First Things First: Balancing Hepatitis C and Human Immunodeficiency Virus

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(See the article by Tedaldi et al. on pages 363–7)

Persons who are coinfected with HIV and hepatitis C virus (HCV) and their providers face a number of dilemmas. These include understanding how the natural history of each virus is affected by the presence of the other, balancing the risks and benefits of treating each of these viral infections, deciding on the order and timing of treatment, and understanding how medication toxicity may be modified in patients with coinfection. Previous studies have addressed the natural history of HCV in HIV-infected patients, but given the long natural history of HCV infection, many of these studies were conducted before the widespread use of HAART [1, 2]. Several recent studies have suggested that HCV infection is an independent predictor of mortality in HIV infection [3–5], possibly by impeding immune reconstitution after the initiation of HAART [6]. The article by Tedaldi and colleagues [7] in this issue of Clinical Infectious Diseases addresses whether HCV infection alters the morbidity and mortality associated with HIV infection in a cohort of patients during a period when HAART was available.

This study found that there were proportionately more deaths among HIV-HCV–coinfected patients than there were among patients infected with HIV alone. However, when the authors adjusted for age, baseline CD4⁺ cell count, and duration of HAART, HCV infection was not an independent predictor of survival. Several differences between the HIV-HCV–coinfected group and the HIV-monoinfected group were notable. HIV-HCV–coinfected patients were more likely to have injection drug use as their HIV transmission risk (69.7% vs. 5.4% of those with HIV infection alone); to be nonwhite, older, and less educated; and to receive care with use of public funds. HIV-HCV–coinfected patients had lower baseline CD4⁺ cell counts (242 vs. 316 cells/mm³), a delay in the initiation of HAART of 4.5 years (compared with 3.2 years for patients with HIV infection alone), and lower CD4⁺ cell counts before the initiation of HAART (164.5 vs. 231.5 cells/mm³ for the one-half of the HIV-only cohort for whom these data were available).

This study is reassuring in its finding that, during the relatively short observation period examined, there was not an increase in mortality among HIV-HCV–coinfected patients that was attributable to HCV infection. However, this study excluded patients who had HCV infection diagnosed before 1996; thus, it may have eliminated the patients with the highest likelihood of having advanced liver disease and an impaired ability to tolerate HAART. The natural history of HCV-related liver disease is one of progressive damage over the course of years, even in patients with HIV coinfection. Estimates vary widely, but severe liver disease is found in 12%–50% of patients by 15–25 years after presumed infection with HCV [8, 9]. In this cohort, only 4.5% of the patients had cirrhosis diagnosed, suggesting that this cohort was studied earlier in the disease process. However, this is consistent with the findings of another large US cohort studied during a similar time frame [10] in which death was not associated with HCV infection once the authors adjusted for use and effectiveness of HAART. We will need longer-term follow-up of cohorts such as this one to determine whether HCV infection has an impact on mortality in persons living with HIV infection over decades.

HCV infection has been shown to increase the risk of severe hepatotoxicity associated with HAART [11]. However, a potential source of variability in studies examining the role of HCV infection in progression of HIV disease and tolerability of HAART is that the definition of HCV infection is often limited to HCV antibody seropositivity. This definition of HCV infection encompasses patients who are an-
Body positive but virus negative—and, thus, who do not have chronic infection—and patients with liver disease of variable severity. It is logical to assume that the ability to tolerate HAART may be quite different between a patient with minimal liver inflammation and a patient with advanced fibrosis. However, this information is often not known, because performing a liver biopsy is the only means to definitively define the extent of liver damage, and there are currently no reliable noninvasive tests that accurately predict the extent of histologic injury [12]. The relationship between HAART tolerability and the extent of liver disease is an important area for future research. As seen in the present study, if a major factor in survival among HIV-HCV–coinfected persons is the tolerability of HAART, another important and still unanswered question is whether treatment of HCV-associated liver disease will improve the tolerability of HAART, thus improving effective and durable control of HIV infection.

Studies that compare HIV-HCV–coinfected patients with patients who have HCV infection alone try to answer questions about the role of HIV on progression of severe liver disease due to HCV [8]. These cohorts tend to be relatively homogeneous and typically comprise either persons with hemophilia or persons with a history of injection drug use. In contrast, studies that compare HIV-HCV–coinfected patients with HIV-monoinfected patients examine the role of HCV in modifying outcomes in persons with HIV infection. As in the present study, these studies tend to compare patients who had sexual transmission of HIV with those for whom injection drug use is the primary risk factor. The differences seen between patients with and patients without HCV infection in this study brings up a larger question of whether HCV infection status should raise a flag about broader issues related to the care of persons with a history of injection drug use. Injection drug use has also been shown to be a predictor of progression to AIDS-defining illness or death [13, 14]. HCV antibody status may be serving as a marker for poorer access to care and competing problems with addiction that lead to delays in care or failure to implement the standard of care, as suggested by the greater time to initiation of HAART and lower median CD4+ cell count before the initiation of HAART noted in the present study. If we are to improve the health statuses of patients with HIV-HCV coinfection, perhaps we should focus on these issues as well as the presence of 2 viruses.

References