Hepatitis B in Patients Coinfected with HIV

Maximo Brito, MD
Mohammed Alhyraba, MD

Hepatitis B virus (HBV) and HIV are often found coinfecting a single patient because the pathogens share transmission routes. The prevalence of HBV/HIV coinfection varies by geographic region and risk factor exposure, but studies suggest that up to 10% of patients with HIV have chronic HBV coinfection.[1,2]

The impact of HIV infection on the course and outcome of HBV infection is considerable. Infection with HIV not only increases the risk that a person will progress from acute infection to chronic HBV infection, but can also accelerate the progression of liver disease, resulting in increased morbidity and mortality. Furthermore, the management of the coinfected patient is complex as the presence of one infection can affect the management of the other in a number of ways. HBV infection increases the risk for hepatic toxicity associated with HIV antiretroviral therapy (ART). Because several antiviral agents have activity against one or both viruses, the issues of HIV and HBV drug resistance must be considered when selecting therapeutic regimens. In addition, patients are at risk for hepatic flares and decompensation throughout the disease course, particularly with immune reconstitution during ART. Unfortunately, there is a paucity of studies evaluating treatment of coinfected patients, and evidence to guide therapeutic decision making is often lacking. This article reviews the epidemiology and natural course of HIV/HBV coinfection and discusses the current state of therapy for HBV disease in the HIV-coinfected population. Detailed discussion of HIV ART is beyond the scope of this article.

TAKE HOME POINTS

- The estimated prevalence of chronic hepatitis B virus (HBV) infection in patients with HIV infection is between 7.6% and 11% in the United States.
- Patients with HIV/HBV coinfection progress to liver disease more rapidly, have higher serum HBV DNA levels, lower rates of spontaneous seroconversion, and higher rates of liver-related death and other complications as compared with patients with HBV monoinfection.
- In HIV/HBV coinfection, flares of elevated transaminases may result from immune reconstitution, adverse reactions to antiretroviral agents, discontinuation of agents with anti-HBV activity, and emergence of resistance.
- The goal of HBV treatment is to delay or stop the progression of liver inflammation and fibrosis by inhibiting viral replication.
- If patients require treatment for HBV alone, options include pegylated interferon alfa, adefovir, and telbivudine. Patients who require treatment of both infections should be treated with combination antiretroviral therapy that includes nucleoside/nucleotide analogues effective against both diseases.

EPIDEMIOLOGY

Worldwide more than 350 million persons are chronically infected with HBV,[3] and approximately 33 million persons are infected with HIV.[4] An estimated 1.25 million persons in the United States are infected with HBV.[5] There is considerable geographic variability in the prevalence of coinfection, with higher rates observed in areas where chronic HBV infection is common, such as Sub-Saharan Africa[1] and Asia. In those areas, the rate of chronic HBV infection is inversely related to age at exposure, which in most cases occurs at birth or in early childhood. In the United States, chronic HBV infection is uncommon, and the majority of infections occur in adults, with transmission occurring via sexual or intravenous routes. In a large cohort of HIV-infected patients followed by the Centers for Disease Control and Prevention, the estimated prevalence of chronic HBV infection was 7.6% among unvaccinated individuals. The same

Dr. Brito is an assistant professor of medicine and fellowship program director, Section of Infectious Diseases, University of Illinois at Chicago, Chicago, IL; Dr. Alhyraba is a critical care medicine fellow, Mayo Clinic, Rochester, MN.

