**Tenofovir Disoproxil Fumarate Therapy for Chronic Hepatitis B in Human Immunodeficiency Virus/Hepatitis B Virus–Coinfected Individuals for Whom Interferon-α and Lamivudine Therapy Have Failed**

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A significant proportion of human immunodeficiency virus (HIV) infected patients are coinfected with hepatitis B virus (HBV). Currently available treatments for chronic hepatitis B (interferon [IFN]-α and lamivudine [3TC]) have limited long-term utility because of side effects or of the development of resistance. Tenofovir disoproxil fumarate (TDF) is a nucleotide analog with excellent activity in vitro against HBV, which is also active against 3TC-resistant HBV variants. In this 24-week pilot study, the anti-HBV activity of TDF was prospectively evaluated in a cohort of 6 HIV coinfected subjects for whom 3TC and IFN therapy had previously failed. At baseline, all patients were taking 3TC or FTC and were hepatitis B surface antigen and hepatitis B e antigen positive; 4 had cirrhosis. Baseline HBV load was 7.95 log10 copies/mL. By weeks 12 and 24, HBV load had decreased by 3.1 log10 copies/mL and 4.3 log10 copies/mL, respectively. There was a transient increase of transaminases after the initiation of treatment. No patient developed HBe antibodies. TDF is a very promising drug for the treatment of chronic hepatitis B in HIV-infected individuals.

The increased survival of human immunodeficiency virus (HIV)-infected individuals has made other comorbidities important in the long-term management and prognosis of this infection. A significant proportion of HIV-infected patients are coinfected with hepatitis B virus (HBV). These patients are at risk of developing HBV disease–associated outcomes, such as cirrhosis, hepatocellular carcinoma, and, eventually, death [1, 2].

The US Food and Drug Administration (FDA)-approved agents for the treatment of HBV infection are interferon (IFN)-α and lamivudine (3TC). IFN-α therapy for 3–6 months is associated with loss of HBV DNA and hepatitis B e antigen (HBeAg) 37% and 33% of patients, respectively [3]. However, IFN-α is expensive and may be accompanied by frequent and unpleasant side effects.

Treatment with 3TC for 12 months for HBeAg-positive chronic hepatitis showed similar results. The primary limitation of treatment of chronic hepatitis B with 3TC is the development of resistance, associated with the appearance of the YMDD and other mutations at the domain C of reverse transcriptase (RT) [4, 5].

Many HIV-HBV coinfected individuals have received 3TC therapy as part of their antiretroviral combination regimen. In general, the HBV virologic benefits are transient, because of a time dependent appearance of HBV resistant mutants [3, 6]. The frequency of this problem may be even higher than in HIV-negative subjects. The proportion of HIV-coinfected patients with HBV resistance mutations was ∼25% and 52% after continuous exposure to 3TC for 1 and 2 years, respectively [7, 8].

Tenofovir is a nucleotide analog with excellent activity in vitro against HBV and is also active against 3TC-resistant HBV variants [9]. Tenofovir disoproxil fumarate (TDF; orally bioavailable as a prodrug) is FDA approved as an antiretroviral agent. In this pilot study, we prospectively evaluated the anti-HBV activity of TDF in a cohort of HIV-coinfected subjects, for whom 3TC and IFN therapy had previously failed.

**Subjects and Methods**

Subjects. HIV-positive subjects with evidence of persistent HBV replication despite prior anti-HBV treatment with IFN-α who were receiving 3TC or emtricitabine (FTC) at the time of enrollment, were eligible for the trial. Clinical evidence for resistant HBV was defined as having a virus load >10^6 copies/mL while receiving 3TC or FTC treatment, persistent positive hepatitis B surface antigen (HBsAg), absence of anti-HBs, or anti-HBe.

Patients with alcohol dependency, hemochromatosis, evidence for
or being triply infected with HBV, HIV, and hepatitis C virus were excluded. All patients with hepatocellular carcinoma were excluded. A serum creatinine <1.5 mg/dl at baseline was required. Study participants were naive to TDF and had to be receiving a potent antiretroviral regimen (2 nucleoside analogs and a nonnucleoside RT inhibitor or a protease inhibitor).

**Drug regimen.** Tenofovir (300 mg once/day orally) was added to the potent antiretroviral regimen the patients were receiving. Patients were seen at weeks 4, 8, 12, and 24. During every visit, a directed physical examination and laboratory work-up was performed. 3TC or FTC treatment was continued in 5 patients. One subject discontinued 3TC at the time of initiation of tenofovir.

**Laboratory testing.** Serum samples of every individual were tested for HBV serologic responses, including HBsAg, HBeAg, anti-HBe, anti-HBs, and anti-HBc (qualitative testing). HBV DNA load was measured using a real-time quantitative polymerase chain reaction (PCR) assay by TaqMan Universal PCR (ABI applied Biosystems; Specialty Lab). The detection limit was 1.5 × 10^3 copies/mL. Undetectable values were made equal to 1499 copies/mL.

**Statistical analysis.** One-way repeated measures within subjects' analysis of variance (ANOVA) was conducted, with the factor being the number of weeks receiving tenofovir treatment and the dependent variable being the log_{10} of the HBV load. SPSS version 11.0 (SPSS) was used for all statistical analysis.

## Results

Six patients participated; baseline characteristics are shown in table 1. All had previous IFN-α treatment failure (mean duration of treatment, 12 weeks) and were currently receiving 3TC or FTC (median duration, 38 months; range, 26 months to 6 years). One patient had failed treatment with FTC that he had been receiving for 30 months. Three of the subjects had multiresistant HIV with evidence of 3TC resistance (M184V substitution in the RT gene) and a detectable HBV RNA load.

