Immune Reconstitution Hepatitis in HIV and Hepatitis B Coinfection, Despite Lamivudine Therapy as Part of HAART

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(See the editorial commentary by McGovern on pages 133–5)

Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfection occurs commonly. The introduction of antiretroviral therapy can result in immune reconstitution hepatitis. We describe 2 coinfected patients who developed clinical flares of HBV disease, despite the inclusion of lamivudine, a drug with anti-HBV activity, in their HAART regimens. Potential strategies to manage individuals with HBV/HIV coinfection are discussed.

Hepatitis B virus (HBV) coinfection with HIV is common, affecting 5%–10% of HIV-infected patients [1]. Hepatic damage in chronic HBV infection is predominantly immune mediated, with CD8 cytotoxic T lymphocytes targeting HBV antigens on infected hepatocytes, resulting in hepatocellular inflammation and necrosis [2]. Coinfection with HIV alters the natural history of HBV disease. The immunodeficiency of progressive HIV infection results in higher rates of hepatitis B e antigen (HBeAg) positivity and higher levels of HBV DNA but lower alanine aminotransferase (ALT) levels and similar or reduced necroinflammatory activity noted upon histological examination [3]. Despite this, liver disease progresses more rapidly [4].

Acute flares of HBV disease result from an alteration in the balance between the level of HBV replication, as reflected by the HBV DNA level, and the intensity of the immunologic response [2]. Flares can occur when antiviral therapy with anti-HBV activity is withdrawn, such as when therapy is switched from lamivudine to another antiretroviral regimen that does not have anti-HBV activity or when drug resistance to lamivudine develops [5, 6]. Flares may also occur in HBV/HIV coinfected patients during immune reconstitution following the introduction of HAART in the presence of high levels of HBV replication [7]. Flares may also occur as a result of hepatotoxicity associated with HAART therapy [8].

We describe 2 cases in which patients with HBV/HIV coinfection had clinical flares of hepatitis B disease following commencement of HAART, despite the inclusion of lamivudine in the initial regimen.

Patient 1. A 38-year-old, HIV-infected Ethiopian woman with a CD4 cell count of 203 cells/μL (CD4 cell percentage, 10%) and a plasma HIV RNA level of 94,800 copies/mL recommenced treatment with a HAART regimen of lamivudine, stavudine, indinavir, and ritonavir at a dosage of 100 mg b.i.d. after a 3-month break from therapy. She had previously received this regimen for 8 months without complication. She had chronic asymptomatic HBV infection (i.e., she was hepatitis B surface antigen [HBsAg] positive, HBeAg negative, and hepatitis B e antibody [anti-HBe] positive), with an albumin level of 30 g/L but otherwise normal liver function test (LFT) results (ALT, 15 U/L; γ-glutamyl transferase [GGT], 12 U/L; alkaline phosphatase [ALP], 80 U/L; and bilirubin level, 5 μmol/L).

Two weeks later, she presented with symptoms of fatigue, abdominal pain, and jaundice. LFT results demonstrated a hepatitic pattern (albumin level, 23 g/L; aspartate aminotransferase [AST], 2493 U/L; ALT, 1265 U/L; ALP, 187 U/L; and bilirubin level, 81 μmol/L) (figure 1). Coagulation was normal (international normalized ratio [INR], 1.2), and findings of abdominal ultrasonography were unremarkable. Results of a hepatitis A IgM test, a hepatitis C antibody (HCV-Ab) test and PCR, and hepatitis D virus antigen (HDV-Ag) and antibody (HDV-Ab) tests were negative. The serum lactate level was normal, at 1.3 mmol/L. The patient had not taken additional medication, either conventional or alternative, and did not imbibe significant amounts of alcohol. Results of hepatitis B serological tests demonstrated persistent presence of anti-HBe with undetectable HBeAg and an HBV DNA level of 387 pg/mL. At this point, the CD4 cell count had risen to 452 cells/μL (CD4 cell percentage, 16%), and the plasma HIV RNA level had decreased to 4500 copies/mL, indicating immune reconstitution.