Table. Recommended Initial Testing for Patients with HIV/HBV Coinfection

Complete blood count (CBC) and biochemical profile
Aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, international normalized ratio, prothrombin time
Hepatitis B serology
Hepatitis B surface antigen (HBsAg)
Hepatitis B surface antibody (anti-HBs)
Hepatitis B core antibody (anti-HBc)
Hepatitis B e antigen (HBeAg)
Hepatitis B e antibody (anti-Hbe)
HBV DNA
Antibodies to hepatitis A, C, and D
CD4 cell count, HIV RNA
Monitoring if HBV treatment is initiated
CBC, biochemical profile, CD4 cell count, HIV RNA, HBV DNA, HBeAg, anti-HBe (depending on pretreatment status) every 3 mo
Liver ultrasound and alpha-fetoprotein level every 6–12 mo

HBV = hepatitis B virus.

study reported chronic HBV infection rates of 7.1% in injection drug users, 9.2% among men who have sex with men (MSM), and 11.7% among MSM who use injection drugs.[2] Patients with HIV infection who become newly infected with HBV are more likely to progress to chronic HBV infection as compared with immunocompetent persons, with chronic infection developing in 21% of HBV/HIV coinfected patients versus 7% of immunocompetent patients.[6]

HBV GENOTYPES

Eight major genotypes of HBV have been described (genotypes A through H). Genotypes are distinguished by a random genomic sequence variation of 8% or greater.[7,8] Genotypes show a characteristic geographical distribution and may influence the course of the liver disease and the response to antiviral agents.[9,10] Genotypes A and D predominate among HBV/HIV coinfected individuals in the United States and Europe,[11,12] while genotypes B and C are prevalent in Southeast Asia, genotype A is prevalent in sub-Saharan Africa and Europe, and genotype F predominates in South America. Genotypes A and D are more frequently associated with hepatitis B e antigen (HBeAg) seroconversion and respond better to therapy with pegylated interferon, a finding recently observed in a randomized clinical trial.[13] Several studies have reported that genotype C is associated with more severe liver disease and a diminished response to interferon therapy.[14,15] Although the idea of employing HBV genotyping in clinical practice is provocative, the quality and volume of present data are insufficient to warrant a recommendation for its routine use.[16]

INITIAL EVALUATION AND DIAGNOSIS OF HBV INFECTION

Upon confirmation of HIV infection, all patients should be questioned about their HBV vaccination history and tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc). The recommended initial testing for patients with HIV who are diagnosed with chronic HBV is outlined in the **Table**.

HBsAg is the main marker of HBV disease and appears shortly after acute infection. The persistence of HBsAg beyond 6 months after resolution of the acute disease is considered a chronic infection. Patients who clear the HBsAg after the initial infection mount an antibody response that portends lifelong immunity (anti-HBs). The anti-HBc appears relatively soon after the initial infection and remains elevated for life. Detection of this marker in patients with a negative HBsAg indicates prior infection. In some cases, detection of an isolated anti-HBc may represent an active, subclinical infection (*see* Isolated anti-HBc Pattern). The HBeAg is a marker of infectivity that suggests high levels of HBV replication in serum. Clearance of this antigen and development of the hepatitis B e antibody usually results in control of the viral replication and better long-term prognosis. Transient acute flare-ups of hepatitis can occur at the time of HBeAg seroconversion. Some patients who are HBeAg-negative have a precore mutant that prevents the development of this antigen. These patients usually have a more aggressive course with ongoing HBV replication and continued liver injury.

Isolated anti-HBc Pattern

Chronic hepatitis B infection is defined by the persistence of HBsAg for at least 6 months; however, HIV-positive persons with chronic HBV infection can present with atypical results in serologic tests for HBV. One such profile is the presence of anti-HBc in the absence of HBsAg and anti-HBs. Isolated anti-HBc is presumed to be associated with ongoing viral replication and histologic liver damage in some patients. Isolated detection of anti-HBc and the presence of HBV DNA in the serum or liver is called occult HBV infection. The reported prevalence of occult HBV in HIV-positive patients varies among studies.[17–19] Persistent HBV infection, defined as the presence of HBV DNA in serum, was found in nearly 90% of 57 patients with isolated anti-HBc belonging to the Swiss Cohort Study.[19] The

authors concluded that in HIV-infected patients, anti-HBc as the sole serologic marker of HBV must be considered indicative of chronic HBV infection. Although there is no clear consensus on whether HBV DNA should be measured in all patients who have isolated anti-HBc, some authors recommend it.[20]

NATURAL HISTORY OF HIV/HBV COINFECTION

HIV has a substantial impact on the course and outcome of HBV disease. The rate of HBV viral clearance is decreased in HIV-infected patients after an acute HBV infection. In addition, although coinfected patients often have lower levels of serum transaminases,[21,22] they progress to liver disease more rapidly, with a shortened period between acquisition of infection and end-stage liver disease.[22,23] HBV reactivation and replication are enhanced in coinfected patients, and serum HBV DNA levels are usually higher. Patients with HIV infection also have lower rates of spontaneous HBsAg and HBeAg seroconversion.

