

## Perspective

# HIV and Hepatitis B Virus: Options for Managing Coinfection

*At the International AIDS Society–USA course in New York in October 2002, Douglas T. Dieterich, MD, presented the case history of a patient coinfecting with HIV and hepatitis B virus (HBV). HBV infection in patients with HIV is associated with worse prognosis for HBV disease than in patients without HIV and complicates management of both diseases. However, newer treatment options for chronic HBV infection increase the potential for successful management.*

## Case History: HIV/HBV Coinfection

### Case Presentation

A 44-year-old man with chronic HIV and hepatitis B virus (HBV) infections was referred for treatment in 1999. His prior liver biopsy showed chronic hepatitis with portal/periportal necroinflammatory activity, septal fibrosis, and architecture distortion, yielding a diagnosis of transition to cirrhosis (grade 3-4). The patient had been treated with interferon alfa 5 MU per day for 3 months prior to referral but had discontinued treatment owing to intolerable, disabling adverse effects. He was receiving an unusual antiretroviral regimen of abacavir/stavudine/nevirapine.

Initial laboratory results showed elevated liver enzymes with alanine aminotransferase (ALT) of 164 U/L and aspartate aminotransferase (AST) of 136 U/L, albumin of 3.8 g/dL, and platelet count of 69,000, with the higher ALT and lower albumin and platelet values all suggesting cirrhosis. INR was 1.5; HBV DNA level was 46 million copies/mL, a relatively low concentration; and the patient was HBV e-antigen-positive, indicating active viral replication, and e-antibody-negative. HIV infection was well con-

trolled on the current antiretroviral regimen, with plasma HIV-1 RNA level of 150 copies/mL and CD4+ cell count of 352/ $\mu$ L. The HBV-related diagnosis was chronic HBV infection with cirrhosis.

### Discussion: Characteristics of HBV Disease in HIV/HBV Coinfection

Worldwide, there are approximately 40 million individuals infected with HIV and approximately 400 million infected with HBV, including approximately 1 million and 1.25 million, respectively, in the United States. It is estimated that 10% of HIV-infected individuals are HBV surface antigen-positive (Rustgi et al, *Ann Intern Med*, 1984) and that HIV-infected individuals are 3 to 6 times more likely to develop chronic HBV infection than HIV-uninfected individuals (Bodsworth et al, *J Infect Dis*, 1991). Although HIV is an RNA virus and HBV is a DNA virus, both integrate into the host cell genome, with the primary targets being CD4+ cells and hepatic cells, respectively. Both also utilize reverse transcriptase in replication, are susceptible to nucleoside reverse transcriptase inhibitors (nRTIs) and nucleotide

reverse transcriptase inhibitors (nRTIs), and exhibit mutations that confer resistance to nRTIs.

The effect of HIV/HBV coinfection on liver-related mortality is demonstrated by recently reported data from the Multicenter AIDS Cohort Study (Thio et al, 9th CROI, 2002). As shown in Figure 1, follow-up of approximately 5000 patients over more than 14 years has shown that individuals with HIV/HBV coinfection have risk of liver mortality that is 14 times greater than that in individuals who are HIV-uninfected and HBV surface antigen-negative; the risk is also markedly greater than that in those who are HIV-infected/HBV surface antigen-negative or HIV-uninfected/HBV surface antigen-positive. HIV/HBV coinfection is also associated with much higher rates of cirrhosis than is HBV infection alone (Colin et al, *Hepatology*, 1999).

### Clinical Course: Initial Treatment

Treatments approved by the US Food and Drug Administration (FDA) for chronic HBV infection currently consist of interferon alfa 5 MU once daily or 10 MU 3 times weekly for at least 16 weeks,

