Antiretroviral Therapy and HIV/Hepatitis B Virus Coinfection

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Among human immunodeficiency virus (HIV)–infected individuals, the prevalence of hepatitis B surface antigen (HBsAg) seropositivity is ∼10-fold higher than in the general population. HIV/hepatitis B virus (HBV)–coinfected patients have an increased risk of cirrhosis and liver-disease–related death. The strategy and management of anti-HBV therapy in HIV-infected persons must take into consideration both viral infections. Among HIV/HBV-coinfected patients, lamivudine promptly inhibits HBV replication. The emergence of resistance to lamivudine has been documented in HBV strains. Adefovir has been shown to be effective in the treatment of lamivudine-resistant HBV in HIV/HBV-coinfected patients. Tenofovir has recently been shown to have significant activity against both HIV and HBV. HBsAg seropositivity has been identified as an independent predictor of highly active antiretroviral therapy–related hepatotoxicity. However, further research is needed to determine the exact role of HBV and the mechanisms involved in antiretroviral-associated hepatotoxicity in HBV/HIV-coinfected patients.

Chronic infection with hepatitis B virus (HBV) affects ∼5% of the world population [1]. In Western Europe, Australia, and the United States, the prevalence of chronic carriage of hepatitis B surface antigen (HBsAg) is <1% of the population. Among HIV-infected individuals, this prevalence is ∼10-fold higher [2]. Until recently, there have been relatively few studies of the effects of HBV infection in HIV-seropositive patients. The natural history of chronic HBV (CHB) infection is modified by coinfection with HIV. After initial HBV infection, both the development and persistence of CHB infection are greater in patients with prior HIV infection [3, 4]. Among individuals with chronic HBsAg carriage, a high level of HBV replication or the presence of hepatitis B e antigen (HBeAg) are common in those with HIV/HBV coinfection [3, 4]. These 2 conditions may be predictive of poor survival. However, studies of deeply immunosuppressed patients performed prior to the era of HAART found mild necroinflammatory liver lesions to be associated with low serum transaminase levels [5–7]. More recent studies conducted during the HAART era have reported a higher incidence of liver-related cirrhosis and mortality in HIV/HBV-coinfected patients, compared with persons only infected with HIV [8–10].

Factors that affect the progression to cirrhosis in HIV/HBV-coinfected patients remain unknown. HAART-related immune restoration may switch the immune reaction to HBV from a tolerant to an intolerant phase, leading, in a few cases, to the complete control of HBV replication or, in the majority of patients, to an exacerbation of chronic hepatitis. HAART-related hepatotoxicity could also contribute to the worsening of liver damage. On the other hand, improvement of liver lesions may be observed in patients receiving antiretroviral regimens that contain lamivudine. Finally, the effect of HIV infection on the natural history of CHB infection could also be modified by a longer life expectancy, which may allow more time for cirrhosis to develop. Therefore, because of the complex and potent interactions between these 2 viruses, as well as their interactions with the immune system and antiretroviral...
therapy, the strategy and management of anti-HBV therapy in HIV-infected persons must take into consideration both viral infections.

Therapy for CHB in HIV-positive patients has been insufficiently studied. Most of the reported trials have been non-randomized, included a small sample size of patients, and been performed during the pre-HAART era. In addition, these studies did not consider liver histology as an end point. Lamivudine has been the most studied drug in this area; recently, adefovir has been tested for the treatment of lamivudine-resistant HBV. Additionally, the anti-HBV activity of tenofovir in HIV-infected persons has been reported recently.

**LAMIVUDINE**

Lamivudine is effective against both HIV and HBV replication. Among HIV/HBV-coinfected patients, lamivudine (150 mg twice daily) given for HIV infection as monotherapy or as part of an antiretroviral regimen, promptly inhibits HBV replication [11, 12]. The anti-HBV activity of lamivudine was first assessed in a prospective open-label study in 40 patients with advanced HIV infection [11]. After 1 year of treatment, 96.3% of patients had an undetectable serum level of HBV DNA (<5 pg/mL, by molecular hybridization). Anti-HBe seroconversion and HBeAg seronegativity were observed in 11% and 18.5% of cases, respectively. In patients with detectable serum levels of HBV DNA (>5 pg/mL), increases in serum alanine aminotransferase (ALT) levels were observed 2–8 weeks after the initiation of lamivudine therapy. Subsequently, at week 52 of treatment, ALT levels significantly decreased, compared with baseline. A retrospective analysis of HIV/HBV-coinfected patients prospectively enrolled within the CAESAR trial has been reported [12]. This was a randomized, double-blind, placebo-controlled trial of lamivudine (150 mg twice daily) or lamivudine plus loviride added to zidovudine-containing regimens for patients with advanced HIV infection [13]. Among patients included in the CAESAR study, 122 were coinfected with HBV (97 in the lamivudine arm and 25 in the placebo arm). Although randomization was not based on HBV infection, there were no differences between patients in the lamivudine arm and those in the placebo arm with respect to baseline demographic characteristics, HIV disease, serum ALT levels, and HBV virological status. The main virological and biological results are summarized in figure 1. At week 52, the median serum HBV DNA reduction was 2.7 log10 copies/mL as measured by PCR (quantification range, 2.6–7.6 log10 copies/mL; Amplicor; Roche) in the lamivudine treatment arm, compared with no reduction in the placebo arm. Using a sensitive method, serum HBV DNA was undetectable in 40% of lamivudine-treated patients at week 52. Finally, the tolerance profile of lamivudine (150 mg twice daily) was described as excellent in both HIV-infected and HIV/HBV-coinfected patients. However, no information regarding the underlying liver disease was available in either of these 2 studies [11, 12].