Liver-related death and other complications are increased in coinfected patients. An analysis done in the Multicenter AIDS Cohort Study on liver-related mortality in 5293 homosexual men concluded that the likelihood of death from liver disease in HIV/HBV coinfected patients is 19 times higher than in those with HBV monoinfection and approximately 8 times higher than in those with HIV monoinfection.[24] Predictors of severe liver disease in HIV/HBV coinfection include older age,[25] necroinflammatory changes and fibrosis on histology,[26] ongoing HBV replication, HBeAg persistence, and CD4 depletion.[24]

The effects of HBV infection on the progression of HIV disease are less clear. The finding that some HBV products, such as the HBV X protein, enhance HIV replication suggests that HBV could have an impact in HIV progression. Nonetheless, these findings have not been corroborated by clinical studies.[27]

Flares and Immune Reconstitution

A hepatitis flare is defined as an intermittent elevation of aminotransferases to more than 10 times the upper limit of normal and more than twice the baseline value during the natural course of a chronic HBV infection.[20] In HIV/HBV coinfection, flares of elevated transaminases have a variety of possible etiologies, including immune reconstitution, adverse reactions to antiretroviral agents, discontinuation of agents with anti-HBV activity (lamivudine, emtricitabine, tenofovir), and emergence of resistance to lamivudine (or emtricitabine). Less common causes include HBeAg seroconversion, infection with another hepatitis virus (eg, hepatitis A, C, or D), and certain opportunistic infections such as cytomegalovirus and *Mycobacterium avium-intracellulare*. Clinicians also should consider other noninfectious etiologies such as alcohol, medications, and nonalcoholic steatohepatitis as the culprit of a hepatitis flare.

Hepatitis flares secondary to immune reconstitution in HIV-infected patients have been reported.[28,29] They can occur when initiation of ART leads to an elevation in the CD4 cell count, resulting in an improved host immune response to HBV and other latent opportunistic infections. In patients with high levels of HBV DNA and/or those with advanced liver disease, the reaction can be severe and may lead to hepatic decompensation and even death. The potential severity of this condition underscores the need to screen all HIV patients for HBV infection before initiating ART and to consider agents active against both viruses if coinfection is detected.

Compared with HIV monoinfected patients, HIV/HBV coinfected individuals have higher rates of ART-associated hepatotoxicity with elevated transaminases.[30,31] Hepatotoxicity can be caused by different mechanisms such as direct liver toxicity, idiosyncratic or immunoallergic mechanisms,[32] and depletion of liver mitochondrial DNA due to certain drugs.[33] Coinfected patients often develop liver enzyme elevations with the use of antituberculosis agents, particularly isoniazid, rifampin, and pyrazinamide.[34]

When switching ART regimens in patients with HIV/HBV coinfection due to treatment failure, toxicity, or other reasons, clinicians need to be mindful that hepatitis flare reactions can occur upon discontinuation of agents with anti-HBV activity (lamivudine, emtricitabine, and tenofovir). A drug that is effective against HBV should not be discontinued unless another drug with anti-HBV activity is substituted for it or HBeAg seroconversion has occurred.[20] Hepatitis flares may also occur with the emergence of HBV strains resistant to lamivudine (or emtricitabine). Lamivudine resistance is a common cause of "late flare," which is characterized by elevated levels of HBV DNA and liver enzymes and is associated with the appearance of the *YMDD* resistance mutation in the HBV DNA polymerase gene.[35,36]

