Hepatitis B and Human Immunodeficiency Virus Coinfection

Chloe L. Thio

Coinfection with human immunodeficiency virus-1 (HIV) and hepatitis B virus (HBV) is common; worldwide, an estimated 10% of HIV-infected persons have chronic hepatitis B. Because the incidence of traditional acquired immunodeficiency syndrome–related opportunistic infections has decreased with successful anti-HIV therapy, liver disease has emerged as a leading cause of morbidity and mortality in HIV-infected individuals. HIV infection negatively impacts all phases of the natural history of hepatitis B leading to increased rates of persistent infection, higher HBV DNA levels, lower rates of hepatitis B e antigen loss, increased cirrhosis and liver-related mortality, and increased risk of hepatocellular carcinoma at lower CD4+ T cell counts. The management of hepatitis B in HIV infection is complicated by the dual activity of several nucleoside analogs, the more rapid development of lamivudine-resistant HBV in patients who are HIV-positive, and the paucity of studies in this population. Until further research emerges on the optimal treatment for this population, data from HBV monoinfected persons will need to be extrapolated to the HIV-HBV coinfectected population. Further research is also needed to determine the mechanism(s) for the increased liver disease progression and optimal treatment goals. (HEPATOLOGY 2009;49:S138-S145.)

Introduction
Both human immunodeficiency virus-1 (HIV) and hepatitis B virus (HBV) are transmitted through sexual and percutaneous routes; thus, coinfection with both viruses is common. Worldwide, it is estimated that 10% of the 40 million HIV-infected individuals have chronic hepatitis B. Since the introduction of highly active antiretroviral therapy (HAART) in the United States and other industrialized countries, deaths from AIDS-related causes have declined, but liver disease has emerged as one of the leading causes of morbidity and mortality. As HAART is introduced into areas of the world with high HBV endemicity, hepatitis B–related liver disease is expected to increase in the HIV-infected population; thus, it is important to understand the interaction of these two chronic viral infections. Management of hepatitis B in patients infected with HIV is complicated not only by the differences in natural history but also by other issues such as the activity of several drugs against both viruses and development of drug-resistant HIV and HBV variants. In this review, the epidemiology, natural history, and management of hepatitis B in HIV-infected individuals will be discussed, highlighting differences from HBV monoinfected individuals.

Epidemiology
Coinfection with hepatitis B is common among HIV-infected individuals. The prevalence of HBV varies markedly among different HIV-infected populations, but one of the major determinants is geographical location. In areas with low HBV endemicity, such as the United States, Australia, and Europe, HBV and HIV are usually acquired in adulthood through either sexual or percutaneous transmission. HBV is ~100-fold more likely to be transmitted than HIV, thus, HBV infection often precedes HIV infection. In these low endemicity areas, the prevalence of HBV coinfection is 5%-7% of HIV-infected individuals but varies depending on the route of infection. The highest prevalence of coinfection is
among men who have sex with men, ranging from 9%-17%, and the lowest prevalence is from heterosexual transmission (Fig. 1).

In countries with intermediate and high HBV endemicity, the principal routes of HBV transmission are perinatal or in early childhood; thus, HBV infection usually precedes HIV infection by decades. In these countries, the majority of studies show HBV coinfection prevalence of 10%-20%,6-8 but some show prevalence rates as low as 6%.9

Natural History

HIV adversely affects all phases of the natural history of adult-acquired hepatitis B (Table 1). After HBV infection, HIV-infected individuals are up to six-fold more likely to develop chronic hepatitis B than are HIV-negative individuals.10,11 Bodsworth et al. retrospectively studied 77 men who acquired HBV infection, of whom 31 were HIV-infected prior to HBV infection.10 Of the HIV-infected men, 23% developed chronic hepatitis B compared to 4% of the HIV-uninfected men (P = 0.03). Of note, the mean CD4+ T cell counts were lower in the HIV-infected men who developed chronic hepatitis B compared to the HIV-infected men who did not become chronically infected. HIV infection also decreases the rate of hepatitis B e antigen (HBeAg) clearance up to five-fold and increases the level of HBV replication as manifested by higher HBV DNA levels.12-14 Even HIV-infected persons who acquire protective antibody to hepatitis B surface antigen (anti-HBs) remain at risk for loss of anti-HBs and subsequent reactivation of HBV (reverse seroconversion).15,16