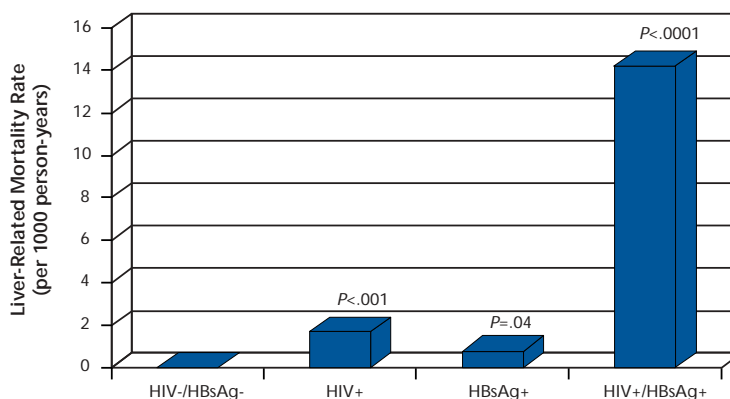


Figure 1. Liver-related mortality rates in Multicenter AIDS Cohort Study subjects who are HIV-uninfected and hepatitis B virus (HBV) surface antigen-negative (HIV-/HBsAg-), HIV-infected and HBsAg- (HIV+), HBV surface antigen-positive and HIV- (HBsAg+), and HIV+/HBsAg+. Adapted with permission from Thio et al, 9th CROI, 2002.

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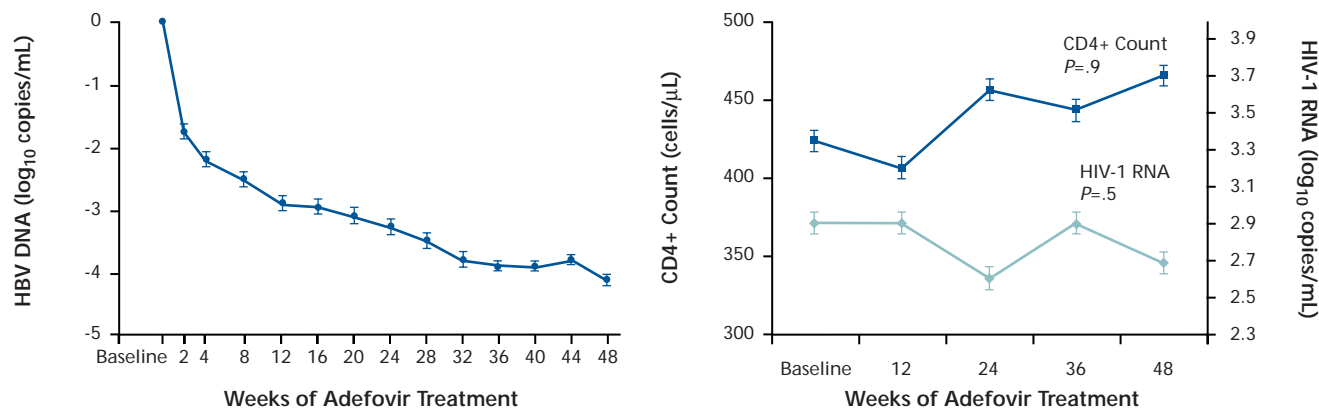


Figure 2. Left: Effect of adefovir treatment on hepatitis B virus (HBV) DNA level by study week in 31 HIV/HBV-coinfected patients with lamivudine-resistant HBV. Right: Effect of treatment on plasma HIV-1 RNA level and CD4+ cell count. Adapted with permission from Benhamou et al, *Lancet*, 2001.

lamivudine 100 mg once daily for at least 12 months, and, as of September 2002, adefovir 10 mg once daily. At the time of the patient's presentation in 1999, would any of the following constitute rational treatment for the patient?

- Addition of lamivudine 100 mg daily
- Initiation of pegylated interferon alfa 1.5 μg/kg weekly plus ribavirin 11.5 mg/kg
- Addition of lamivudine 150 mg twice daily plus famciclovir 500 mg twice daily
- Institution of no treatment due to high risk associated with borderline decompensated cirrhosis

**Discussion: Lamivudine Resistance**

Lamivudine at a suboptimal dose for treating HIV infection should not be used in this setting because of the risk of emergence of HIV resistance to the drug. Withholding of any HBV treatment is not recommended since the patient could benefit from treatment. Pegylated interferon alfa plus ribavirin is indicated for use in hepatitis C virus infection, and the pegylated interferon alfa part of this combination probably has good activity against HBV (as well as some activity against HIV), but the combination is not yet FDA-approved for use against HBV infection. The patient started lamivudine at the 150 mg twice-daily dose recommended for use in HIV infection and famciclovir 500 mg twice daily, a combination that has some synergistic activity in vitro and in vivo. The patient's ab-

cavir/stavudine/nevirapine regimen was continued.