The risk of reactivation of HBV replication and disease activity exists at all stages in the natural history of hepatitis B in coinfected patients. Reactivation of HBV is characterized by the reappearance of detectable HBeAg in previously HBeAg-negative patients. Reappearance of HBsAg or HBeAg has also been documented in patients who have cleared the HBsAg (anti-HBs-positive/HBsAg-negative).[37]

MANAGEMENT

Patients with HIV infection who test negative for markers of previous HBV infection or immunity (ie, anti-HBs) should be vaccinated.[11] Because the response rate to HBV vaccination is a function of the CD4 cell count, response to the vaccine may be diminished in HIV-positive individuals who are severely immunocompromised. At CD4 cell counts exceeding 500 cells/μL, nearly 80% of patients respond to the vaccine, but the response rate drops to approximately 25% in patients with CD4 cell counts below 200 cells/μL.[38] Some authors recommend administering booster doses and/or a repeat cycle with the 40-μg dose of the vaccine to those who fail to respond to a standard course of the vaccine (20 μg).[39] Protective antibodies are short lived in HIV-infected individuals,[40] and yearly measurement of anti-HBs levels with revaccination (if the antibody level drops below 100 IU/I) may be indicated. Hepatitis A vaccine should be administered to all coinfected individuals with a negative hepatitis A virus antibody IgG test result.

Patients diagnosed with HBV infection should receive counseling about the risk of transmission of viral hepatitides, and close contacts should be vaccinated. Counseling should include advice to abstain from alcohol and drugs, information on safe sex practices, and a discussion of potential hepatotoxins.

Approach to Therapy

The management of chronic HBV disease in HIV-infected patients is complex due to the dynamic nature of the disease, drug toxicities, antiviral resistance, potential for hepatitis flares, and the paucity of data regarding treatment of this subpopulation of patients.[41,42] Much of the current recommendations are based on data from studies involving HBV monoinfected patients. Clinical trials are needed to address issues regarding which patients should be treated, at what disease stage therapy should be initiated, and the optimal regimen to use.[41,43]

HBV is a lifelong disease, and current therapies are seldom curative. The goal of HBV treatment is to delay or stop the progression of liver inflammation and fibrosis by inhibiting viral replication, thereby preventing the development of cirrhosis and hepatocellular carcinoma.[11,41,44,45] Long-term suppression of viral replication is perhaps the most realistic therapeutic goal since HBeAg or HBsAg seroconversion occurs in only a small fraction of monoinfected and coinfected patients. Nonetheless, studies have demonstrated that long-term suppression leads to better outcomes. In 1 study, the clearance of HBeAg after interferon therapy resulted in improved overall survival and fewer complications.[46] In a study involving 309 patients with cirrhosis B, clearance of HBsAg was associated with a lower risk of liver cancer or liver-related death.[47]

Recently published HIV/HBV treatment guidelines[11] base the decision to initiate therapy on evidence of active HBV replication and inflammatory liver disease as evidenced by an HBV-DNA level above 2000 U/mL, an elevated alanine aminotransferase level, and evidence of significant liver fibrosis. Recent data suggest that the risk of cirrhosis and hepatocellular carcinoma is already significantly increased at HBV-DNA levels of 10^4 copies/mL.[48,49] Liver fibrosis should be assessed in all coinfected patients by either a liver biopsy or by using newer noninvasive techniques such as elastometry or serum biochemical studies. These noninvasive techniques, although promising, have not been well studied in HBV infection.