Of all these negative consequences, the most important is that HIV accelerates the progression of HBV-related liver disease. Cirrhosis is more common in HIV-HBV coinfection despite lower alanine aminotransferase (ALT) levels than in HBV monoinfection,12 and may be related to lower CD4+ T cell counts.17 Thio et al. found that HIV coinfection impacted liver-related mortality in an analysis of 5293 men of whom 326 were positive for hepatitis B surface antigen (HBsAg).18 The HIV-HBV coinfected men were over 17 times more likely to die of liver-related causes compared to those monoinfected with HBV. One unanswered question on the natural history of HBV is the effect of HIV coinfection on development of hepatocellular carcinoma (HCC). There is some evidence that lower CD4+ T cell counts are associated with increased risk for HCC in HIV-HBV coinfected individuals,19 but whether HIV in general increases the risk is not known.

All of the natural history studies cited here were conducted in areas of the world where HBV is acquired in adulthood; thus, it is unknown whether the effects of HIV are the same when HIV is acquired years after a chronic hepatitis B infection is established, as in countries with high HBV endemicity.

Pathogenesis of Liver Disease

It seems paradoxical that HBV-related liver disease, which is an immune-mediated process, is exacerbated by

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<tr>
<th>Effect</th>
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<tr>
<td>Increases risk for developing chronic HBV infection</td>
<td>Studies in men who have sex with men. Lower CD4+ T-cell count with higher risk of chronicity.</td>
<td>(10,11)</td>
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<td>Decreased rate of HBeAg clearance</td>
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<td>Increased HBV replication</td>
<td>Demonstrated with higher HBV DNA levels</td>
<td>(12,13)</td>
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<td>Increased likelihood of loss of anti-HBs</td>
<td>Increased risk associated with lower CD4+ T cell counts</td>
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<td>Decreased inflammatory response to chronic hepatitis B</td>
<td>Lower ALT levels</td>
<td>(12)</td>
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<td>Increased liver disease progression</td>
<td>More cirrhosis and higher liver-related mortality</td>
<td>(12,18)</td>
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<td>Increased risk for HCC</td>
<td>Overall 33% increased risk per 100 cell decrease in recent CD4+ T-cell count. Risk greater among men who have sex with men than in injection drug users with co-infection</td>
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the immunodeficient state caused by HIV. There are several possible reasons for this paradoxical relationship. In HIV-infected persons, a rapidly progressive form of liver disease due to viral cytopathic effect rather than the immune response, which is known as fibrosing cholestatic hepatitis, has been described. Thus, it is plausible that HBV variants, which can be more common in HIV infection, may account for a proportion of the increased liver disease in HIV coinfection. In support of this hypothesis, Revill et al. described a novel deletion mutation in the precore/core region of the HBV genome and found it to be more common among HIV-HBV coinfected than HBV monoinfected individuals. Coinfected persons with this mutation had higher HBV DNA levels than those without the mutation. In HBV monoinfected patients, core deletion mutations have been associated with more aggressive liver disease; thus, this novel deletion mutant may contribute to liver disease progression in the setting of HIV infection.

It has also been hypothesized that HIV modulation of the HBV-specific immune response can alter the hepatic cytokine environment and subsequently affect liver disease. However, this hypothesis has not been studied to date.

Lastly, it has been postulated that immune activation from HIV-related microbial translocation may be a mechanism for accelerating liver disease progression. It was recently shown that HIV increases microbial translocation from the intestine, which is associated with increased immune activation. This increased immune activation may contribute to worsening liver disease, as has been demonstrated in a rat model of alcohol-induced liver injury. Although this hypothesis has not been studied in HIV-HBV coinfection, a study of individuals coinfected with HIV and hepatitis C virus (HCV) found that cirrhosis was associated with higher systemic markers of microbial translocation. However, this study could not exclude the possibility that the increased microbial translocation markers were a result rather than a cause of liver disease.

