Resolution of Hepatitis C Virus–Induced Steatosis Improves Tolerability of Antiretroviral Drugs Associated with Hepatotoxicity in an HIV-Infected Individual

To the Editor—We read with interest the article by Labarga et al. [1], who reported that successful treatment of hepatitis C virus (HCV) infection in HIV/HCV-coinfected patients resulted in increased tolerability of hepatotoxic antiretroviral drugs. In their study, the majority of patients had evidence of advanced fibrosis prior to treatment for HCV. We present a case of an HIV/HCV-coinfected patient without evidence of fibrosis on biopsy, but with severe steatosis (likely due to his genotype 3 HCV infection), who was unable to tolerate multiple highly active antiretroviral therapy (HAART) regimens until HCV had been successfully treated and steatosis had been resolved.

The patient was a 46-year-old man who had a CD4-cell-count nadir of 10 cells/mm³ and a history of multiple opportunistic infections, including Kaposi sarcoma, Pneumocystis jiroveci pneumonia, and disseminated Mycobacterium avium infection between 1993 and 1995. Treatment with stavudine, lamivudine, and indinavir was initiated, with a subsequent recovery of CD4 cell count to 409 cells/mm³ and no detection of HIV RNA. Prior to initiation of HAART, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in serum were 33 U/L and 44 U/L, respectively. Over the next 5 years, he remained on the same HAART regimen, and AST and ALT levels were noted to be ~60 U/L and ~100 U/L, respectively. He was tested for HCV antibodies and was found to be positive. Liver biopsy showed no fibrosis but did reveal severe steatosis.

In July 2001, ritonavir, at a dosage of 100 mg twice a day, was added to his regimen, and indinavir was reduced to 800 mg twice a day. AST and ALT subsequently rose to 232 U/L and 438 U/L, respectively (figure 1). The patient’s HAART regimen was discontinued, and aminotransferase levels were normalized. Treatment with abacavir, lamivudine, and efavirenz was initiated, but the patient developed an abacavir-hypersensitivity reaction; therefore didanosine was substituted for abacavir, with marked elevations in aminotransferases. HAART was again discontinued, and the patient’s aminotransferase levels decreased. Treatment with tenofovir, fixed-dose zidovudine/lamivudine, and indinavir was then initiated, but the patient developed severe anemia and remained anemic despite reduction of his

Figure 1. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in relation to initiation and discontinuation of antiretroviral drugs in a patient coinfected with HIV and hepatitis C virus who had severe steatosis but no evidence of fibrosis. d4T, stavudine; ddI, didanosine; EFV, efavirenz; IDV, indinavir; peg IFN, pegylated interferon; RBV, ribavirin; TDF, tenofovir; 3TC, lamivudine.
zidovudine dose. HAART was again discontinued.

In October 2003, the patient agreed to start HCV therapy to see if resolution of HCV infection—and, thus, of steatosis—would improve his tolerance of antiretroviral drugs. His HCV RNA level was >500,000 IU/mL. His underlying steatosis was thought to be related to genotype 3 HCV infection, because his body-mass index was normal, as were the levels of fasting triglycerides, cholesterol, and glucose; the patient denied alcohol use.

The patient tolerated a 48-week course of pegylated interferon and ribavirin while maintained on a course of tenofovir, lamivudine, and indinavir, which had been started 2 months prior to initiation of HCV therapy. His CD4 count was 320 cells/mm³, and HIV RNA was not detected when HCV therapy was initiated.

Six months after completion of HCV therapy, no HCV RNA was detected in the patient. AST and ALT levels were 26 U/L and 31 U/L, respectively. Abdominal ultrasound showed no evidence of steatosis. Ritonavir was added to the patient’s HAART regimen, and the indinavir dose was reduced. In contrast to what had been observed when ritonavir had previously been added to his regimen, the patient’s aminotransferase levels remained in the normal range. Furthermore, when stavudine was added to his regimen for 4 weeks, elevation of aminotransferase levels was not observed. Most recently, the patient’s AST and ALT levels during treatment with tenofovir, lamivudine, indinavir, and ritonavir were 15 U/L and 18 U/L, respectively.

This case shows not only that HCV genotype 3–induced steatosis resolves after treatment of HCV infection, a finding that supports prior data on HCV–monoinfected individuals [2], but also that resolution of steatosis leads to tolerability of antiretroviral drugs previously associated with marked elevation of aminotransferase levels. Resolution of steatosis is an important consideration, because steatosis appears to be prevalent in HIV/HCV–coinfected patients: published studies have reported prevalences of 23%–72% [3–9]. Genotype 3 HCV infection [3, 6], obesity [3, 5, 9], and the nucleoside analogs didanosine and stavudine [6, 9] have been associated with steatosis in HIV-infected patients. In our patient, the addition of stavudine and didanosine to the treatment regimen likely contributed to a worsening of his genotype 3 HCV–induced steatosis. Ritonavir has also been associated with hepatotoxicity; direct liver injury related to alterations in the ability of the cytochrome p450 system to metabolize ritonavir has been postulated [10]. Didanosine and stavudine, on the other hand, are thought to inhibit mtDNA polymerase γ, which, in turn, leads to inhibition of fatty-acid oxidation and steatosis [11].

In summary, HCV treatment should be considered for HIV-infected patients with genotype 3 HCV infection and steatosis, to improve tolerability of antiretroviral drugs that have been associated with hepatotoxicity—especially when HIV treatment options are limited. These recommendations extend current HIV/HCV treatment guidelines, which recommend that, because of the reported favorable response rates, treatment of genotype 3 HCV infection should be initiated regardless of the stage of fibrosis. Whether interventions to reduce steatosis, due to fat or metabolic disorders, can improve tolerability to antiretroviral drugs needs to be investigated.

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References


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