

Spontaneous Hepatitis C Virus Clearance in HIV-Infected Patients: New Insights for Improving Management

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(See the article by Soriano et al., on pages 1337–44.)

Progressive chronic liver disease associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality in patients infected with HIV. As many as one-third of HIV-infected individuals are coinfecting with HCV, and 10%–45% of these patients will die from complications associated with HCV-related liver disease. Numerous studies have shown that infection with HIV exacerbates the natural history of chronic HBV and HCV infection. Increased rates of liver fibrosis and progression to end-stage liver disease (ESLD) have been well documented in HIV-infected individuals coinfecting with HBV and/or HCV. In prospective studies, HIV/HCV coinfection is associated with a higher cumulative incidence of ESLD and shorter survival times than HCV monoinfection [1].

HCV and HIV have similar modes of transmission, but the transmission efficiency of each virus differs. HCV is most efficiently spread through exposure to contaminated blood or blood products,

particularly via injection drug use. Rates of vertical and perinatal transmission are relatively low (3%–6%), although they are increased 2-fold when the mother is infected with HIV. Sexual transmission of HCV is inefficient, and the exact risk related to different types of sexual activity is unknown. However, there is increasing evidence of sexually transmitted HCV in HIV-infected men who have sex with men (MSM). For example, in one cohort, the incidence of HCV infection among HIV-seropositive MSM increased 10-fold after the year 2000. Sexually acquired HCV infection has been associated with sexually transmitted diseases and traumatic anal receptive intercourse. Because of the relative efficiency of transmission, the prevalence of HCV coinfection varies depending on the route of HIV transmission, ranging from 10% to 14% among persons reporting high-risk sexual exposure to ~85%–90% among those reporting injection drug use. In the United States and Europe, 33% of all HIV-infected persons are infected with HCV [2].

The successful control of viral infections depends on the generation and maintenance of long-lasting specific memory CD4 T cells, which support the production of antibodies and the function of specific CD8 T cells. In the case of HIV and HCV infection, early containment (HIV-1) or clearance (HCV) of infection is associated with the induction of strong CD4 and CD8 T cell responses. In contrast, it has been suggested that these

same kinds of responses may play a role in the pathogenesis of disease, because of the accelerated destruction of hepatocytes in the case of HCV and of lymphocytes in the case of HIV-1. Many findings indicate that CD4 T cell responses represent a critical component of a successful immune response against HCV. During the acute phase of HCV infection, the breadth of this response correlates with early control. It is well known that subjects with chronic HIV-1 infection rarely demonstrate strong HIV-1-specific CD4 T cell proliferative responses, with the exception of individuals who have long-term nonprogressive infection. The proliferative response of CD4 T cells on stimulation with HCV proteins is also weak in individuals with chronic HCV infection, but vigorous CD4 T cell responses have been detected in individuals in whom the infection spontaneously resolves [3, 4].

The study by Soriano et al. [5] in this issue of the *Journal* adds new and interesting information to the area of HIV/HCV coinfection. The objective of the study was to evaluate the variables influencing serum HCV RNA levels and genotype distribution in HIV-infected individuals from the EuroSIDA cohort as well as the factors determining spontaneous clearance after HCV exposure. Of 1940 HCV antibody (Ab)-positive patients in the EuroSIDA cohort, 1496 (77%) were serum HCV RNA positive. Injection drug users (IDUs) were less likely to have

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cleared HCV spontaneously compared with MSM (20% vs. 39%), whereas patients who were positive for hepatitis B surface antigen (HBsAg) were more likely to have cleared HCV compared with those who were negative (43% vs. 21%). Among patients with HCV viremia, 786 (53%) carried HCV genotype 1, and 53 (4%), 440 (29%), and 217 (15%) carried HCV genotype 2, 3, and 4, respectively. Higher HCV RNA levels were associated with a greater chance of having HCV genotype 1 infection.

Although the study by Soriano et al. [5] reported HCV clearance in approximately one-quarter of patients, this rate was observed as a consequence of a single point determination using an HCV RNA test with a dynamic range of 615 to 1×10^7 IU/mL. A more-thorough evaluation of virus clearance by patients needs to be done by repeatedly using a more-sensitive test, such as a transcription-mediated amplification.

