Coinfection with Hepatitis C Virus and HIV: More than Double Trouble

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(See the article by d’Arminio Monforte et al on pages 612–22)

Before highly active antiretroviral therapy (HAART) became available, human immunodeficiency virus (HIV)–related morbidity and mortality were so high that they largely overshadowed the potential clinical consequences of coinfection with hepatitis C virus (HCV), the impact of which was often found to be negligible. In the HAART era, the dramatic decrease in AIDS illnesses and mortality brought to light the clinical consequences of chronic HCV infection in HIV-infected patients. It thus appeared that the evolution of chronic HCV infection was worsened by HIV infection, with a risk of faster liver disease progression and a higher risk of cirrhosis, end-stage liver disease, hepatocarcinoma, and, finally, hepatic-related death [1]. Mortality as a whole has been extensively studied (whatever the cause of death), but there are fewer data on the specific risk of HIV disease progression. Several cohort studies found a higher risk of AIDS-defining illnesses, AIDS-related death, or hospitalization in HCV-HIV–coinfected patients [2–5], whereas other studies did not [6–9]. The question of a “reciprocal” negative impact of HCV infection on the progression of HIV infection thus remains unanswered.

In this issue, d’Arminio Monforte et al [10] analyzed the risk of developing AIDS among a large prospective cohort of 5397 HIV-infected patients, totaling 25,105 patient-years of follow-up. HCV positivity was found to be associated with a 2.6-fold higher risk of AIDS-defining illnesses. Among these illnesses, bacterial infection and mycotic and HIV-related diseases occurred significantly more frequently among HCV-coinfected patients. These detailed analyses, performed for the first time in a study dealing with this topic, may be helpful in understanding the potential underlying mechanisms, even though the overall risk is likely to be based on multiple factors, including the interdependence of the natural histories of HIV and HCV, the role of HAART, and other patient-related factors.

The first hypothesis is that HCV has a direct effect on the immune system. Although the steeper natural decrease in CD4 cell count observed in a few clinical pre–HAART era studies [11] was not observed in more recent studies [5, 12], it has been shown that HCV could inhibit the proliferation of CD4 cells and accelerate and/or trigger their apoptosis [13, 14]. Moreover, CD8 cell activation is increased in HCV-HIV–coinfected patients [15, 16], which may lead to a defective response to opportunistic pathogens and may contribute to a higher risk of HIV disease progression [17]. HCV may also be associated with a decrease in the number of functional HIV-specific CD8 cells, which is potentially associated with a decrease in the CD4 cell count [18]. During receipt of HAART, some immune function abnormalities may persist, even though they may have been attenuated [14]. A meta-analysis of 8 trials involving 6216 patients concluded that the magnitude of immune system recovery in HIV-HCV–coinfected patients was lower than that in HIV-monoinfected patients [19], although this point still remains controversial [5, 7, 8].

Indeed, patient characteristics and behavior may also have an impact, in particular adherence to HAART, which was never directly assessed in the different studies, including the study by d’Arminio Monforte et al [10]. This could be a key factor because adherence was often found to be lower among HCV-HIV–coinfected patients [20, 21], especially among those with ongoing drug or alcohol abuse [21, 22], and thus may significantly affect HIV disease progression in HCV-HIV–coinfected patients. Another important point that is infrequently assessed is the timing of HAART initiation. Indeed, it has been observed in other studies that the introduction of HAART was often deferred in
HIV-HCV–coinfected patients [3, 12, 23] for different reasons, including social difficulties, ongoing substance abuse, and the fear of lower adherence and/or of a higher risk of liver toxicity during receipt of HAART. It is of particular interest that, in the study by d’Arminio Monforte et al [10], the rate of unemployment was 3 times higher among HCV-HIV–coinfected patients and that the median time from the positive result of an HIV test to enrollment in the cohort was much longer for those patients (although neither factor appeared to be significantly associated with AIDS-defining clinical outcomes). However, although the immunological gain during HAART is similar regardless of the CD4 cell count at the time of HAART introduction [24], the lower the CD4 cell count at HAART introduction, the lower the CD4 cell count and/or the longer the delay to reach a high CD4 cell count during receipt of effective HAART [25] and, finally, the higher the risk of developing HIV-related diseases [26–28].

Other patient-related factors contribute to the risk of some AIDS-defining illnesses, in particular previous exposure to infectious agents. The higher frequency of tuberculosis among HCV-HIV–coinfected patients may be linked less to immunodepression than to a high rate of exposure to Mycobacterium tuberculosis as previously observed in HCV-monoinfected patients [29]. On the other hand, ongoing GB virus C coinfection, which is also frequent among HCV-HIV–coinfected patients, might, in contrast, positively influence the immunological evolution [30] and is thus unlikely to be associated with a higher risk of AIDS-defining illnesses.

HCV therapy is also unlikely to play a deleterious role, despite side effects such as lymphopenia, neutropenia, or anemia, because of the low percentage of HCV-HIV–coinfected patients who are treated, the limited duration of treatment, the reversibility of hematological side effects, and the lack of significant related clinical consequence in therapeutic trials [31]. On the contrary, HCV therapy might, in fact, decrease the risk of AIDS-defining events, in particular through prevention of evolution to cirrhosis. Indeed, another point of interest in the study by d’Arminio Monforte et al [10] is that HCV-induced cirrhosis was significantly associated with AIDS onset, although the causal relationship remains unclear. It could be argued that advanced immunodepression and uncontrolled HCV replication, which have been shown to accelerate the progression of fibrosis and the development of cirrhosis [32], may contribute to this association. On the other hand, it has been established that patients with cirrhosis are at risk of bacterial infections, in particular AIDS-defining pneumococcal pneumonia [33]. The question as to whether the inflammation induced by HCV or by an increased frequency of bacterial translocations in portal hypertension worsens the evolution of HIV infection in a vicious circle has not yet been assessed.

Although the study by d’Arminio Monforte et al [10] included more patients for a longer time, often with more cofactors taken into account, than did previous studies, the interpretation remains uncertain because of incomplete information, in particular on the timing of adherence to, and time spent receiving HAART; immunological and HIV virological kinetics; and HCV RNA status, as well as a lack of systematic assessment of liver histology. Because the increasing efficacy of HAART should help identify “residual” risk factors of HIV progression that are not directly influenced by HAART, it underlines the need for new, large, prospective, observational studies, with a long follow-up and completed by physiopathological studies. Moreover, nonhepatic, non–AIDS-defining, and nonfatal clinical events should also be considered, because they could be overrepresented among HCV-HIV–coinfected patients [34].

Whatever the respective weight of the different underlying mechanisms, the study by d’Arminio Monforte et al [10] provides important findings that may affect the clinical management of HCV-HIV coinfection. It highlights and strengthens the need for careful follow-up of HCV-HIV–coinfected patients, including preventive measures (screening, prophylaxis, and vaccination for preventable diseases), effective management of associated comorbidities (particularly addictions), and early and effective therapies against HIV and HCV.

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References

10. d’Arminio Monforte A, Cozzi-Lepri A, Castagna A, et al. Risk of developing specific...
24. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. J Acquir Immune Defic Syndr 2007; 45:183–92.