Treatment with stavudine, indinavir, and ritonavir was thus ceased, and the patient continued to receive lamivudine at a dosage of 300 mg q.d. A week later, she was symptomatically stable, and transaminase levels had decreased slightly (ALT,

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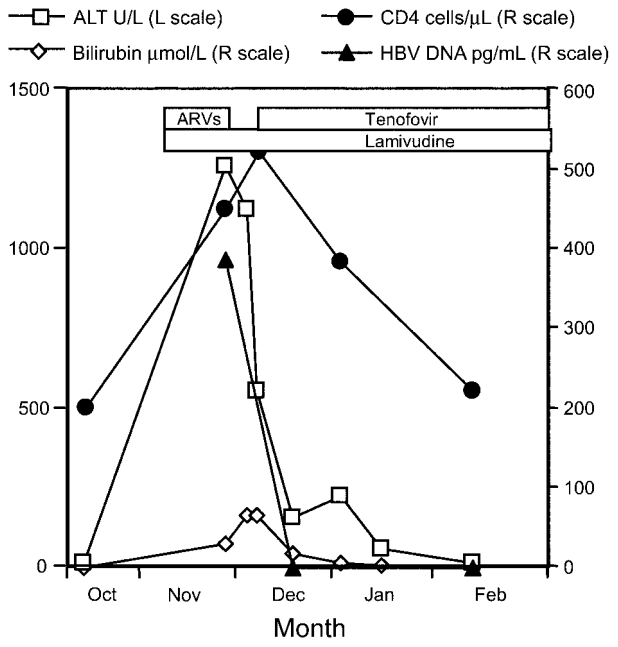

Figure 1. Patient 1: alanine aminotransferase levels (ALT), bilirubin levels, CD4 cell counts, and HBV DNA levels during treatment with antiretroviral agents (ARVs).

1130 U/L), but her jaundice had worsened with deteriorating synthetic liver function (albumin level, 19 g/L; bilirubin level, 168 μmol/L; and INR, 1.4). Consequently, treatment with tenofovir at a dosage of 300 mg q.d. was commenced. Four days later, the patient was symptomatically much improved and had a marked decrease in levels of transaminases and bilirubin and normalization of the INR (albumin level, 17 g/L; AST, 571 U/L; ALT, 279 U/L; bilirubin level, 96 μmol/L; and INR, 1.2). HBV DNA levels became undetectable 11 days after commencement of treatment with tenofovir. Three weeks after the introduction of tenofovir, the patient was symptomatically healthy, with resolution of jaundice, and zidovudine and abacavir were then added to her drug regimen. Six months after reinstitution of HAART, HBV DNA levels remained undetectable and results of LFTs were normal, except for a persistently low albumin level of 28 g/L. Retrospective HBV polymerase sequencing demonstrated no evidence of lamivudine resistance at the onset of symptoms. She underwent liver biopsy 9 months after the onset of symptoms, and this demonstrated Scheuer Grade 2 necroinflammatory activity and stage 3 fibrosis.

Patient 2. A 45-year-old, HIV-infected Ghanaian woman was admitted to our institution (The Alfred Hospital, Melbourne, Australia) with septic shock and multiorgan failure secondary to severe cellulitis with *Salmonella typhimurium* septicemia. Results of LFTs were abnormal at admission (albumin level, 14 g/L; ALT, 145 U/L; ALP, 86 U/L; bilirubin level, 45 μmol/L; and INR, 1.4), and hepatosplenomegaly was noted. Serological testing demonstrated positive results for HBsAg and HBeAg but negative results for HBeAb, with an HBV DNA level of 132 pg/mL. The results of an HDV-Ag test were negative, but results of a HDV-Ab test and HDV PCR were positive, and results of tests for hepatitis A IgM and HCV-Ab were negative. Abdominal imaging showed an irregular heterogeneous liver with no focal lesions and mild splenomegaly. Her CD4 cell count was 131 cells/μL (CD4 cell percentage, 6%), and the plasma HIV RNA level was 47,500 copies/mL.