Diagnosis of Hepatitis B in HIV Infection

It is important to accurately diagnose and assess the state of HBV infection in the HIV-infected individual because therapeutic management is dependent on the correct diagnosis and staging (see below). All patients who are HIV-infected should be screened for hepatitis B with tests for HBsAg, anti-HBs, and antibody to hepatitis B core antigen (anti-HBc). Those persons who are negative for anti-HBs and HBsAg are at risk for acquiring HBV and should receive the HBV vaccine. Those who are diagnosed with chronic hepatitis B, as marked by the presence of HBsAg for at least 6 months, should have their disease stage evaluated with testing for HBeAg, antibody to HBeAg (anti-HBe), HBV DNA, serum ALT, bilirubin, albumin, prothrombin time, and platelet count.

HIV infection can complicate the diagnosis of hepatitis B because spontaneous reverse seroconversion marked by the disappearance of anti-HBs and reappearance of HBsAg can occur, especially if CD4+ T cell counts are less than 200 cells/mm³, allowing re-emergence of HBV replication (see Natural History). Thus, in an HIV-infected patient with a prior positive anti-HBs test, HBV serological testing should be repeated if unexplained liver disease emerges. Isolated anti-HBc is a serological pattern that is found in HIV-infected individuals. The significance of an isolated anti-HBc is controversial and no clear liver disease has been associated with it to date. In HIV cohorts with isolated anti-HBc reactivity, the presence of latent hepatitis B (defined by the presence of detectable HBV DNA in the absence of HBsAg) ranges from a few percent up to 89%, allowing re-emergence of HBV DNA in the absence of HBsAg. Thus, in an HIV-infected patient with isolated anti-HBc, a rate that was similar to that in individuals who were negative for anti-HBc. In a longitudinal study from Taiwan with a median follow-up of nearly 5 years, 41% of 179 patients with isolated anti-HBc reactivity, the majority of whom were receiving HAART, became positive for anti-HBs; another 4% developed HBsAg.

Management of Chronic Hepatitis B

HIV-infected persons with chronic hepatitis B should be tested for evidence of HCV infection, counseled regarding prevention of liver damage, vaccinated against hepatitis A (if not immune), and counseled about abstaining from alcohol. HIV-HBV coinfected patients should also be screened for possible HCC using serum tests for alpha-fetoprotein and imaging of the liver every 6 months. There is no evidence that more frequent screening in the setting of HIV infection is necessary because it is not clear that HIV infection increases the risk for or the rate of developing HCC.

Liver biopsy may also be helpful to stage liver disease when treatment decisions are not clear (see below) and remains the gold standard for assessing disease severity in HIV-HBV coinfection. Noninvasive markers of liver disease have emerged as alternatives to staging liver disease with the primary methods being serum markers and transient elastography. None of these have been studied in
HIV-HBV coinfection, and few have been studied in suitably large cohorts with chronic hepatitis B monoinfection. In a study from France of 202 HBV monoinfected patients, liver stiffness by transient elastography correlated well with the extent of fibrosis on liver biopsy.32 The area under the receiver-operating characteristics curves for transient elastography compared to Metavir fibrosis scores of greater than 2 was 0.81, for scores greater than 3 (bridging fibrosis) was 0.93, and for scores of 4 (cirrhosis) was 0.93. In a study from Singapore, transient elastography and the aspartate aminotransferase to platelet ratio index (APRI), another commonly used noninvasive means of assessing fibrosis, were compared to fibrosis scores from liver biopsy.33 Transient elastography performed comparably to the French study and was superior to the APRI.