In coinfected patients, the status of HIV infection and the need for ART are major determinants in choosing an HBV treatment strategy. If patients do not meet criteria for HIV treatment (CD4 cell count > 350 cells/μL) but treatment for HBV alone is required, options include pegylated interferon alfa, adefovir 10 mg, and telbivudine. HIV/HBV coinfected patients who require treatment of both infections should be treated with combination ART, which includes a backbone of nucleoside/nucleotide analogues effective against both diseases.[11,50] The HIV antiretroviral drugs tenofovir, lamivudine, and emtricitabine have activity against both viruses, making them the logical choice in these patients. Tenofovir plus emtricitabine or lamivudine is the preferred first-line therapy. None of these agents should be used alone for the treatment of HBV due to the high risk of developing HIV drug resistance. In a study that included individuals who were naïve to therapy and required treatment for both HBV and HIV, the combination of tenofovir and lamivudine was effective in suppressing HBV DNA levels and preventing the development of resistance.[51]

Treatment Options

Currently, the agents available for the treatment of HBV infection include 6 nucleoside/nucleotide analogues as well as interferon.

Interferon. There is a considerable body of data regarding the use of interferon alfa for the treatment of HBV in monoinfected patients. In a meta-analysis of published randomized trials,[52] interferon alfa was shown to be effective in suppressing HBV replication and eradicating the chronic-carrier state across the studies included in the analysis. In that same review, HIV coinfection was observed to be a marker of poor response to interferon treatment. Long-term follow-up of patients treated with interferon has shown that those

who cleared the markers of HBV replication (HBeAg and HBV DNA) experienced a decrease in the frequency of HBV-related clinical complications.[46] In contrast, coinfected patients who have a low CD4 cell count (< 200 cells/μL) and are treated with interferon have poorer response rates, more frequent HBV reactivations, and an increased incidence of cirrhosis and cirrhosis-related death.[26] Interferon treatment should be considered for HBeAg-positive coinfected patients with higher CD4 cell counts who do not require ART. Treatment with the pegylated form of interferon has also been shown to be superior to lamivudine in HBV monoinfected patients, resulting in favorable rates of HBeAg and HbsAg seroconversion.[53] Pegylated interferon administered weekly is currently the preferred agent; dosing depends on the formulation used (eg, 180 μg once weekly for pegylated interferon alfa-2a). In general, the rate of HBeAg seroconversion is higher with interferon therapy than with nucleoside analogues.[11]

Lamivudine. Lamivudine is a nucleoside analogue of cytosine and is a common component of combination ART. The drug is approved at different doses for the treatment of both HIV and HBV infections, but generally the dose used in coinfected patients is 300 mg/day. Lamivudine has been shown to improve liver histology in patients with chronic HBV.[54] The anti-HBV efficacy of lamivudine in HIV/HBV coinfected patients was demonstrated by the CAESAR trial and other studies, which showed that the drug reduced HBV-DNA levels below detection in 40% to 87% of treated patients.[55,56] Emergence of lamivudine resistance occurs in approximately 20% of HBV/HIV coinfected patients per year[36] and is a major limiting factor for using lamivudine as long-term monotherapy for HBV in HIV-coinfected patients. Resistance to lamivudine is most commonly due to mutations in the *YMDD* motif of the HBV polymerase gene, although other less common mutations associated with lamivudine resistance have also been described.[57]

Emtricitabine. Emtricitabine is a 5-fluorinated derivative of lamivudine that is approved for the treatment of HIV infection and has activity against HBV. Data from randomized trials suggest that emtricitabine has good antiviral activity against HBV and leads to improvement in liver histology when compared with placebo.[58,59] When administered as a component of an HIV ART regimen to coinfected patients, emtricitabine results in satisfactory HBV DNA suppression.[60] Emtricitabine is not approved for monotherapy against HBV. Because emtricitabine is structurally similar to lamivudine, it should not be used in patients in whom lamivudine therapy has failed as cross-resistance is likely.