In the absence of HIV infection, spontaneous HCV clearance occurs in ~20% of patients [6, 7]. Spontaneous HCV clearance, which seldom occurs >12 months after primary infection, is less likely in men, people of black race, chronic carriers of HBV, and probably those who become infected after early childhood [8]. Clearance of HCV does not convey immunity, because new exposure can result in reinfection. The rate of spontaneous clearance may be 2-fold higher (~40%) in IDUs who clear their primary infection in the absence of HIV coinfection [9]. Nonetheless, the majority of HCV reinfections become chronic, as seen in persons with hemophilia who used contaminated plasma derivatives before 1983 [10, 11]. Mehta et al. [9] noted that, compared with primary infection, clearance of HCV reinfection increased among HIV-negative but not HIV-infected IDUs. Anecdotal cases of spontaneous HCV clearance have been described in coinfecting patients after liver transplantation despite long-term immune-suppressive therapy [12].

Another interesting observation by Soriano et al. is that patients from southern

Europe and Argentina had decreased odds of spontaneous HCV clearance compared with subjects from central or northern Europe. This was particularly clear for patients from northern Europe, who had a 47% increased likelihood of HCV clearance compared with those from southern Europe and Argentina (adjusted odds ratio [aOR], 1.47 [95% confidence interval {CI}, 1.03–2.09]; $P = .032$). Furthermore, patients who were HBsAg positive had an increased likelihood of spontaneous HCV clearance (aOR, 2.91 [95% CI, 1.94–4.38]; $P < .001$).

These results suggest that the possibility of spontaneous clearance of HCV infection does not solely depend on viral and immunological factors or risk category but also depends on geographical origin and other host factors. Genetic variability of the virus allows it to evade the immune system, whereas host HLA class II genotype plays an important role in host susceptibility. Indeed, HLA-DRB1*11 alleles and DQB1*0301 are consistently associated with decreased severity of disease due to HCV infection worldwide. In French populations with HCV infection, DQB1*0301 is associated with viral clearance in females, and DRB1*11 is associated with protection from disease progression in males [13]. Other studies have demonstrated an association between DRB1*11 and HCV clearance in French females [14]. HLA-DQB1*0301 is linked to HCV clearance in US populations, showing a stronger association in African Americans [15]. Carriers of the HLA-DR11 and DQB1*0301 alleles may present HCV epitopes to CD4 T cells more efficiently than do carriers of other alleles and, thus, show efficient viral clearance. Moreover, interleukin-10 haplotypes are possible additional predictors of spontaneous clearance of HCV infection [16, 17]. Infection with >1 hepatitis virus can also affect the capacity for spontaneous clearance [18]. In anti-HIV-positive patients, HBV/HCV coinfection is characterized by reciprocal inhibition of viral replication, more evident HBV ex-

pression in plasma, and at times progression to occult HBV infection.

Soriano et al. showed that 53% of the patients with HCV viremia in their population were infected with HCV genotype 1 and that this genotype was associated with higher serum HCV RNA levels. Baseline serum HCV RNA level and HCV genotype are the main predictors of a sustained virological response to pegylated interferon plus ribavirin in coinfecting patients, as they are in those who are HCV mono-infected. Thus, Soriano et al.'s findings indicate that the majority of patients in the EuroSIDA cohort have a reduced likelihood of responding to anti-HCV therapy and are potential progressors to ESLD and death. Given data supporting the concept that antiretroviral therapy may produce beneficial effects regarding the clinical course and outcome of liver disease in patients with HIV/HCV coinfection [19], strong consideration should be given to treating these patients with antiretroviral therapy in view of the limited rates of response to anti-HCV therapy.

In conclusion, patients with HIV/HCV coinfection in Europe and Argentina have a high probability of being chronically infected with HCV genotype 1 with a high viral load and are not good candidates for anti-HCV therapy. Given their low rate of spontaneous clearance and poor response rates, preservation of immune function with early antiretroviral treatment may be the best way to avoid a poor outcome of liver disease in HIV-infected patients. Further study of this strategy is warranted.

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