injury) or sexual activity. During acute and chronic infection, HBV DNA can be detected in blood, saliva, and genital secretions. In the United States, chronic HBV infection causes approximately 5000 deaths per year as a result of cirrhosis or HCC.

Among HIV-infected persons, 90% to 95% have serologic evidence of past or current HBV infection, and approximately 10% to 15% are chronic carriers.<sup>[3-5]</sup> A chronic carrier of HBV may be defined as a person with persistent serologic evidence of HBsAg. However, 10% to 40% of persons with hepatitis B core antibody (HBcAb) but without HBsAg are in fact chronic HBV carriers, as evidenced by the presence of HBV DNA.<sup>[6]</sup> Coinfection with HIV increases the likelihood of a patient with acute HBV infection becoming a chronic carrier by 3- to 6-fold. This is especially true in patients with low CD4<sup>+</sup> cell counts.<sup>[7,8]</sup> These epidemiologic findings stress the importance of prevention of HBV infection in HIV-infected persons through risk reduction, vaccination, or both. Although vaccination is recommended for those with HIV infection who are not immune to HBV, it is important to note that response rates are significantly lower than rates in immunocompetent hosts.<sup>[9]</sup>

HBV is a DNA virus that belongs to the Hepadnaviridae family. After HBV infects a hepatocyte, viral messenger RNA is produced and then undergoes reverse transcription by the HBV DNA polymerase to form new viral DNA. The viral DNA associates with core particles, producing an infectious virion.<sup>[2]</sup> During the initial phase of HBV infection, persons are asymptomatic, because even though the virus is actively replicating, hepatocellular damage is not occurring. The hepatitis B core antigen-derived peptides are then expressed on the surface of hepatocytes, leading to immune recognition and destruction of infected cells by CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs). The CTL response may cause an increase in liver function test parameters, although patients can remain asymptomatic.

Clearance of the infection occurs next with production of anti-HBe antibodies (HBeAb). With subsequent development of anti-HBs antibodies (HBsAb), the patient is rendered immune to HBV. During these latter 2 stages of the immune response, transaminase levels return to normal. There have been several reported cases of HBV reactivation among persons with HIV infection despite their previously having had HBsAb and/or HBcAb. These cases were thought to occur because of a decline in and loss of HBsAb over time as a result of immune deficiency.<sup>[10]</sup> A summary of serologic markers of HBV and their clinical significance is included in the table.

**Table. Interpretation of Hepatitis B Serologic Marker Test Results**

Test	Result	Interpretation
HBsAg	Negative	Patient susceptible to HBV infection
HBcAb	Negative	
HBsAb	Negative	

HBsAg	Negative	Patient immune as result of natural HBV infection
HBcAb	Positive	
HBsAb	Positive	
HBsAg	Negative	Patient immune as result of HBV vaccination
HBcAb	Negative	
HBsAb	Positive	
HBsAg	Positive	Patient acutely infected
HBcAb	Positive	
HBcAb IgM	Positive	
HBsAb	Negative	
HBsAg	Positive	
HBsAg	Positive	Patient has chronic HBV infection
HBcAb	Positive	
HBcAb IgM	Negative	
HBsAb	Negative	
HBsAg	Positive	

HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus.

Adapted from Centers for Disease Control and Prevention. 2002.<sup>[31]</sup>

If after HBV infection HBeAb and HBsAb are not produced and HBsAg and HBV DNA persist for more than 6 months, the person is classified as having chronic HBV infection. These patients are usually asymptomatic and have fluctuating transaminase levels, but liver biopsy shows active inflammation with hepatocellular necrosis. The severity of inflammation and necrosis will vary among patients, leading to differing rates of fibrosis and cirrhosis. In patients with chronic HBV infection, there is an estimated 12% annual probability of the development of cirrhosis.<sup>[2]</sup>

The influence of HIV coinfection on the course of chronic HBV infection is unsettled. Early studies in patients with HBV-HIV coinfection did not find a significant acceleration of histologic liver damage believed to be a result of immune compromise and the lack of a CTL response to HBV that is required for hepatocellular necrosis.<sup>[11]</sup> More recent studies, however, suggest that the course of chronic HBV infection is accelerated in HIV-coinfected patients as a result of higher HBV viral loads in such patients.<sup>[7]</sup> Conversely, chronic HBV infection does not appear to influence the course of HIV infection.<sup>[3]</sup>

HAART may have an effect on HBV infection. While all antiretroviral agents may be directly hepatotoxic and cause elevations in transaminase levels in patients with chronic hepatitis, HAART-induced immune reconstitution can also cause an initial flare of the transaminase levels. This is the result of an enhanced CTL response, which is followed by normalization of the transaminase levels and clearance of HBV DNA.