In response to treatment, HBV viral load dropped below detection limits (<200 copies/mL by polymerase chain reaction) by December 1999 after approximately 3 months of therapy. By June 2000, however, HBV viral load had increased to 500 million copies/mL. HBV resistance to lamivudine is predictable and occurs with more rapidity in HIV/HBV-coinfected patients, appearing in almost half of this group after 2 years and in 90% after 4 years (Lai et al, *N Engl J Med*, 1998; Chang et al, *Antivir Ther*, 2000; Benhamou et al, *Hepatology*, 1999).

With regard to the patient's HIV infection status, in February 2000, his plasma HIV-1 RNA level increased to 56,000 copies/mL, with a CD4+ cell count of 320/μL. In March 2000, treatment was changed to didanosine/stavudine/lopinavir/ritonavir, and lamivudine/famciclovir for the HBV infection was continued. The patient's CD4+ cell count increased to 562/μL, and plasma HIV-1 RNA level was suppressed to less than 50 copies/mL for prolonged periods interspersed with blips up to 150 to 900 copies/mL.

Although not available for use in this patient at the time of the HBV relapse, adefovir is now an option in the case of HBV resistance to lamivudine. This drug was initially developed for use in HIV infection at much higher doses than that used for HBV infection and is associated with unacceptable risk for nephrotoxicity at these higher doses. At lower doses,

however, adefovir has been found to maintain activity against HBV resistant to lamivudine as a result of the presence of the M204I, M204V, L180M plus M204I, or L180M plus M204V mutations. In an open-label pilot study of adefovir in HIV/HBV-coinfected patients with lamivudine-resistant HBV reported by Benhamou and colleagues (*Lancet*, 2001), adefovir 10 mg per day produced a decrease in HBV DNA of 4 log<sub>10</sub> copies/mL over 48 weeks of treatment (Figure 2). No alteration in HIV-1 RNA level was observed, indicating that adefovir at this dosage has little likelihood of anti-HIV effects and thus is unlikely to confer resistance. A substantial but not statistically significant increase in CD4+ cell count was observed, likely associated with control of HBV replication rather than any anti-HIV effect. In this study, reversible grade 1 increases in serum creatinine levels were observed in 2 patients, with neither case considered related to adefovir treatment, and no serum phosphate abnormalities were observed.

**Clinical Course: Adverse Events**

In October 2000, the patient noted numbness and tingling in his feet while he was still receiving didanosine/stavudine/lopinavir/ritonavir for anti-HIV therapy and lamivudine/famciclovir for anti-HBV therapy. He was diagnosed with neuropathy, and his serum lactate level was 5.6 mmol/L. Adefovir had become available through a compassionate-use program. How should treatment be changed?

- Addition of adefovir 10 mg for HBV treatment and substitution of zalcitabine for stavudine in the antiretroviral regimen
- Substitution of adefovir for the lamivudine/famciclovir regimen
- Addition of tenofovir
- Discontinuation of all treatment

### Discussion: Symptomatic Hyperlactatemia and Activity of Tenofovir

In this case, the best choice was to discontinue all treatment since the patient had symptomatic hyperlactatemia. This option was further supported by the patient's liver disease status. The liver is a primary organ in lactate metabolism, and serum lactate levels serve as a measure of liver function. Data from 210 cases of paracetamol-induced acute liver failure reported by Bernal and colleagues (*Lancet*, 2002) indicate that arterial lactate level is an effective predictor of death from liver failure, with mean lactate levels being 8.5 mmol/L in those who died and 1.4 mmol/L in those who survived. The onset of symptomatic hyperlactatemia usually occurs when serum lactate levels are 3 mmol/L or higher; increases to greater than 5 mmol/L are often associated with acidosis, and mortality rates are extremely high in acidotic patients. Risk factors for symptomatic hyperlactatemia include female sex, obesity, and hepatitis C virus infection, HBV infection, or other liver disease.