Resistance to lamivudine is well recognized in HIV strains, and it is encoded within the YMDD motif near to the catalytic site of reverse transcriptase [14]. The key mutation, M184V, occurs in almost all treated individuals. Mutations (M550V together with L526M and M550I alone) in the YMDD motif of the HBV DNA polymerase confer resistance to lamivudine [15, 16].

An incidence of HBV resistance to lamivudine was reported to be 50% after 2 years and 90% after 4 years of therapy in a retrospective cohort study of HIV/HBV-coinfected persons [17, 18]. Decrease in CD4 cell count, high body mass index, and duration of lamivudine therapy have all been associated with
Table 1. Anti–hepatitis B virus (HBV) activity of tenofovir (TNV) in HIV/HBV-coinfected patients.

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>No. of patients</th>
<th>Infecting HBV strain</th>
<th>Duration of TNV therapy, weeks</th>
<th>Change from baseline in serum HBV DNA, log10 copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benhamou et al. [32]</td>
<td>12</td>
<td>Wild type</td>
<td>12</td>
<td>−3.83 ± 0.38a</td>
</tr>
<tr>
<td>Cooper et al. [33]</td>
<td>12</td>
<td>3TC resistant</td>
<td>7</td>
<td>−5 ± 0.7a</td>
</tr>
<tr>
<td>Nelson et al. [34]</td>
<td>20</td>
<td>11</td>
<td>52</td>
<td>−4b</td>
</tr>
<tr>
<td>Ristig et al. [35]</td>
<td>6</td>
<td>6</td>
<td>24</td>
<td>−3.6 ± 0.4b</td>
</tr>
</tbody>
</table>

NOTE. 3TC, lamivudine.

a Mean.
b Median ± SD.

an increased risk of the emergence of HBV resistance. The emergence of resistance is characterized by a rise in serum HBV DNA load and a moderate increase in serum ALT levels [17, 19]. At breakthrough, serum HBV DNA levels are lower than levels before lamivudine therapy. However, the serum HBV DNA load returns to pretreatment levels within 6–12 months [17]. The clinical consequences of HBV resistance in HIV-positive patients are unknown. However, as observed in patients singly infected with HBV, cases of CHB exacerbation and liver failure have been reported in individuals infected with HIV and lamivudine-resistant HBV [20–22]. Thus, the progression of liver damage related to chronic infection with lamivudine-resistant HBV is expected in patients who remain untreated.

Lamivudine, when used as an anti-HIV drug at a dosage of 150 mg twice daily is effective and well tolerated for the control of HBV replication in HIV-coinfected individuals. However, there is no documented improvement of liver lesions in patients with HBV suppression, and the anti-HBe seroconversion rate is low. A rebound in serum HBV DNA and ALT levels occurs rapidly after the discontinuation of lamivudine therapy and is associated in some cases with the exacerbation of CHB [17, 23]. Therefore, the duration of lamivudine therapy in patients who do not seroconvert to anti-HBe is unknown. On the other hand, the durability of the response to lamivudine therapy is limited by the emergence of HBV-resistant strains, with an approximate annual incidence of 15%-20%.

ADEFOVIR

The efficacy of adefovir in HBV-infected, HIV-negative patients has been demonstrated in vitro and in vivo using wild-type and precore HBV replication assays [24–27]. Among HIV/HBV-coinfected patients, adefovir has been investigated for the treatment of lamivudine-resistant HBV [28].

In an ongoing, open-label pilot study conducted with 35 HIV/HBV-coinfected subjects with lamivudine-resistant HBV and controlled HIV infection, adefovir (10 mg once daily) was administered concurrently with lamivudine (150 mg twice daily) [28]. Mean decreases in serum HBV DNA concentrations from baseline (8.64 log10 copies/mL) were −3.40 log10 copies/mL at week 24 (n = 31) and −4.01 log10 copies/mL at week 48 (n = 29; P < .0001). Two patients experienced hepatitis anti-HBe seroconversion, at weeks 32 and 36. The interruption of adefovir therapy was followed by a rebound in serum HBV DNA loads. A transient increase in serum ALT concentrations was observed in 15 patients by week 8–24. By week 60, serum ALT levels were significantly lower than baseline levels [29]. During 48 weeks of adefovir therapy, there was no rebound in serum HBV DNA levels, and no mutations in the genes encoding HBV DNA polymerase and HIV RNA reverse transcriptase were identified. A significant decrease in necroinflammatory lesions was observed in the 15 patients who had liver biopsies at baseline and at week 48 [29]. No significant changes in either HIV RNA or CD4 cell counts were observed. Adefovir was generally well tolerated.