The development of HCC has been clearly linked to the presence of chronic HBV infection. HCC is usually preceded by the development of cirrhosis and represents end-stage HBV infection that has been ongoing for 20 to 30 years. The relative risk of the development of HCC in a patient with chronic HBV infection ranges from 5% to 20%. Concurrent cigarette smoking and alcoholism, as well as HCV coinfection, have also been associated with an increased risk of HCC.<sup>[12]</sup>

The HIV-HBV-coinfected patient may also be infected with hepatitis delta virus (HDV) and/or HCV. HDV is a defective virus that requires HBV to replicate and cause disease. HBV-HDV coinfection is associated with worsening liver disease and is less likely to respond to treatment. A diagnosis of coinfection with HDV is made by checking for the presence of HDV antibody. In contrast, patients coinfecting with HBV and HCV

seem to suppress HBV replication; therefore, HCV infection appears to predominate.<sup>[13]</sup> Determination of both HBV and HCV loads will clarify which virus is causing active disease.

The goals of treating HBV infection are to eradicate the virus and prevent progression to cirrhosis and HCC. As with HIV infection, options for the treatment of chronic HBV infection are progressing, and combination therapy will likely become the treatment of choice. Initially, high-dose interferon alfa-2b (IFN alfa-2b), 10 million units subcutaneously thrice weekly or 5 million units subcutaneously daily for 4 months, was the only treatment option. IFN alfa-2b acts by directly inhibiting HBV replication and enhancing CTL response to HBV. Although approximately 40% of patients have an end-of-treatment response, in only about 10% is the virus completely eradicated.<sup>[14]</sup> Unfortunately, IFN alfa-2b treatment alone in patients with HBV-HIV coinfection is unlikely to eradicate HBV.<sup>[3]</sup>

3TC is a nucleoside analogue used successfully in the treatment of HIV infection.<sup>[15-17]</sup> 3TC inhibits HIV reverse transcriptase but also HBV DNA polymerase, the enzyme responsible for reverse transcription of HBV messenger RNA. Because of its direct anti-HBV activity, treatment with 3TC may lead to normalization of transaminase levels, and treatment for 1 year results in high rates of HBV DNA suppression and significant histologic improvement.<sup>[18]</sup> Abrupt discontinuation of 3TC in HBV-infected patients has resulted in severe hepatitis flares and should be avoided.<sup>[19,20]</sup> In the HBV-HIV-coinfected patient, using 3TC as part of the antiretroviral regimen to reconstitute the immune system while at the same time inhibiting HBV replication may be an opportunity to eradicate HBV.<sup>[21]</sup> Long-term follow-up of these patients to determine the incidence of eradication of HBsAg is under way.

Despite its efficacy, 3TC monotherapy has been associated with the development of resistant viral mutants. The most common mutation associated with 3TC use occurs in the YMDD motif of the HBV DNA polymerase. This mutant strain of HBV occurs in up to 32% of patients treated for 1 year; the cumulative incidence approaches 50% after 3 years of therapy.<sup>[22]</sup> Case reports of fulminant hepatic necrosis and death in patients harboring the YMDD mutant strains have been described.<sup>[23,24]</sup> For patients infected with the YMDD mutant of HBV, efficacy data are available on the use of tenofovir disoproxil fumarate (TDF) and adefovir dipivoxil.<sup>[25-28]</sup>

Bochet and colleagues<sup>[26]</sup> described an open-label study where TDF, 300 mg/d, was added to therapy with 3TC, 150 mg twice daily, in 10 patients with YMDD-mutant HBV. At 12 weeks, they found that the addition of TDF to 3TC had activity against HBV, evidenced by significant reductions in serum HBV DNA levels. Similarly, adefovir dipivoxil has also been added to 3TC therapy in patients with the YMDD-mutant HBV with success. Benhamou and colleagues<sup>[27]</sup> evaluated the addition of adefovir dipivoxil, 10 mg/d, to 3TC, 150 mg twice daily, in 35 HIV-1-HBV-coinfected patients in an open-label trial. Adefovir was shown to reduce HBV DNA concentrations at a median 48 weeks.