The patient recovered slowly with intensive supportive measures, tissue debridement, and treatment with broad-spectrum antimicrobials; however, results of LFTs remained abnormal (albumin level, 12 g/L; ALT, 36 U/L; ALP, 552 U/L; bilirubin level, 39 μmol/L; and INR, 1.1), and she underwent a liver biopsy on day 32 of hospitalization. This revealed established macronodular cirrhosis (Scheuer fibrosis stage 4) and patchy interface and parenchymal hepatitis (necroinflammatory activity grade 3). Changes were reported as being compatible with HBV infection, and no CMV inclusions were detected. Her course of therapy was complicated by tibial osteomyelitis, an intracerebral lesion, and cytomegalovirus (CMV) viremia (CMV DNA level, 21,900 copies/mL), for which she received broad-spectrum antibiotics (teicoplanin and ciprofloxacin), empirical toxoplasmosis therapy (clindamycin and pyrimethamine), and ganciclovir, respectively.

On day 58 of the patient's hospitalization, we believed she was healthy enough to initiate HAART, and she began receiving lamivudine, abacavir, indinavir, and ritonavir at a dosage of 100 mg b.i.d. Results of LFTs at this time were as follows: albumin level, 16 g/L; bilirubin level, 22 μmol/L; ALT, 28 U/L; and ALP, 535 U/L. Four weeks after the commencement of HAART, she became ill with vomiting, abdominal pain, and deteriorating liver function (albumin level, 21 g/L; ALT, 482 U/L; ALP, 526 U/L; bilirubin level, 82 μmol/L; and INR, 1.4) (figure 2). Results of tests for HBeAg were now positive at a low level, HBV DNA titers had decreased to 49 pg/mL, and HBeAb and HBcIgM test results remained negative. HBV polymerase sequencing demonstrated no evidence of lamivudine resistance. The CD4 cell count had risen from 62 cells/μL (CD4 cell percentage, 4%) at the start of treatment to 96 cells/μL (6%), and plasma HIV RNA levels had decreased to <50 copies/mL. Results of HCV RNA testing were negative, CMV was now undetectable by PCR, and the lactate level was normal, at 1.8 mmol/L. The patient did not drink any alcohol. She had received phenytoin for seizures for 6 weeks prior to the onset of her hepatitis flare, but no other concurrent conventional or alternative therapy was added to her drug regimen. HAART, with the exception of lamivudine at a reduced dose of 100 mg daily, was ceased.

Her health continued, however, to deteriorate, with encephalopathy, coagulopathy, and worsening liver function (albumin level, 23 g/L; ALT, 642 U/L; ALP, 436 U/L; bilirubin level, 403

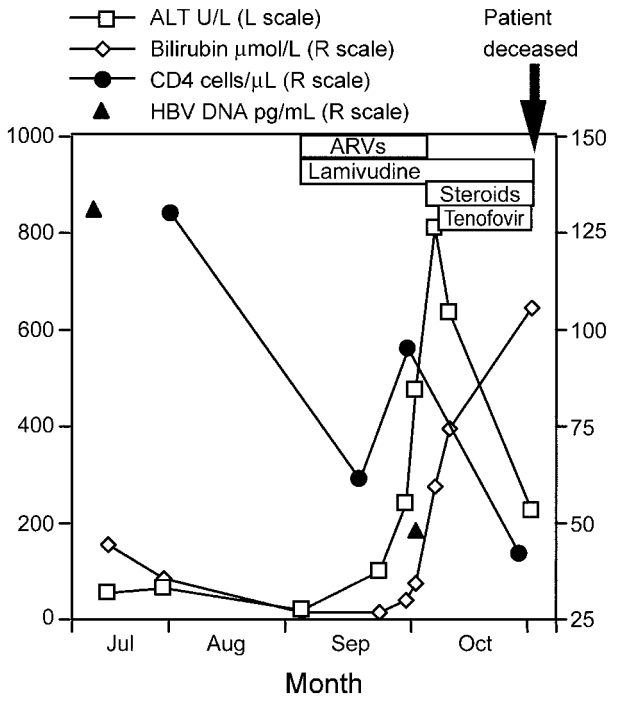

Figure 2. Patient 2: alanine aminotransferase levels (ALT), bilirubin levels, CD4 cell counts, and HBV DNA levels during treatment with antiretroviral agents (ARVs).

