**Perspective**

**Diagnosis and Management of Hepatitis B Virus and HIV Coinfection**

HIV and hepatitis B virus (HBV) coinfection increases HIV and HBV replication, hepatitis flares, and risk of progression to chronic HBV infection, cirrhosis, and hepatocellular carcinoma. HIV and HBV coinfection decreases frequency of hepatitis Be antibody (anti-HBe) and hepatitis B surface antibody (anti-HBs) seroconversion, increases risk of antiretroviral therapy-related hepatotoxicity, and reduces efficacy of HBV therapy. All newly diagnosed HIV patients should be screened for hepatitis A, B, and C viruses and vaccinated if not immune to hepatitis A or B viruses. HBV serology often is atypical in coinfection. Diagnosis of HBV coinfection in HIV infection is made on the basis of hepatitis B surface antigen (HBsAg)-positive, hepatitis B core antibody (anti-HBc total)-positive, anti-HBs-positive status. Alanine aminotransferase levels in coinfected patients often are not reliable markers of liver inflammation. HBV infection should always be treated if coinfected patients are receiving antiretroviral therapy, since immune reconstitution under antiretroviral therapy poses risk for immune-associated liver damage in these patients. This article summarizes a presentation on HIV and HBV coinfection made by Marion G. Peters, MD, at an International AIDS Society—USA Continuing Medical Education course in San Francisco in May 2007. The original presentation is available as a Webcast at www.iasusa.org.

Hepatitis B virus (HBV) infection is a life-long dynamic disease that can be controlled but not cured. The risks of end-stage liver disease and liver cancer increase with ongoing inflammation and viremia. Fibrosis can be reversed, and drug treatment can reduce progression. The relationship between immune response and liver damage in HBV infection is of particular importance in HIV-coinfected patients. If there is no immune response, liver damage does not occur; however, if there is immune response—eg, with immune reconstitution during antiretroviral therapy—liver damage will occur.

**Characteristics of Coinfection**

According to some estimates, there are approximately 400 million people worldwide with HBV infection, with approximately 4 million of those coinfected with HIV. Rates of coinfection range from 5% to higher than 30% depending on the cohort and locale examined. For example, the prevalence of coinfection is 5% to 10% in injection drug use cohorts, is 8.7% in the EuroSida cohort, and has been reported at 9%, 16.9%, 25.9%, and 73% in small cohorts in Tanzania, Malawi, Nigeria, and Uganda, respectively.

In HIV-infected patients, HBV infection increases HIV replication, increases antiretroviral therapy–related hepatotoxicity, and decreases CD4+ cell counts in patients with cirrhosis and hypersplenism. There is also some evidence that HBV infection itself reduces CD4+ cell counts. In HBV-infected patients, HIV increases HBV replication, hepatitis flares, progression to chronic HBV infection, progression to cirrhosis, and risk of hepatocellular carcinoma, and it reduces hepatitis B envelope antibody (anti-HBe) and hepatitis B surface antibody (anti-HBs) seroconversion. Coinfection is also associated with reduced efficacy of antiretroviral therapy, including greater risk of lamivudine resistance and decreased response to interferon alfa.

An example of the poor outcomes associated with coinfection is provided by findings in a Multicenter Cohort Study reported by Thio and colleagues. The study population included 4967 men who have sex with men (MSM) who were hepatitis B surface antigen (HBsAg)-negative, of whom 47% had HIV infection, and 326 MSM who were HBsAg-positive, of whom 65% had HIV infection. Patients with HIV and HBV coinfection had a 19-fold higher risk of liver death than those with HBV monoinfection, with risk of liver-related mortality increasing with alcohol consumption, low nadir CD4+ cell count, and antiretroviral therapy. Rates of liver-related mortality by 1000 person-years were 14.1 with HIV and HBV coinfection, 1.7 with HIV monoinfection, 0.8 with HBV monoinfection, and 0 with neither HBV nor HIV infection (Thio et al, Lancet, 2002). More recent data from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study showed that after AIDS (31%), liver-related mortality accounted for the most deaths (15%) in HIV-infected persons with access to antiretroviral therapy, exceeding heart disease (9%) and cancer (9%) in this regard. A multivariate model for factors associated with liver death showed that hepatitis C virus (HCV) infection was the strongest predictor (relative risk [RR], 6.7), followed by HBV infection (RR, 3.7), injection drug use (RR, 2.0), older age (RR, 1.5), and low CD4+ cell count (RR, 1.23). The rate of hepatocellular carcinoma was 82 per 10,000 in this cohort, markedly higher than that in the general population.