### Therapeutic Goals and Benefits

Viral eradication is not possible with current anti-HBV agents, because they do not clear the highly stable, latent covalently closed circular HBV DNA found in the nucleus of infected cells. As in HBV monoinfection, a major therapeutic goal of hepatitis B therapy is preventing development of end-stage liver disease. Several studies support this as a feasible goal in HIV-HBV coinfected patients. An analysis of the HBV-HIV international intercohort study group demonstrated that after a mean of <4 years of lamivudine-containing HAART, there was a 27% reduction of risk in liver-related death per year of lamivudine.34 However, the limitation of this study was its relatively short duration of follow-up, so the effect of lamivudine-resistance on liver-related outcomes in HIV coinfection could not be assessed. Benhamou et al. also demonstrated that adefovir dipivoxil is associated with improvement in liver fibrosis in HIV-HBV coinfected men.35 Additional goals of therapy are to minimize the risk of hepatotoxicity from HAART and of the immune reconstitution inflammatory syndrome (see Special Considerations).

### When to Initiate Therapy

Decisions regarding when to initiate anti-HBV therapy require consideration of the HIV treatment status because several of the nucleoside analogs are active against both HIV and HBV. If HIV infection needs to be treated, then the first-line therapy for HIV includes tenofovir disoproxil fumarate and emtricitabine as the nucleoside backbone.26 Because both of these agents are active against HBV, HBV is treated simultaneously by default.

If HIV is not treated, a decision regarding whether to initiate anti-HBV therapy is required. The current recommendations are to weigh both the replication status of HBV as well as the stage of liver disease to guide treatment decisions. There are inadequate data in HIV-HBV coinfection to determine the appropriate cutoff value for HBV DNA levels for treatment initiation, but many experts recommend a level of 2000 IU/mL (≈10,000 copies/mL).36 The liver disease stage is best obtained by a liver biopsy because serum aminotransferase levels tend to be low in patients with HIV infection, even in the presence of cirrhosis.12 The presence of more than mild liver disease is an indication for treatment. As described above, noninvasive markers of liver disease have not been well studied in HIV infection; thus, they cannot be reliably used to determine liver disease stage. In patients with cirrhosis, treatment is recommended in the presence of any detectable HBV DNA.

### What to Start Therapy with When HAART Is Initiated

As described above, if HIV therapy is initiated with tenofovir and emtricitabine as part of an anti-HIV regimen, then additional anti-HBV drugs are not needed because this combination is potent (Table 2). This is also the

| Table 2. Treatment of Chronic HBV Infection in HIV-Coinfected Persons |
| Concomitant HAART |
| Preferred | Tenofovir and emtricitabine | Preferred regardless of presence of rtM204V/I mutations |
| Alternatives | Peginterferon alfa | Efficacy in HIV infection not known. No risk of HIV or HBV resistance. |
| | Entecavir | Need to insure that HIV RNA <50 copies/mL due to anti-HIV effects. Increased resistance with pre-existing rtM204V/I and rtL180M. |
| | Telbivudine | Resistance 25% at 2 years with monotherapy in HBV monoinfection. Rates unknown in co-infection. Not effective with M204V/I mutation. |

| Without concomitant HAART |
| Options | Peginterferon | No known in vitro anti-HIV activity. |
| | Telbivudine | Least potent. |
| | Adefovir | Must include anti-HBV active agents. |

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The best option in patients who may have or are known to have lamivudine-resistant hepatitis B. In a randomized controlled trial from Thailand, 36 HIV-HBV coinfected subjects were randomized to receive either lamivudine, tenofovir, or the combination of tenofovir and lamivudine. At the end of 48 weeks, the average decline in HBV DNA was similar in all three arms, ranging from 4.07-4.73 log_{10} copies/mL. However, suppression of HBV DNA levels to <1000 copies/mL was more frequent in the two tenofovir-containing arms compared to the lamivudine arm (92% and 91% versus 46% in the lamivudine arm, P = 0.01). Drug resistance developed in only two patients, both of whom were in the lamivudine-only arm. In a cross-sectional study from a lamivudine-experienced HIV-HBV coinfected cohort from Australia and the United States, subjects who received a combination of tenofovir with emtricitabine or lamivudine were more likely to have HBV DNA <100 IU/mL than those receiving either tenofovir or lamivudine monotherapy.