All individuals had active HBV replication with a median serum HBV DNA of 7.95 log_{10} copies/mL. All had a detectable HBsAg and were HBeAg-positive. At baseline, the median alanine aminotransferase (ALT) level was 53 U/L (range, 25–141 U/L). The median CD4^+ T cell count was 264 cells/mm^3 (range, 0–910 cells/mm^3), and the median HIV RNA load was 3.1 log_{10} copies/mL (range, undetectable to 183,904 HIV RNA copies/mL).

Five patients underwent a liver biopsy prior to the initiation of TDF therapy; 4 subjects had evidence of cirrhosis. The remaining patient had histopathological features of hepatitis grade 2, stage 2–3, using the Scheuer Classification System for grading [10]. TDF was well tolerated, and the patients completed 24 weeks of treatment. The decrease of HBV load was associated with a very mild increase of ALT level (mean increase by week 12, 17 U/L; P = .10).

At week 12, the HBV load in the serum had decreased 3.1 log_{10} copies/mL (from 7.9 ± 0.6 log_{10} copies/mL to 4.8 ± 1.0 log_{10} copies/mL). At week 24, the HBV load had decreased to 3.6 ± 0.4 log_{10} copies/mL (figure 1). The results of the repeated measures ANOVA test indicated a significant time effect (Wilks’ Lambda = 0.008; F = [2,4] = 260; P < .0001). We conducted 3 pairwise comparisons among the means for weeks 0, 12, and 24. P = .05 was considered to be significant. The Bonferroni correction was used to correct for multiple comparisons.

Two of the 6 subjects had HBV load values under the limit of detection at week 24. No patient developed new anti-HBe. The response to TDF seemed to be independent of the degree of immunosuppression: in 1 subject with a CD4 T cell count of 0 for more than a year before the initiation of TDF, HBV serum DNA became undetectable.

Consistent with the pivotal trials of TDF for HIV infection, there was also anti-HIV activity. The HIV RNA in the serum decreased by 0.7 log_{10} copies/mL in the subjects with a detectable virus load. The median CD4^+ T cell count remained stable (276 cells/mm^3) at week 24 vs. 264 at baseline.

## Discussion

Therapeutic options for HBV infection are limited. In addition to IFN-α and 3TC, the nucleotide antiviral, adefovir, has shown promising activity in chronic HBV infections and, in September 2002, has been approved by the FDA for the treatment of chronic hepatitis B [11]. The results of this prospective pilot study are very promising and demonstrate the potent anti-HBV activity of TDF in HIV coinfecting individuals and are consistent with 2 small retrospective cohort studies presented elsewhere [12, 13].

Tenofovir is a more attractive option for the treatment of HBV in patients coinfect with HIV than adefovir for several reasons. First, the use of adefovir would represent the addition of yet another drug to a very complicated medication regimen with the risk for increased toxicity and significant drug interactions among HIV-positive patients [14, 15]. Major toxicities, however, have yet to be observed in an ongoing prospective trial of HIV-negative patients. Second, the administration of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age, median years (range)</td>
<td>39 (36–51)</td>
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<tr>
<td>ALT level, median U/L (range)</td>
<td>53 (25–141)</td>
</tr>
<tr>
<td>HBV DNA load, median log_{10} copies/mL (range)</td>
<td>7.95 (6.97–8.72)</td>
</tr>
<tr>
<td>CD4^+ T cell count, median cells/mm^3 (range)</td>
<td>264 (0–910)</td>
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<tr>
<td>HIV RNA load, median log_{10} copies/mL (% undetectable)</td>
<td>3.1 (50)</td>
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**Table 1.** Baseline characteristics in human immunodeficiency virus (HIV)/hepatitis B virus (HBV)-coinfected individuals (n = 6).

NOTE. 3TC, lamivudine; ALT, alanine aminotransferase; IFN, interferon; TDF, tenofovir disoproxil fumarate.

a One subject received 26 months of 3TC treatment and, subsequently, 36 months of emtricitabine.

b Grade 2/stage 2–3, per Scheuer Classification System [10].
adefovir, especially in a patient with incomplete HIV-1 suppression, at a low dose of 10 mg once daily, could potentially put some selective pressure on HIV-1 and lead to the development of HIV-1 RT mutations that would limit future HIV therapeutic options for the patient; this problem, however, was not observed in a recent series [16]. Last, the anti-HIV activity of TDF, which adefovir lacks, and its excellent tolerability in patients with advanced HIV infection, makes it more attractive for the patient with limited therapeutic options in which the goal of antiretroviral therapy is not necessarily to reach HIV undetectability, but to try to lower as much as possible the HIV RNA load.

The success of currently available antivirals for the treatment of HBV has been hampered by the long term development of resistance. The use of combination therapy for HBV infection (i.e., 3TC and TDF), although not formally evaluated yet, is attractive from a theoretical perspective because of the potential for augmented antiviral activity and durability, and the increased genetic barrier for the development of resistance.

Hepatitis B is a potentially controllable disease that occurs very frequently in HIV-infected individuals, especially in some risk groups. Aggressive treatment of this coinfection will hopefully lead to an improved tolerability of antiretroviral therapy and decreased morbidity and mortality associated with it. TDF is a very promising drug for this indication that needs to be evaluated in the setting of prospective, randomized trials.

Acknowledgments

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References