Adefovir. Adefovir is a nucleotide analogue of adenosine monophosphate that is active against wild-type and lamivudine-resistant HBV. The recently published 5-year follow-up data on the use of adefovir 10 mg daily for treatment of HBV showed a durable and continued viral response and low viral resistance levels.[61] Case reports of new resistant mutations (eg, *rtN236T*) have been published, however.[62] Similar efficacy results have been observed with the use of adefovir in HIV/HBV coinfected patients. In a study of lamivudine-resistant coinfected patients, long-term (144 wk) treatment with adefovir resulted in considerable suppression of HBV DNA without the emergence of significant resistance mutations of either HBV or HIV.[63]

Tenofovir. Tenofovir is another nucleotide analogue of adenosine monophosphate approved for the treatment of HIV disease. Tenofovir recently was approved for the treatment of HBV in monoinfected patients. Its use as a first-line agent in patients with HIV/HBV coinfection has become widespread. This practice is borne out of studies that have proven the noninferiority of tenofovir as compared with adefovir for the treatment of HBV in the coinfected population.[51,64,65] Tenofovir appears to be equally potent against wild-type and lamivudine-resistant strains of HBV.[51] In vitro studies have reported decreased tenofovir efficacy in lamivudine-resistant isolates harboring the *rtN236T* mutation, the most common adefovir-associated resistance mutation.[66]

Entecavir. Entecavir is a guanosine analogue with potent anti-HBV activity. In 2 large randomized trials involving HBeAg-positive and HBeAg-negative individuals, entecavir was shown to be superior to lamivudine in terms of histologic and virologic improvement.[67,68] Recently reported 4-year follow-up data on patients receiving entecavir showed a favorable resistance profile for nucleoside-naïve patients, with a probability of a virologic breakthrough remaining low at 0.8%; the probability of breakthrough is approximately 39.5% for lamivudine-resistant strains.[69] When entecavir was originally approved, it was recommended for treatment of HBV infection in patients who did not meet criteria for treatment of HIV; this recommendation was based on a previous study that showed the compound had selective activity for HBV but not HIV.[70] Nonetheless, recent case reports and in vitro analysis of viruses obtained from coinfected patients on entecavir monotherapy revealed that entecavir is a partial inhibitor of HIV replication and can select for the *M184V* mutation in the HIV reverse transcriptase gene, causing cross-resistance with lamivudine and emtricitabine.[71] Based on these findings, the drug is no longer recommended for coinfected patients who are not receiving ART.[72]

Telbivudine. Telbivudine is an L-nucleoside analogue

of thymidine recently approved for the treatment of chronic HBV infection; it has no apparent activity against HIV. No published data on the efficacy of telbivudine in HIV/HBV coinfected patients are available, but 48-week data of telbivudine use in monoinfected patients showed superiority to lamivudine.[73] Telbivudine shares cross-resistance mutations with lamivudine, limiting its use in patients experienced with this drug. A trial comparing telbivudine, lamivudine, and the combination of both drugs demonstrated better virologic and biochemical responses in the telbivudine arm as compared with lamivudine. The response rate in the combination arm was similar to that observed in the lamivudine monotherapy arm.[74]

MONITORING

When both viremias are undetectable in plasma in patients with HIV/HBV coinfection, monitoring generally should be done every 3 months with the studies outlined in the Table. If during 1 of these visits the viral load of either virus is increased, the respective genotype should be obtained and changes to therapy should be made on the basis of these results. In this situation, consultation with experts with experience in management of coinfection is strongly advised.

CONCLUSION

The patient with chronic HBV/HIV coinfection presents a unique and complex set of management issues. Liver damage progresses more rapidly in the coinfected population, leading to increased liver-related mortality and morbidity. Furthermore, the burden of liver disease in coinfected persons is increasing as HIV-infected patients are living longer due to the reduction in the incidence of HIV-related opportunistic infections. Treatment of HBV infection should always be closely coordinated with HIV therapy. Patients should be carefully monitored to detect reactivation of HBV, hepatitis flares, and antiviral resistance at their early stages. Additional research is needed to better understand the natural history and interaction of these viruses as well as identify better correlates of disease progression and treatment responses. Clinical trials are also needed to further our knowledge of the appropriate use of currently available antiviral agents in the setting of coinfection, including the use of combination therapy. The role of experimental therapies needs to be evaluated in the coinfected population as well. **HP**

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Corresponding author: Maximo Brito, MD, Section of Infectious Diseases, University of Illinois at Chicago, 808 South Wood Street, Room 888, Chicago, IL 60612; mbrito@uic.edu.

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