The combination group was also significantly less likely to have HBV DNA >200,000 IU/mL. The limitation of this study is that it was cross-sectional rather than prospective, but it provided some evidence that combination therapy was superior to monotherapy in HIV-HBV coinfected subjects with lamivudine-resistant HBV.

If tenofovir cannot be included as part of the anti-HIV regimen, options include entecavir, adefovir dipivoxil, or peginterferon. Of those, entecavir is the preferred option because of its potency and high genetic barrier to resistance; however, one needs to confirm that the anti-HIV regimen achieves an undetectable HIV RNA because entecavir is active against HIV and can lead to the emergence of drug-resistant HIV. Entecavir is also effective in lamivudine-resistant HBV, but in the HBV monoinfected patient, resistance to entecavir occurs more rapidly on the background of rtM204V/I and rtL180M mutations. In an unpublished study, 68 subjects who were coinfected with HIV-HBV and who were on lamivudine-containing HAART received either entecavir for 48 weeks (n = 51) or placebo (n = 17) for 24 weeks followed by entecavir for 24 weeks. The mean change in HBV DNA during the first 24 weeks was \(-3.65 \log_{10}\) copies/mL in the entecavir group compared to \(+0.11 \log_{10}\) copies/mL in the placebo group. Of those who received 48 weeks of entecavir, 8% achieved an HBV DNA <300 copies/mL. Data on emergence of drug resistance were not reported. Entecavir was recently shown to effectively suppress HBV DNA levels in 51 HIV-HBV coinfected persons with lamivudine-resistant HBV. After 48 weeks of entecavir, the mean HBV DNA decline was 4.2 log copies/mL with four patients (8%) achieving HBV DNA levels <300 copies/mL. Although none of these patients experienced virological breakthrough at week 48, two (5%) had emergence of substitutions that confer entecavir resistance. This rate compares to 1% of HBV monoinfected subjects with lamivudine-resistance who develop entecavir resistance at 1 year. Thus, further work is needed to determine whether entecavir resistance will arise more rapidly in HIV-HBV coinfected than HBV monoinfected patients. Furthermore, there is a theoretical possibility that entecavir resistance mutations may accumulate more quickly if the anti-HIV regimen contains lamivudine because the two drugs have overlapping resistance patterns.

Although adefovir is a second option that is active against both lamivudine-sensitive and lamivudine-resistant HBV, it is probably not a feasible choice if tenofovir has been eliminated for HIV treatment because these agents are closely related in structure and activity. Furthermore, adefovir is less potent than the combination of tenofovir and lamivudine, so it is less likely to be effective in HIV-HBV coinfected patients who have high levels of HBV DNA. The last option in this situation is peginterferon-alfa 2a or peginterferon-alfa 2b, but these agents have not been adequately evaluated in patients infected with HIV. In one study, 10 HIV-HBV coinfected individuals with inadequate viral suppression on lamivudine initiated peginterferon alfa-2a therapy; after 24 weeks, only seven of the 10 patients had a decline in HBV DNA, which ranged from 1-3 \log_{10} IU/mL. Five of these patients then received tenofovir for the next 24 weeks, all with a good response.

In patients with chronic hepatitis B without the lamivudine-resistant rtM204V/I mutation, telbivudine is another option. However, the relatively rapid development of resistance to telbivudine in HBV monoinfection is a barrier to its use as single-agent anti-HBV therapy. Furthermore, telbivudine has not been evaluated in HIV-HBV coinfected cohorts, so the rates of emergence of drug-resistant variants are unknown in this patient population.