Lactic acidosis and other metabolic abnormalities have been associated with mitochondrial toxicity due to nRTI use. Cihlar and Chen investigated the potential for causing mitochondrial toxicity via incorporation of active forms of nRTIs and the nRTI tenofovir by cellular polymerase  $\gamma$  enzymes (*Antiviral Chem Chemother*, 1997). Their results indicate that stavudine, didanosine, and zalcitabine exhibit relatively high incorporation and that tenofovir, lamivudine, and zidovudine exhibit low incorporation. In a recently reported study comparing tenofovir/lamivudine/efavirenz (n=299) and stavudine/lamivudine/efavirenz (n=301) over 48 weeks in patients with HIV disease, nRTI- and nRTI-associated toxicities occurred in 3% of patients receiving the former regi-

men and 11% receiving the latter. Peripheral neuritis/neuropathy occurred in 2% versus 7%, lipodystrophy in 1% versus 4%, lactic acidosis in 0% versus less than 1% (3 cases), and pancreatitis in 0% for both groups (Staszewski, 14th Int AIDS Conf, 2002).

Tenofovir is currently approved by the FDA for treatment of HIV infection only. The drug has been shown to be active against both lamivudine-susceptible and -resistant HBV, however, with no difference in 50% inhibitory concentration. Studies in HIV-infected patients indicate that tenofovir monotherapy results in a 0.6- $\log_{10}$  copies/mL decrease in plasma HIV-1 RNA level. In a large study of patients with HBV infection, half of whom had lamivudine-resistant virus, tenofovir 300 mg once daily produced a decrease in HBV DNA level of 4  $\log_{10}$  copies/mL from baseline over 48 weeks and a 5- $\log_{10}$  copies/mL decrease compared with placebo (Figure 3; Cooper et al, 14th Int AIDS Conf, 2002). In a small study of 12 HIV/HBV-coinfected patients with suppression of plasma HIV-1 RNA level but uncontrolled HBV replication, the addition of tenofovir 300 mg once daily to lamivudine 150 mg twice daily produced a nearly 4- $\log_{10}$  copies/mL decrease in HBV DNA level over 24 weeks, accompanied by a CD4+ cell increase of approximately 70/ $\mu$ L. As in the study of adefovir, the CD4+ cell increase appears to be due to control of HBV replication, since the patients' HIV-1 RNA levels were suppressed below detection limits throughout the study (Bochet et al, 9th CROI, 2002).

### Clinical Course: Resuming Treatment

All of the patient's medications were stopped for 3 months, during which time serum lactate level declined to 1.8 mmol/L. Treatment was restarted with tenofovir/abacavir/lopinavir/ritonavir. After 3 months on treatment, the patient was HBV e-antigen-negative and e-antibody-positive, with HBV DNA level reduced to less than 200 copies/mL. Plasma HIV-1 RNA level was less than 50 copies/mL and CD4+ cell count had increased to 676/ $\mu$ L.

### Future Treatment Options

Lamivudine and tenofovir offer the prospect of treating HIV and HBV infection with the same drug, and adefovir and tenofovir offer options in the setting of lamivudine-resistant HBV, although, as previously mentioned, tenofovir for treatment of HBV infection is not yet FDA-approved. Investigators are currently studying the use of combination therapy for HBV infection and data supporting its use should be available soon. Like HIV, HBV mutates frequently, and single-nRTI therapy for HBV infection has been shown to lead to drug resistance, making a strong argument for using at least 2 drugs active against HBV. There are few data on HBV resistance associated with nRTIs such as tenofovir and adefovir.