In summary, adefovir (10 mg once daily) is the only extensively studied therapeutic alternative for lamivudine-resistant HBV infection in HIV-coinfected patients. It is important for physicians to note that adefovir therapy in HIV/HBV-coinfected patients can be associated with a transient increase in the serum level of ALT, but this is not related to drug toxicity. The effect of discontinuing lamivudine therapy in HIV/HBV-coinfected patients treated with adefovir is unknown. However, it is anticipated that HBV replication would remain controlled with continued adefovir therapy, even if lamivudine was discontinued [30].

TENOFOVIR

Tenofovir has recently been shown to have significant activity against both HIV and HBV. Tenofovir is a nucleotide reverse-transcriptase inhibitor, and it has been shown to have potent in vitro activity against both wild-type and lamivudine-resistant HBV [31]. Tenofovir is approved for the treatment of HIV-1
infection as a once-daily 300 mg tablet. In short-term pilot studies, tenofovir demonstrated anti-HBV activity in HIV/HBV-coinfected patients [32–35] (table 1). HBeAg seroconversion was observed in one-quarter of the cases after 52 weeks of treatment. However, studies of tenofovir treatment of a larger patient population and for a longer period are necessary to assess the extent and durability of HBV suppression with this drug. Other important areas of research into tenofovir include its long-term tolerance profile, the potential emergence of resistance to tenofovir, and the HBeAg seroconversion rates in treated patients.

**HAART-RELATED HEPATOTOXICITY IN HIV/HBV-COINFECTED PATIENTS**

HBsAg seropositivity has been identified as an independent predictor of HAART-related hepatotoxicity in HIV-positive patients [36–39]. However, in the reported studies, hepatotoxicity was defined as an arbitrary and heterogeneous increase in serum ALT levels after the onset of HAART. The history of HBV serological test results and serum HBV DNA loads were unknown in most analyses, and information about underlying liver damage was lacking. It was also unknown whether lamivudine was included in the supposed hepatotoxic HAART regimen. No analyses of associated cofactors were undertaken. In these studies, the overall prevalence of ALT elevations was 15%, and HAART was discontinued by <10% of patients. Furthermore, some patients experienced a decline in serum ALT levels despite the continuation of HAART [36].

The possible mechanisms that are implicated in hepatotoxic events in HIV/HBV-coinfected patients include hypersensitivity, an intrinsic toxic effect, and immune reconstitution (sometimes described as a "hepatic flare"). Intrinsic toxic effects are often dose related. Cofactors involved in the development of these hepatic events include viral hepatitis (hepatitis C infection) and alcohol consumption.

Thus, the effects of HBsAg seropositivity in relation to HAART-related hepatotoxicity are speculative. Specific studies of the natural history of CHB infection in HIV-positive patients receiving HAART are needed to assess the respective role of immune restoration, the anti-HBV activity of lamivudine and tenofovir, and hepatotoxicity. The serological and virological status of patients should be determined both at the start of and throughout the study. The precise composition of the HAART regimen, including any changes in drugs, should be determined during the study. In particular, it should be known whether the regimen contains drugs that affect HBV replication, such as lamivudine or tenofovir. Other factors that affect ALT levels should also be monitored, such as hepatitis C infection status, alcohol intake, and other hepatic insults. The consequences of ALT elevations on liver lesions should be followed in a prospective manner.

The management of elevations in serum ALT levels in HIV/HBV-coinfected patients is complex and needs careful assess-
ment. The algorithm shown in figure 2 summarizes the most frequent situations associated with ALT elevations in HIV/HBV-coinfected patients.

CONCLUSIONS

The prevalence of HBV infection in HIV-positive patients is high. HIV/HBV-coinfected patients have an increased risk of cirrhosis and liver-disease–related death. Both HIV and HBV infections must be taken into account when treatment is considered, because of the dual antiviral activity of lamivudine and tenofovir. Lamivudine, when it is used as part of an antiretroviral regimen, has been shown to be effective and safe for the control of HBV replication in coinfected patients. However, HBV resistance may occur at an annual incidence of 15%–20%. Preliminary reports of anti-HBV activity by tenofovir-containing HAART regimens have shown encouraging results for the treatment of both wild-type and lamivudine-resistant HBV. The efficacy and safety of adefovir has been demonstrated in patients infected with lamivudine-resistant HBV. Further research is needed to assess the exact role of HBV in the risk of antiretroviral-induced hepatotoxicity, to determine the mechanisms involved in antiretroviral-associated liver injury in HBV/HIV-coinfected patients, and to improve the anti-HBe seroconversion rate in this population.

References

30. Peters M, Hann HW, Martin P, et al. Adefovir dipivoxil alone and in