**What Therapy to Start When HAART Does Not Need to Be Started**

If HIV treatment is not initiated, anti-HBV treatment options are more limited due to the dual activity of many nucleoside analogs and the risk of developing drug-resistant HIV. The only current options are adefovir, peginterferon-alfa, and telbivudine. Of the three agents, telbivudine is the most potent, but it is limited by development of drug-resistant HBV in the monoinfected patient. Although telbivudine has not been studied in vivo in the setting of high levels of HIV RNA, in vitro evidence suggests that it is not active against HIV. In a single-round replication assay, telbivudine did not affect HIV repli-
cation (data not shown). Peginterferon-alfa has the advantage that drug-resistant HBV will not emerge, so it is a reasonable option if the patient can tolerate the injections and the side effects. It is possible that a combination of one or more of these three agents may be effective in this situation, but it has not been studied. Thus, each of these approaches to anti-HBV therapy in HIV-infected individuals who do not receive concurrent HAART therapy is suboptimal. For these reasons, an additional option is to initiate HAART earlier than is required by HIV guidelines. Early initiation of HAART may be an increasingly attractive option, especially because HIV increases the rate of liver disease progression and earlier HIV treatment is now being advocated even in HIV monoinfection.

Monitoring During Therapy

Because several of the antiviral drugs have dual activity, it is important to monitor both HIV and HBV infections during therapy. HIV should be monitored by a caregiver experienced in HIV treatment who works closely with the physician treating the hepatitis B infection. Because treatment of HIV-HBV coinfecion has not been well-studied, it is advisable to monitor HBV DNA and ALT levels every 3 months. Frequent monitoring allows for early detection of the emergence of drug-resistant virus. In addition, in patients with HBeAg-positive chronic hepatitis B, HBeAg and anti-HBe testing should be repeated every 3-6 months.

If a HAART regimen containing anti-HBV agents needs to be discontinued, subsequent monitoring for reactivation of hepatitis B is essential. In a large study of 147 HIV-HBV coinfected patients, ALT elevations occurred in 29% within the first 6 months after withdrawal, with 2% and 3.4% reaching grade 3 and 4 levels of liver injury. If reactivation occurs, resuming an agent that is active against HBV is required. Reactivation can also be avoided by continuing an anti-HBV specific agent when HAART is discontinued.

Special Considerations

Following initiation of HAART, a clinical syndrome has emerged during which exacerbation of an opportunistic infection occurs in conjunction with immune reconstitution and has been termed “the immune reconstitution inflammatory syndrome.” This syndrome can occur in response to any pathogen and is seen within the first 4-8 weeks of initiating HAART, usually accompanied by a rapid decline in HIV RNA levels and rise in CD4+ T cell counts. Because the hepatic damage in chronic hepatitis B is primarily the result of the immune response to the hepatitis B–infected hepatocytes, immune reconstitution may lead to worsening liver disease. There are case reports of hepatic decompensation in the setting of HAART initiation in HIV-HBV coinfected despite use of lamivudine in the HAART regimen. Thus, some experts recommend that anti-HBV therapy be started before HAART initiation especially if HBV DNA levels are high; this strategy, however, has not been tested. Because there are many other causes for liver ALT elevations in HIV-infected persons, including direct medication toxicity, it is difficult to prove that immune reconstitution inflammatory syndrome can exacerbate chronic hepatitis B. Reconstitution of HBV-specific T cell responses has been observed in HIV-infected patients receiving HAART, supporting the possibility that worsening of hepatitis B is a component of the immune reconstitution inflammatory syndrome.

Needs for Future Research

HIV affects both the natural history and treatment of chronic HBV infection, making it difficult to extrapolate findings from research on patients with HBV monoinfection to those with HIV-HBV coinfecion. Although it is clear that HIV increases the progression of liver disease, the mechanisms responsible require further elucidation, and the findings from such studies are likely to throw light on the underlying elements responsible for disease progression and perhaps provide targets to prevent progression. Clinical studies are needed to determine the threshold HBV DNA level that warrants initiation of anti-HBV treatment in HIV-HBV coinfected patients, as well as the optimal on-treatment HBV DNA level at which disease progression is prevented. Further work is also needed on how to optimize anti-HBV therapy in HIV-HBV coinfected persons, including strategies to avoid immune reconstitution inflammatory syndrome, and to determine which combinations are most effective and least toxic together with anti-HIV regimens. Finally, with the recent introduction of potent and safe agents against HBV, it is important to delineate the different patterns of resistance that emerge in this population and how to minimize the development of antiviral resistance from long-term anti-HBV therapy.

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References


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