**Initial Evaluation**

At initial evaluation, patients should be screened for HBsAg, hepatitis B core antibody (anti-Hbc), and anti-HBs. Diagnosis of HBV coinfection in HIV infection is made on the basis of HBsAg-positive, anti-Hbc total-positive,
anti-HBs-positive status. If patients are HBsAg-positive, hepatitis B envelope antigen (HBeAg), anti-HBe, and HBV DNA should be measured. If patients are HBsAg-negative, they should receive HBV vaccination. In addition to history and physical examination, the HIV-infected patient with newly diagnosed HBV coinfection should have a complete liver panel, complete blood cell (CBC) count, and international normalized ratio (INR), as well as measurement of alpha-fetoprotein (AFP). In addition, baseline liver ultrasound should be performed. Patients should be screened for hepatitis A virus (HAV) Ab total and vaccinated if they are anti-HAV antibody-negative. They should also be screened for hepatitis D virus if they are from endemic areas or injection drug users. Household and sexual contacts should be screened for HBV and vaccinated if they are uninfected.

The need to confirm HBV serologic status with additional testing arises because HIV infection is associated with atypical serologic results. A study in the Swiss HIV Cohort showed that infection was manifest as anti-HBc alone in 57 HIV-infected patients, with this remaining the sole marker of infection for 31 months in 98% of patients. Polymerase chain reaction (PCR) results showed that 60% were positive for HBsAg and hepatitis B core antigen (HBcAg), and 36% had necroinflammatory disease. Thus, if patients are anti-HBc-positive and negative for both HBsAg and anti-HBs, HBV DNA should be measured. If this test result is positive, patients should be treated for HBV; if negative, they should be vaccinated.

HIV-infected patients have a diminished response to the HBV vaccine and lose protective antibodies more rapidly. The response rate is greater than 87% in those with CD4+ counts above 500 cells/µL and 33% in those with counts of 200 to 500 cells/µL. A strategy of revaccinating nonresponders with a doubled dose has met with poor success. The AIDS Clinical Trials Group (ACTG) is assessing whether response can be improved by coadministration of granulocyte and macrophage colony-stimulating factor.

Management

The goal of treatment of HBV disease is to make active disease become inactive. Control of HBV disease is indicated by reduced inflammatory response (normalization of alanine aminotransferase [ALT] level), reduced viral replication (reduced HBV DNA level), and improved immune control (seroconversion to anti-HBe- and anti-HBs-positive status). As an example of the risk posed by uncontrolled disease, elevated HBV DNA levels among HBV-infected patients with ALT levels in the normal range dramatically increased risk for hepatocellular carcinoma in patients over age 30 years (Figure 1; Chen et al, JAMA, 2006). The association of HBV DNA level with risk of cirrhosis was very similar in this study. Figure 2 shows the therapeutic endpoints achievable over time in HBV-infected patients. ALT is not a very useful measure of inflammation in coinfected patients, with many such patients with normal ALT levels having necroinflammatory disease on biopsy.
Drugs Wild-type Hepatitis B Virus YMDD Mutation Used in HIV Treatment?
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Lamivudine Susceptible Resistant Yes
Adefovir Susceptible Susceptible No
Entecavir* Susceptible (0.5-mg dose) Susceptible (1-mg dose) No
Emtricitabine Susceptible Resistant Yes
Telbivudine Susceptible Resistant No
Tenofovir** Susceptible Susceptible Yes

* There is a black box warning to not use entecavir in HIV and HBV-coinfected patients not receiving antiretroviral therapy. In patients with YMDD-resistant virus who are on high-dose entecavir, resistance to entecavir occurs more frequently.
** Tenofovir is not approved by the US Food and Drug Administration for the treatment of hepatitis B virus infection.

Antiviral drugs used in treating HBV infection are listed in Table 1, along with their activity against wild-type HBV, activity against HBV with the lamivudine-resistance YMDD mutation; and whether they are active against HIV. In patients with the YMDD mutation alone, adefovir, double-dose entecavir, and tenofovir generally remain active. US guidelines for treatment of coinfection are currently being revised. In drug-naïve coinfected patients who are candidates for both HBV and HIV treatment, the current Department of Health and Human Services (DHHS) guidelines indicate a preference for dual anti-HBV agents, specifically tenofovir plus emtricitabine. However, other nucleoside and nucleotide reverse transcriptase inhibitor (nRTI) combinations are acceptable, including tenofovir with emtricitabine, lamivudine, or entecavir. In patients requiring treatment for HBV alone, peginterferon alfa can be used in the setting of high CD4+ cell count, high ALT level, and low HBV DNA level, all uncommon in HIV patients. Other options include adefovir or telbivudine. However, there is the theoretical possibility that HIV resistance may emerge with these drugs, as occurred with entecavir.