μmol/L; and INR, 1.5). High-dose oral steroid therapy was commenced to treat a presumed immune reconstitution–mediated flare of hepatitis, and tenofovir was added to her drug regimen. Despite these measures, she developed progressive hepatic and renal failure and died on day 122 of hospitalization.

Discussion. These 2 patients with chronic HBV/HIV coinfection had clinical flares of HBV disease with hepatic decompensation associated with the commencement of HAART and rapid immune reconstitution in the presence of high-level HBV replication. Both the rapid onset of abnormal LFT results with an increase in CD4 cell count within weeks after commencing HAART and the absence of an alternative explanation in both cases suggest that immune reconstitution was the likely cause. Moreover, both cases of hepatitis flares occurred, despite the incorporation of lamivudine (an agent with anti-HBV activity) as a component of HAART from the outset.

Hepatotoxicity associated with receipt of HAART can also result in abnormal LFT results. Neither patient was receiving nevirapine or full-dose ritonavir, the therapies described prospectively as most commonly associated with severe hepatic damage [9, 10]. Furthermore, in the first case, the therapy was a previously tolerated regimen. The second case was also confounded by multiple concomitant medications. Most of the medications were not significant hepatotoxins, except for phenytoin and ciprofloxacin. Because the patient, many weeks into therapy with both drugs, had a stable cholestatic pattern of LFTs, which then evolved into a hepatitis flare with decompensation within a short period after the introduction of HAART, it is highly unlikely that the drugs would have been responsible for the deterioration.

We postulate that, in order to prevent flares of HBV disease, active HBV replication should be controlled prior to or in conjunction with the commencement of HAART. Of greatest concern in these cases was the fact that the flares occurred in patients with documented wild-type HBV infection, despite the inclusion of lamivudine, an antiviral agent active against HBV, in the HAART regimen. It is well known that immune reconstitution can occur within days after the introduction of HAART [11], meaning that it can occur prior to a significant lamivudine-induced reduction of HBV DNA levels, which can take 1 month to become undetectable by nonamplification assays [12]. The poor prognosis of the second case was at least in part due to underlying established cirrhosis with decreased hepatic reserve, in contrast with the first case, in which only stage 3 fibrosis was present.

These cases highlight the need to maximally suppress HBV replication from the outset. One of the patients recovered fully following commencement of treatment with tenofovir, a potent nucleotide analogue known to be active against both HIV and HBV. This agent has a potential role as a component of combination therapy for patients coinfected with HIV and HBV, because it enables HBV virus loads to be more rapidly reduced, and recent evidence suggests that the combination of lamivudine and tenofovir is more effective at reducing virus loads in these cases than is lamivudine monotherapy [13]. We suggest that a strategy to control HBV replication that incorporates combination therapy with lamivudine and tenofovir into the HAART regimen should be employed at least for cirrhotic patients at risk for hepatic decompensation and, perhaps, even for all coinfected patients with HBV replication. Such a strategy, because of the activity of tenofovir against lamivudine-resistant HBV virus [13], will also reduce the likelihood of development of HBV drug resistance, which occurs with lamivudine monotherapy at a prevalence of 50% at 2 years and 90% at 4 years [14]. Another potential strategy for high-risk coinfected patients may be to initially omit the third component of HAART to reduce the rate of immune reconstitution. Such approaches need to be formally studied in a clinical trial.

The cases we describe also highlight the importance of accurate assessment of HBV status prior to the commencement of HAART for HBV/HIV coinfected patients. Both patients had advanced fibrosis, as determined by liver biopsy, and the patient who died had established cirrhosis, which suggests that patients with advanced fibrosis are unable to tolerate a hepatitis flare following immune reconstitution unless the HBV DNA level is effectively reduced first. We suggest that the level of active HBV replication, as indicated by HBV DNA levels (preferably de-

termined using quantitative HBV PCR), should be assessed when HBV is first diagnosed. In addition, the presence of underlying hepatic damage should be determined, with histological examination of the liver, if possible, because advanced fibrosis is more likely in cases of HBV/HIV coinfection, and the risk of hepatic decompensation is increased [4].

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