Adefovir dipivoxil, a nucleotide HIV reverse transcriptase and HBV DNA polymerase inhibitor, has also been used in patients without 3TC resistance and is undergoing the final phase of clinical evaluation.<sup>[29]</sup> Although adefovir is associated with nephrotoxicity at dosages of 60 to 120 mg/d when used to treat HIV infection, low-dosage adefovir (10 mg/d) appears to be both safe and effective as therapy for HBV infection.

Famciclovir, a nucleoside analogue approved for the treatment of herpes simplex and varicella-zoster virus infection, also inhibits HBV DNA polymerase but is less efficacious than 3TC. Although famciclovir is not indicated for the treatment of chronic HBV infection, investigations of famciclovir in combination with 3TC or interferon are under way.

In addition to medical treatment of HBV infection, liver transplantation also may be appropriate in those with cirrhosis. Roland and associates<sup>[30]</sup> presented data identifying 10 subjects eligible for liver transplantation from 8 US medical centers that suggest that in the era of HAART, survival and functional-graft rates in HIV-infected transplant recipients appear to be acceptable. As new and improved agents in HAART continue to prolong survival, the use of liver transplantation for cirrhotic patients coinfecting with HIV and HBV may

increase.

## Conclusions

Chronic HBV infection represents another potential comorbidity for the patient with HIV infection. Chronic immunodeficiency combined with coinfections and the use of hepatotoxic agents is likely to lead to poor outcomes such as those in the case described. Just as we have begun to more aggressively manage coinfection with HCV, we must do the same for coinfection with HBV, in light of treatment advances for both HIV and HBV infection. When HAART is indicated, use of 3TC and/or tenofovir as part of the regimen should be considered for patients coinfecting with HIV and HBV.

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## Editorial Comment: A Tale of Two Viruses

It is the best of times for new drugs for hepatitis B, and it is the worst of times because of nucleoside analogue-resistant hepatitis B. New nucleoside analogues for hepatitis B are being produced at a rapid pace. Many of these new drugs, such as adefovir and tenofovir disoproxil fumarate (TDF), are active against lamivudine (3TC)-resistant hepatitis B virus (HBV) even in HIV-infected patients,<sup>[1-4]</sup> and the investigational drug emtricitabine (FTC) may cause less resistance than has been reported for 3TC.<sup>[5]</sup> That is the good news.

The bad news is that only about 14% of the 13,012 persons in the Adult/Adolescent Spectrum of Disease Study received more than 1 dose of HBV vaccine.<sup>[6]</sup> That is a shameful rate of vaccination in a high-risk, sexually active group with about a 5-fold higher rate of HBV infection than the overall population. More bad news is that 60% of HIV-HBV-coinfecting patients demonstrated HBV replication while receiving treatment with 3TC, although 45% actually had the demonstrable mutations consistent with 3TC resistance.<sup>[7]</sup>

How do we deal with this issue in the real world? First and foremost, we must vaccinate our HIV patients for both HBV and hepatitis A virus. The frequency of vaccination would be helped by insurers' policies, particularly government insurers, regarding payment for vaccines for adults and children with HIV infection. Vaccination rates and reimbursement rates, if vaccine costs are reimbursed at all, are woefully inadequate in this day and age.

Next is the issue of the patients we see on a daily basis. How do we deal with them? What have we learned from HIV that can help us better understand HBV? The early days of HIV treatment were characterized by nucleoside analogue sequential monotherapy leading to multidrug-resistant viruses. HBV, while a DNA virus, essentially is a "closet" retrovirus because it uses a reverse transcriptase enzyme. Mutations in this gene can cause nucleoside analogue resistance just as in HIV. In HIV-HBV-coinfecting patients, these mutations occur

at a much more rapid rate. So, how do we deal with HBV infection in HIV-infected patients?