With regard to entecavir, use of the agent in coinfected patients has been studied only in patients on antiretroviral therapy. There was a surge in use of entecavir over the past 18 months as practitioners sought to reduce the risk of immune reconstitution by treating HBV before initiating antiretroviral therapy. There are now at least 5 reported cases of resistance associated with the M184V mutation in coinfected patients receiving entecavir alone, and treatment is associated with a reduction in plasma HIV RNA level of 0.5 log₁₀ copies/mL; prior lamivudine treatment occurred in only 2 of these cases. This finding has resulted in a US Food and Drug Administration (FDA) black box warning indicating that entecavir monotherapy should not be used in coinfected patients not receiving antiretroviral therapy. This issue may not be specific to entecavir and it may alter HBV therapy in patients without current indications for HIV therapy.

Among newer drugs, telbivudine has no anti-HIV activity, but it is not effective in patients with the YMDD mutation. Studies of the drug in coinfection are under way. A study in monoinfected patients showed that reduction of HBV DNA to undetectable levels at 24 weeks with telbivudine treatment was associated with a high likelihood of remaining HBV DNA-negative at 1 year and having normalized ALT levels (see Table 2). Conversely, 93% of patients with HBV DNA level above 3 log₁₀ copies/mL at week 24 failed to seroconvert by year 1 (Lai et al., *Hepatology*, 2005).

Clevudine, which is currently licensed in Korea but not in the United States, was shown to induce good reduction in HBV DNA levels in HBV monoinfected patients, with 59% of patients having undetectable levels at the end of 24 weeks of treatment (Table 3; Yoo et al., *Hepatology*, 2005). The investigational drug pradefovir has more liver targeting and thus less renal toxicity than the related drug adefovir, allowing it to be used at a 30-mg dose. In a recent study in chronic HBV monoinfection, reductions in HBV DNA level at 48 weeks were 4.09, 4.84, 4.89, and 5.54 log₁₀ copies/mL at pradefovir doses of 5, 10, 20, and 30 mg, compared with 4.19 log₁₀ copies/mL with adefovir 10 mg (Lee et al., EASL, 2006).

HBV infection should be treated

Table 2. One-year Outcomes in Patients Receiving Telbivudine for Hepatitis B Virus (HBV) Infection According to HBV DNA Level at Week 24

<table>
<thead>
<tr>
<th>Week 24 HBV DNA Level (copies/mL)</th>
<th>&lt;3 log₁₀</th>
<th>3 to 4 log₁₀</th>
<th>&gt;4 log₁₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA-negative (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>69</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>HBeAg-</td>
<td>67</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Normal ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>89</td>
<td>79</td>
<td>53</td>
</tr>
<tr>
<td>HBeAg-</td>
<td>68</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>4</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>HBeAg-</td>
<td>7</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>26</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

if coinfected patients are receiving antiretroviral therapy, since immune reconstitution under antiretroviral therapy poses a substantial risk for immune-associated liver damage in these patients. ALT flares can occur in coinfected patients for a variety of reasons other than immune reconstitution. This can occur with ALT flares in association with spontaneous HBeAg seroconversion, but such seroconversion is less frequent in HIV-infected patients. Flares can occur when patients stop antiretroviral therapy (eg, through nonadherence or patient choice) or with the emergence of HBV resistance. Flares may also be due to drug hepatotoxicity or acute HCV or HAV infection. After initiating treatment, ALT, aspartate aminotransferase, and HBV DNA levels should be monitored every 3 months. If there is no HBV DNA-level decrease by 12 to 24 weeks of therapy, the patient should be assessed for HBV resistance and adherence, and treatment should be modified by changing drugs or adding a drug. In monoinfected patients, it is recommended that imaging for hepatocellular carcinoma and measurement of AFP be performed every 6 months starting at the age of 40 years. Given the increased risk of hepatocellular carcinoma in coinfection, it may be prudent to monitor coinfected patients according to this schedule regardless of age, but there are currently no data to support this.


Dr Peters received honoraria from GlaxoSmithKline for Data Safety Monitoring Board and from Gilead. She served as a consultant to Idenix and Roche.

### Suggested Reading