A number of new agents for treating HBV infection are also in development. Assessment of Ld-thymidine (LdT) and Ld-cytidine (LdC) in the woodchuck model of HBV, which precisely mimics

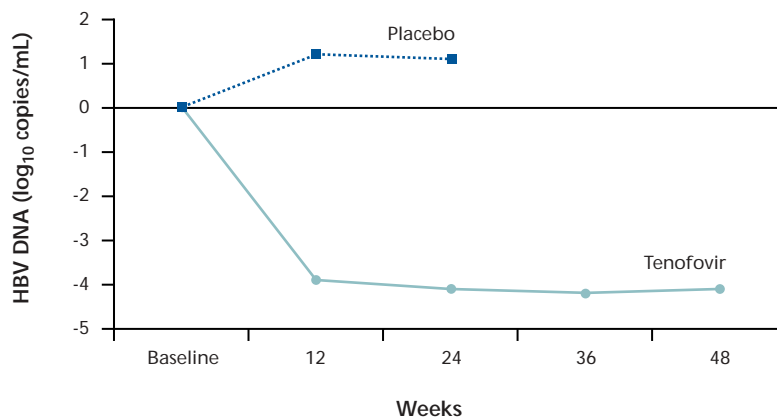


Figure 3. Change in hepatitis B virus (HBV) DNA level over 48 weeks of treatment with tenofovir or 24 weeks with placebo in 12 patients with HBV infection, half with lamivudine-resistant HBV. Adapted with permission from Cooper et al, 14th Int AIDS Conf, 2002.

the HBV carrier state in humans, has shown a pronounced effect of LdT 10 mg/kg in reducing HBV viral load and synergism of the LdT and LdC at doses of 1 mg/kg. LdT is being investigated in a phase 2B trial in 105 patients with chronic HBV infection. Week 12 safety and antiviral results were submitted to the FDA and supported initiation of phase 3 studies. Weeks 12 and 24 data will be available in the near future. The valine ester of LdT (val-LdT), which exhibits a prolonged half-life compared with the parent compound, is being developed as an anti-HIV drug and also exhibits anti-HBV activity. In an ongoing phase 1/2 trial examining doses of 50 mg to 400 mg in patients with HBV infection, val-LdT 200 mg and 400 mg both produced 2- $\log_{10}$  copies/mL decreases in serum HBV DNA level over 4 weeks.

Entecavir is an investigational guanine analogue that inhibits all 3 HBV polymerase functions (priming, negative strand formation, and positive strand synthesis). In phase 2 trials, reductions in serum HBV DNA of between 2  $\log_{10}$  and 3  $\log_{10}$  copies/mL were achieved with entecavir doses of 0.5 mg and 1.0 mg once daily (de Man et al, *Hepatology*, 2001). The ongoing entecavir phase 3 program is scheduled to enroll more than 2000 HBV-infected patients worldwide to receive treatment at 0.5 mg (nRTI-naive patients) or 1.0 mg (patients with virologic failure on lamivudine) for 48 to 96 weeks, with a 24-week post-treatment follow-up. The primary end points are liver histology findings and proportion of patients with HBV DNA below limits of detection.

Other new investigational agents with HBV activity include emtricitabine (FTC), diaminopurine dioxolane (DAPD), and clevudine (L-FMAU). Emtricitabine, which has activity against HIV, is not effective against lamivudine-resistant HBV but offers the potential advantage of once-daily dosing. DAPD is also active against HBV and HIV, including many drug-resistant strains of the latter. L-FMAU is a fluorinated uracil compound; unlike fialuridine, a fluorinated uracil compound that caused severe mitochondrial toxicity, L-FMAU does not undergo conversion to the D-isomer form and has not been associated with

mitochondrial toxicity. Use of L-FMAU in combination with either emtricitabine or DAPD results in prolonged decreases in HBV DNA of between 2  $\log_{10}$  and 3  $\log_{10}$  copies/mL after treatment as brief as 4 weeks. Such findings suggest the potential for use of short intensive courses of combination therapy that may permit patients to gain immunologic control in chronic infection.

## Conclusions

In conclusion, HBV infection results in higher rates of liver disease in HIV-coinfected patients than in individuals without HIV infection. Lamivudine resistance in HBV is becoming increasingly common. Adefovir and now tenofovir offer activity against lamivudine-resistant HBV, with the latter also offering anti-HIV activity in coinfecting patients. Drugs in development promise to expand the ability to treat HBV infection, as well as HIV infection in coinfecting patients. Management of HBV infection in HIV-infected patients is now more complex than when few treatment options were available but is also more likely to be successful thanks to the newer treatment options.

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## Suggested Reading

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