In treatment-naive HIV-HBV-coinfected patients who have low viral loads and high CD4<sup>+</sup> cell counts and who would not ordinarily be treated for HIV infection, we should evaluate hepatitis B as we do in HIV-negative patients: with ultrasonography, liver biopsy, and an  $\alpha$ -fetoprotein test to rule out hepatocellular carcinoma. Then, if we decide to treat with nucleoside analogues, we need to use more than 1 that is active against HBV and more than 2 that are active against HIV. A logical combination might be zidovudine (ZDV)-3TC plus TDF. This may even be considered as a once-daily regimen based on pharmacokinetic data presented recently on once-daily ZDV. Other possible regimens include stavudine (d4T)-3TC plus TDF, with use of the extended-release formulation of d4T possibly allowing once-daily dosing as well. TDF and didanosine (ddI) interactions may preclude using those 2 drugs together because TDF raises ddI levels by 50% to 70%. This may be even more of an issue in persons with liver disease, because increasing ddI levels may increase mitochondrial toxicity in both the pancreas and the liver.

In the treatment-naive HIV-HBV-coinfected patient who needs HIV treatment, the situation may be different. If one is using a nonnucleoside analogue or a protease inhibitor with a 3TC-containing nucleoside backbone, then the hepatitis B is only being treated with monotherapy. There are some data suggesting 3TC synergism with famciclovir. I would favor using that drug along with 3TC for this group of patients. If a triple-nucleoside regimen can be used, then ZDV-3TC-abacavir (ABC) plus TDF is a good choice. (If one wanted to save TDF until later, the ZDV-3TC-ABC combination plus famciclovir might be effective in providing at least 2 drugs for hepatitis B and 3 for the HIV infection.)

In the treatment-experienced HIV-infected patient with HBV infection who has been receiving 3TC for a long time, how do we measure resistance? We do not have to do HBV genotyping; we can just measure HBV DNA by polymerase chain reaction (PCR). (Remember that the old assay is measured in picograms per milliliter and PCR is in copies. One picogram is equivalent to 150,000 to 250,000 copies of HBV DNA.) Less than 50,000 copies of HBV DNA is probably an insignificant level of virus, depending, of course, on the clinical situation and the biopsy results. If the HBV DNA level is greater than 50,000 copies when the patient is receiving 3TC, then it would be prudent to add TDF to the regimen. TDF has activity against 3TC-resistant virus, and HBV has not demonstrated any resistance yet to TDF. If HIV disease is under control, the question is: Do we continue the 3TC or stop it? There are no data yet on this, although studies are planned. My personal approach is to leave 3TC therapy in place. There is little downside and perhaps some additive activity against HBV. Encouraging, too, is the low in vitro mitochondrial toxicity rate of TDF. In other patients whose HIV is already undetectable, if you add TDF to the regimen, can you discontinue 1 of the other nucleosides (other than 3TC)? This is another good question that needs a study. My thought now is to wait a month or so and then discontinue 1 of the other nucleosides that may have more propensity for long-term toxicity.

Finally, what end point are we using in treating these patients? Generally, in HBV treatment the goal is hepatitis B e antigen to hepatitis B e antibody seroconversion. When that occurs, there is immunologic control of viral replication. This seroconversion is often accompanied by a transient increase in liver enzyme levels (aspartate aminotransferase/alanine aminotransferase) and even a clinical syndrome. This can happen in coinfecting HIV patients, but can we stop HBV therapy then? The answer to this is also uncertain and should be guided by HBV DNA levels and another trial. For now, HIV treatment is lifelong, and HBV treatment may also need to be. We just don't know at present. Hepatitis B is a much more complicated subject in this regard than either HIV infection or hepatitis C. I would urge all of us to stay up-to-date on new drugs and resistance in HBV and to use the lessons we learned from HIV to combat this other potentially deadly virus.

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